CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-597

MEDICAL REVIEW

Medical Officer Review of NDA 21-597: Serostim® [somatropin (rDNA origin) for injection]

Treatment of Short Bowel Syndrome

Date Submitted:		31 October, 2002
Date Completed:		22 May, 2003
Applicant:		Serono, Inc. One Technology Place Rockland, MA 02370 Contact person: Pamela Williamson Joyce Vice President, Regulatory Affairs
Drug:	**Proprietary Name :**	Serostim®
	Non-proprietary name:	somatropin (rDNA origin) for injection
	Chemical Name:	human Growth Hormone (hGH) A single polypeptide chain of 191 amino acids having the normal structure of the principal growth stimulating hormone obtained from the anterior lobe of the human pituitary gland. (1) Growth Hormone (human); (2) somatotropin (human)
	Molecular formula:	$C_{990}H_{1528}N_{262}O_{300}S_7$
	Molecular weight:	22,124
	Formulation:	lyophilized
	Route of Administration:	subcutaneous
	Strengths:	4mg, 5mg, 6mg, 8.8mg
Related NDA:		20-604
Reviewer:		Hugo E. Gallo-Torres, MD, PhD, PNS Medical Team Leader (GI Drugs) HFD-180

Table of Contents

Clinical Review for NDA 21-597

Executive Summary

I. Recommendations

A. Recommendation on Approvability

Serostim® [somatropin (rDNA origin)], a form of human growth hormone produced by recombinant DNA technology, is already marketed for the **treatment of AIDS wasting or cachexia.**

The sponsor is seeking approval of the product for a new indication, **treatment of Short Bowel Syndrome in patients receiving specialized nutritional support.** It is to be noted that the newly proposed indication includes the following wording: ***Serostim® therapy should be used in conjunction with optimal management of Short Bowel Syndrome.***

Based on review of the efficacy and safety of this submission (NDA 21-597), the recommendation is that the NDA ***is approvable.***

Several issues need to be addressed, clarified, and eventually resolved before the application is approved. **[NOTE: These issues were discussed at the June 25, 2003, Advisory Committee Meeting].** Included among these issues were:

1. *Replicability* [results of only one trial of 41 patients (IMP20317) were submitted as part of NDA 21-597];
2. *Generalizability* [in the final analysis, the bulk of the patients in Study IMP20317 originated from one center only, and, due to known variations in the standard of care, **this center may or may not be representative of the general population**];
3. The *clinical validity/relevance/importance* **of the protocol-stipulated primary endpoint of efficacy [a reduction in the Total intravenous parenteral nutrition (IPN) volume requirements (L/wk)]**, instead of the very meaningful proportion of patients that, as a result of the proposed intervention [administration of recombinant human growth hormone (rh-GH) in co-therapy with glutamine (GLN) in patients who are receiving a specialized oral diet (SOD)] are **weaned off IPN** and **remain off IPN long-term** ; and
4. ***Further exploration of dosing.*** Results from two recent well-designed, well-controlled and apparently well-executed randomized clinical trials are worth mentioning. In **Study No.7 (Table 2),** the combination **"high-dose"** rh-GH **(0.14 mg/kg/d)** and **glutamine** *did not increase* body weight, lean body mass, fat mass and bone mass significantly compared to placebo treatment. In another placebo-controlled, randomized crossover trial [**Study No. 9 (Table 2)**] treatment with **"low-dose"** rh-GH (**0.05 mg/kg/d**) *increased* intestinal absorption of energy, nitrogen and fat. In the latter study, body weight, lean

body mass, D-xylose absorption, insulin-like growth factor 1 and insulin-like growth factor binding protein 3 **also increased.**

B. Specific Recommendations to Approve rh-GH for the sought SBS indication

- The following 4 deficiencies must de addressed **before** approval of NDA 21-597 is granted [see current review, XIII. Recommendations for Regulatory Action]: 1. Educational Plan; 2. Additional Data in Support of replicability/generalizability; 3. Initial Data in Support of Durability of Effect and 4. Additional work in progress.
- No Phase IV commitments are being requested.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

The Clinical Program consists primarily of a 3-arm, 41 patient total, double-blind, randomized Clinical trial [Protocol IMP20317].This study was set to assess the effect of rh-GH administered in co-therapy with glutamine and a specialized oral diet, in the **improvement of residual gut absorptive function** in patients with short bowel syndrome. Although the trial was designed to be **"multicenter"** there were only 2 sites involved with patient recruitment and **one site randomized 3 patients only** (1 per treatment arm) while the other randomized a total of 38, in a 2:2:1 ratio. Consequently, **in the final analysis, this was a single-center study**

B. Efficacy

There were 3 arms, identified in the current review as A, B, and C, in the trial. **Group A consisted of active rh-GH plus glutamine placebo** in patients who were receiving SOD. Group B (rh-GH+SOD[GLN] is the group of most interest because it consisted of rh-GH in co-therapy with (active) glutamine, given to SBS patients who were on a specialized oral diet (SOD). The third arm of the study, **Group C**, was the control arm, consisting of (active) glutamine plus the specialized oral diet plus rh-GH placebo.

The most important comparison is that of Group B (rh-GH plus glutamine) to Group C. The comparison of Group A (active rh-GH alone, without glutamine), is also of interest. The protocol stipulated primary efficacy endpoint was the mean change **(decrease)** in Total IPN volume **(measured in liters per week)** from Week 2 to Week 6.

In analyses of the Intent-to-Treat Study Population (Table 6 of the current review), a significant reduction in the Total IPN volume requirement was noted in patients who received rhGH + SOD[GLN] when compared to those receiving SOD + [GLN] plus rhGH placebo. The therapeutic gain was **3.9 liters less** per week. Results of this comparison are also supported and confirmed in the statistical analyses of the Evaluable for Efficacy Study Population.

Owing to the fact that **no clinical nutrition parameters of efficacy** were made use of in Study IMP20317, there remain questions **regarding the most adequate clinical tool (approach)** to demonstrate clinically meaningful benefit of the drug in the treatment of Short Bowel Syndrome in patients who are dependent on IPN.

There is uncertainty if a reduction of Total IPN volume requirement of 3.9 L/wk is clinically meaningful [This is one of the questions asked of the AC]. An unquestionably meaningful and convincing clinical endpoint is the proportion of patients that, as a result of the intervention (administration of rh-GH in co-therapy with GLN in patients receiving SOD) are **weaned completely from IPN and remain off for at least 1 year** following admission into an in-home program. Results using this parameter (Table 8 of the current review) should be considered hypothesis-generating only. For the time-being, results of evaluations using the protocol pre-stipulated study endpoints seem too incomplete to determine if they are predictive of clinical benefit, an issue also discussed at the AC Meeting.

NOTE: Issues regarding the one study approach are discussed further in the following FDA document: **Guidance for Industry. Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, U.S. Department of HHS, FDA, CDER, CBER, May 1998, Clinical 6** [Internet at http://www.fda.gov/cder/guidance/index.htm]

C. Safety

All in all, there are no overt safety concerns with the use of rh-GH in co-therapy with glutamine and a specialized diet in patients with SBS treated for up to 4 weeks. The safety profile of the triple co-therapy (rh-GH+SOD+GLN) appears to be similar to the safety profile of rhGH + SOD.

No labeling revisions to include adverse events emerging from the IMP20317 SBS trial are proposed or needed. This is because, as expected, the majority of AEs reported in this study were related to the underlying clinical situation (SBS patients who were on Total IPN).

For completeness of information purposes, the reviewer has included a short account of some recently published information from patients that were given GH for long periods of time.

D. Dosing

In the proposed package insert, in the DOSAGE AND ADMINISTRATION section, the sponsor proposes to include the following wording: "In patients with Short Bowel Syndrome (SBS), Serostim® should be administered at a dose of 0.1 mg/kg subcutaneously daily to a maximum of 8 mg daily". Although the proposed revision is based on results of Clinical Trial IMP20317, the reviewer does not believe that the dose has been adequately assessed. Although different methodology may have been used, in a recently published well-designed clinical trial (**Study No. 7 in Table 2** of the current review), the combination "high-dose" GH **(0.14 mg/kg/d)** and glutamine did not increase body weight, lean body mass, fat mass, and bone mass significantly compared to placebo treatment. An even more recently well-designed and apparently well-executed published study (**Study No. 9 in Table 2** of the current review) showed that treatment with GH at the **"low-dose of 0.05 mg/kg/d"** increased intestinal absorption of energy, nitrogen and fat. Other parameters that increased included body weight, lean body

mass, D-xylose absorption, insulin-like growth factor 1 and insulin-like growth factor binding protein 3. It was also reported that uptake of GH binding protein decreased without any apparent major adverse event.
In view of the above, there is some uncertainty about whether 0.1 mg/Kg/d is the most effective dose or whether a lower dose of the hormone may be even more effective than the 0.1 mg. The dose and dose regimen issue should be adressed by the sponsor before approval of the NDA.

E. Special Populations

Because the total number of patients who had SBS and were randomized to the rhGH + SOD [GLN] arm was so small (n= 16), assessment of the use of the drug in Special Populations is not very helpful.
Of note, the already approved Package Insert, PHARMACOKINETICS Section, includes information on Pediatric Patients, Gender, those with Renal Insufficiency, and those with Hepatic Insufficiency; but data for race are not available.
Finally, in the PRECAUTIONS Section, information on Pregnancy, Nursing Women, Pediatric Use and Geriatric Use is included.

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Serostim® [somatropin (rDNA origin) for injection] is a human growth hormone produced by recombinant DNA technology. Its amino acid sequence and structure are identical to the dominant form of human pituitary growth hormone.[1]

Somatropin (somatotropin) belongs to the class of growth hormones (GH). Somatotropin is a species-specific anabolic protein that promotes somatic growth, stimulates protein synthesis, and regulates carbohydrate and lipid metabolism. Somatotropin is secreted by the anterior pituitary under the regulation of the hypothalamic hormones, somatoliberin and somatostatin; it also increases serum levels of somatomedins. GHs from various species differ in amino acid sequence, antigenicity, isoelectric point, and in the range of animals in which they can produce biological responses.[2]

The sponsor's Serostim® [somatropin (rDNA origin)] is approved for the **treatment of AIDS wasting or cachexia**, an indication based on analysis of surrogate endpoints in studies of up to 12 weeks in duration.[3]

NOTE: The sponsor also manufactures another form of growth hormone. The brand name for this form is SAIZEN® [somatropin (rDNA origin) for injection], for subcutaneous or intramuscular injection. SAIZEN® is indicated for the long-term treatment of children with growth failure due to inadequate secretion of endogenous growth hormone.

Sponsor's proposed indication:
"Serostim® [somatropin (rDNA origin) for injection] is also indicated for the treatment of Short Bowel Syndrome in patients receiving specialized nutritional support. Serostim® therapy should be used in conjunction with optimal management of Short Bowel Syndrome."

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[1] Serostim® is produced by a mammalian cell line (mouse C127) that has been modified by the addition of the human GH gene. Serostim® is secreted directly through the cell membrane into the cell culture medium for collection and purification. Serostim® is highly purified preparation. **Biological potency is determined by measuring the increase in the body weight induced in hypophysectomized rats.**

[2] There exist human GH, methionyl human GH, bovine somatotropin, porcine somatotropin, etc.

[3] The product information notes that, for patients treated in open-label extension studies, no significant additional efficacy was observed beyond 12 weeks. There are no data available from controlled studies for patients that start, stop, ands re-start treatment. Concomitant anti-viral therapy is necessary. It is also noted that the continued use of Serostim® treatment should be reevaluated in patients who continue to lose weight in the first two weeks of treatment.

Dose, Regimen [from proposed draft package insert]: "In patients with Short Bowel Syndrome (SBS), Serostim® should be administered **at a dose of 0.1 mg/kg subcutaneously daily to a maximum of 8 mg daily."**

Age Groups: The proposed draft package insert does not mention the age of the target population for which the new indication is proposed, not even in the description of the clinical trial submitted in support of the indication being sought. However, in the already approved package insert (for the indication AIDS WASTING), mention is made of Pediatric use[4] and Geriatric use[5].
NOTE: The SBS patient population enrolled in the sponsor's clinical trial were between the ages of 20 and 75 years. Therefore, **the SBS indication would only be supported in adults**. The Agency cannot extrapolate findings to a pediatric population of SBS because there are no PK data in either adults or children with SBS. Although available evidence suggests that rh-GH clearances are similar in adults and children, no clinical studies were conducted in children with SBS.

B. State of Armamentarium for Indication(s)
There are no drugs approved for the treatment of SBS.

NOTE: As mentioned in the recent **AGA Technical Review on SBS and Intestinal Transplantation** [Gastroenterology 124: 1111-1134 (2003)] it is unclear how many individuals in the USA suffer from SBS. But based in the numbers in Europe, the incidence may be ca. 2 to 4 per million, if one considers the incidence of home TPN [SBS constituted the largest single group of patients who required home TPN (35%)]. With a few exceptions, in the literature, the number of patients per center of study (Table 2 of the current review) **varied between 8 and 14.**
By the above information and standards, **41 patients in sponsor's study IMP20317 is considered a relatively big trial.**

Pharmacologic and other non-specific management considerations are briefly summarized below. Two additional approaches to treatment are **surgical procedures and intestinal transplantation** but these approaches are beyond the scope of the present NDA review.

Because of the extensive length of the small intestine and its ability to compensate and functionally adapt after loss of a significant amount of surface area, patients

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[4] Pediatric use: In two small studies, 11 children with HIV-associated failure to thrive were treated subcutaneously with human growth hormone. In one study, five children (age range, 6 to 17 years) were treated with 0.04 mg/kg/day for 26 weeks. In a second study, six children (age range, 8 to 14 years) were treated with 0.07 mg/kg/day for 4 weeks. Treatment appeared to be well tolerated in both studies. These preliminary data collected on a limited number of patients with HIV-associated failure to thrive appear to be consistent with safety observations in growth hormone treated adults with AIDS wasting.

[5] Geriatric use: Clinical studies with Serostim® did not include sufficient number of subjects aged 65 and over to determine whether they respond differently from younger subjects. Elderly patients may be more sensitive to growth hormone action, and may be more prone to develop adverse reactions. Thus, dose selection for an elderly patient should be cautious, usually starting at the lower end of the dosing range.

generally demonstrate few symptoms after resection of up to 50% of the small bowel. However, more extensive reduction of this absorptive surface is associated with symptoms that can often be disabling, socially incapacitating, or even life-threatening. SBS occurs when there is <200 cm of bowel remaining.[6] Those patients at greatest nutritional risk generally have a duodenostomy or a jejunoileal anastomosis with <35 cm of residual small intestine, jejunocolic or ileocolic anastomosis with < 60 cm of residual small intestine, or an end jejunostomy with <115 cm of residual small intestine.[7]

Loss of intestinal function can be complete or partial. ***Intestinal Failure*** is defined as **"reduced gastrointestinal absorption to the extent that macronutrients and/or fluid supplements are required"**, a concept that includes the need for enteral or parenteral supplements to maintain a normal nutritional state.[8] **Intestinal failure** may be described as **acute (usually reversible)** and **chronic (when long-term treatment over weeks, months, or longer is required, especially if continued treatment is needed at home).** Patients who are unable to increase their oral intake sufficiently or are unable to absorb sufficient energy despite significantly increased intake, are defined as patients with intestinal failure and require parenteral nutrition support. A **standardized diet** may be useful for clinically defining functional SBS. For example, one recommendation is to maintain patients with SBS with residual colon on a **high-carbohydrate, low-fat diet.[9] But in reality there are insufficient data with regard to what the composition of the so called standardized diet optimally should be.**

Signs and symptoms of SBS include electrolyte disturbances; deficiencies of calcium, magnesium, zinc, iron, vitamin B_{12}, or fat-soluble vitamin deficiency; malabsorption of carbohydrates, lactose and protein; metabolic acidosis, gastric acid hypersecretion; formation of cholesterol biliary calculi and renal oxalate calculi; and dehydration, steatorrhea, diarrhea, and weight loss.

Non-specific approaches[10] include increasing the absorption of sodium by sipping a sodium-glucose solution, reducing stomal loss by restricting water or low-sodium drinks. If a stoma is situated less than 100 cm along the jejunum, a constant negative sodium balance may necessitate parenteral saline supplements. Gastric antisecretory drugs or a somatostatin analog (**off-label use**) reduce jejunostomy losses in such patients but do not restore a positive sodium balance.

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[6] This is an approximate length as most methods of residual intestine measurement (such as radiologic contrast studies, pathology of the resected specimen, and perioperative measurement of unweighted intestine) are not especially accurate. **Because absorption is related to the amount of residual intestine, it is more important to document the amount of remaining, viable intestine.**

[7] Buchman, A.L. et al. AGA Technical Review on Short bowel Syndrome and Intestinal Transplantation. Gastroenterology 124:1111-1134 (2003)

[8] Malabsorption of a single nutrient, such as vitamin B_{12} or the need for a special diet to exclude a damaging component such as gluten, is not included within this definition.

[9] **Such a diet results in greater caloric absorption than a high-fat, low-carbohydrate diet because malabsorbed carbohydrates are salvaged in the colon whereas malabsorbed fatty acids are not. In addition, fat restriction enhances mineral absorption and decreases oxalate hyperabsorption.**

[10] Lennard-Jones, J.E. Review article: practical management of the short bowel. Aliment. Pharmacol. Ther. 8:563-577 (1994).

Loperamide or codeine phosphate benefit some patients. Magnesium deficiency can usually be corrected by oral magnesium oxide supplements.
It is important to note that **thorough nutritional management is necessary** in the early stages, as is **replacement of excess fluid and electrolyte losses.**
Recommendations regarding the need for parenteral nutrition vary depending on the presence or absence of certain factors: the ileocecal valve, jejunum, and functional colon. **Patients with residual small bowel of 100 cm or less usually require the administration of parenteral nutrition at home.**
The other aspect of SBS management consists of enhancing the natural intestinal adaptation response. Although the mechanisms of intestinal adaptation are not entirely understood, they can be grouped into three broad categories: **luminal nutrition, hormonal factors, and pancreatobiliary secretion.** Animal models of SBS have suggested several gut hormones are involved in postresection intestinal adaptation. These include enteroglucagon, glucagon peptide II, epidermal growth factor, **growth hormone (the subject of the current review),** cholecystokinin, gastrin, insulin, and neurotensin.[11] Other therapies to enhance intestinal growth include fiber, **glutamine (one of the components of the combination being proposed by the sponsor)** and aminoguanidine. Although **none has been approved for the treatment of SBS,** some of the hormones, available in the clinic for other indications or available for human use experimentally, are used in the treatment of SBS. **There are, however, little data on the role of either endogenous or exogenous hormones on intestinal adaptation in humans.**
Similarly, there are very few studies using peptides to slow intestinal transit (e.g. peptide YY or an analogue).[12]

C. **Important Milestones in Product Development**

As mentioned above, Serostim® [somatropin (rDNA origin) for injection] is an approved drug. Important milestones in the development of the sponsor's growth hormone for the indication being sought (**treatment of short bowel syndrome**) from meetings between FDA and the sponsor, are briefly summarized in Table 1.

[11] Sham J. et al. **Epidermal growth factor** improves nutritional outcome in a rat model of short bowel. J. Pediatric Surg. 37:765-769 (2002)
[12] Litvak, D.A. et al. Characterization of two novel **proabsorptive peptide YY analogs,** BIM-43073D and BIM-43004C. Dig. Dis. Sci. 44: 643-648 (1999)

Table 1
Highlights of FDA-Sponsor Meeting minutes

October 19, 1994	• Sponsor was Cato Research • Pre-IND meeting to discuss research plans for the use of the proposed drug combination **[Glutamine (GLN) + Growth Hormone (GH)]** • **Pre-clinical data seemed to indicate that GH administration was associated with increase in gut weight and length, mucosal mass, and villus height and crypt depth as well as enhancement of ileal and jejunal absorption of water, sodium and amino acids.** • Results from a **non-randomized**, single center **(the same center apparently involved in the pivotal trial)** , investigator-sponsor IND in patients considered dependent on parenteral nutrition **(> 7 years)** were discussed. An initial group of 7 patients served as their own control; the experience was later expanded to 24 patients. **The indication studied was the reduction/elimination of TPN in patients with absorptive deficiencies, such was SBS.** These initial results showed **"substantial improvement in nutrient absorption"** (increase in protein absorption of up to 40%) and a decrease in fecal weight of up 33%. • **Dose of GH was between 0.07 and 0.14 mg/kg/day**. • **Dose of I.V. administered GLN was between 0.45 and 0.65 g/kg/day for 4 weeks.** • FDA suggested studying a different temporal sequence (i.e. administering GH alone, followed by glutamine therapy). It was also noted that if the oral supplementation in lieu of the I.V. GLN supplementation could be used, it would be simpler from a regulatory standpoint. • **Lack of randomization did not allow definitive conclusions about GH activity in this indication.**
August 3, 1995	• FDA (DMEDP) letter to sponsor providing comments on design of a clinical trial that would confirm findings and answer questions required for approval. **A 3-arm randomized double blind study with 5 patients receiving GH only, 5 receiving GLN only and 15 patients receiving the combination was recommended.**
June 15, 1997	• FDA (DMEDP) letter to sponsor stating that **the revised protocol "would suffice as a pivotal study for an NDA".** • The study revisions did not include the 3-arm design recommended by the Agency.
March 28, 2000	• The Sponsor (Serono Laboratories and Nutritional Restart Pharmaceutical) submitted a protocol amendment that changed the study design to single center.
June 7, 2000	• Letter from FDA (DMEDP) informing sponsor that **the single center study design is inadequate as the sole source of evidence to support a regulatory approval.**
August 22, 2000	• Meeting between FDA and sponsor. The agency stated that in summary, a single study, single-center for this application can be filed (unless there are other filing issues), **but the hurdles are high for approvability and the burden is on the sponsor to prove that a single-center study is adequate**. The Agency also added that there is no control group and results for a single-center study may not be representative of outcomes in other centers **due to differences in standards of care.** The DMEDP offered its assistance for development of additional protocols, proposals for bolstering enrollment, etc.

September 6, 2002	• Meeting between FDA and the sponsor to discuss results of **Protocol 20317** and the planned submission of a supplemental NDA for the addition of a short bowel syndrome indication to the Serostim® labeling [NOTE: The GI MTL was a consultant to DMEDP aqt this meeting]. • **Study 20317** was a 6-week, multicenter, double-blind, in-patient trial, followed by 12 weeks of outpatient observation in male and female patients aged 18 to 75 years who were wholly or partly dependent on TPN. Following a 2-week run-in phase, patients were randomized to the following 3 treatment groups and **studied for 4 weeks**: • - Group 1: specialized diet including (**active**) glutamine (SD/GLN, n= 9) - Group 2: (**active**) recombinant human growth hormone (**0.1 mg/kg/day**) with specialized diet **excluding glutamine** (SD/rh-GH, n= 18) - Group 3: rh-GH (**active**), at the same dose as that given to subjects **in Group 2 (0.1 mg/kg/d)** with specialized diet including glutamine (SD/GLN/rhGH, n= 18) - Thus **the specialized diet was common to the 3 treatment arms.** - The **primary endpoint of efficacy was the change in TPN volume, with change in TPN calories and TPN frequency as secondary endpoints.** The Agency asked for clarification as to why the endpoint of change in TPN volume was selected, since according to experts in this field, **change in nutritional status** is a more clinically meaningful endpoint. In response, the firm stated that **the nutritional status of the patients was collected and planned to present these data as part of the NDA submission.** Also of concern to the Agency was the **lack of a specialized diet alone arm.** Such an omission did not allow the contribution of the specialized diet to the efficacy to be assessed, particularly since all but 3 patients were enrolled in a single center. It was also noted that although the specialized diet was fixed with regard to relative composition of carbohydrates, fat, and protein, **the amount of food ingested by the patient could differ**. The sponsor was told that information on the amount of food consumed at the beginning and the end of the 4-week treatment is needed to rule out an imbalance between (among) the treatment arms. **NOTE:** It is worth noting that the sponsor has eventually submitted the information requested at this pre-NDA meeting.

D. Other Relevant Information

There are at least three issues that need to be addressed. **One** is the potential toxicity of growth hormone, especially when administered long-term. This is briefly addressed in Sections II and VII. D. of the current review. **The other** is the primary efficacy parameters that need to be used to demonstrate efficacy of pharmacological agents proposed for the treatment of SBS. These should be **clinically meaningful *nutrition* endpoints** and are addressed in section V.B. of the current review. **The third** is the ***replicability/generalizability*** of efficacy findings; this issue is addressed in Section X. of the current review. **The fourth** is the **role of glutamine and the "specialized diet"** as components of the proposed combination. This issue is addressed in Section X. of the current review.

E. Important Issues with Pharmacologically Related Agents

It is worth noting that there are no overt safety issues related to the class. However, one cannot conclude that "there are no important issues". Indeed, as discussed under Safety, the possible long-term toxicity of rh-GH needs to be addressed. **There is simply no information about possible carcinogenic effects**

(in humans). The long-term safety profile of rh-GH in SBS patients, especially Serious Adverse Events is, for all practical purposes, unknown. Some important issues with pharmacologically-related agents (**as previously stated, none has been approved for the sought indication**) are presented below.

- Although an exhaustive review of this issue is beyond the scope of the present review it is worth recapitulating that pharmacologically-related agents include hormones and growth factors. The hormones could be growth-promoting and include substances such as **GLP-2, neurotensin, gastrin and other GHs.** The hormones could also be motility-reducing, such as PYY. The list of **growth factors** is ever growing, but includes substances such as **EGF/TGF-α, trefoil peptides and KGF.** Brief comments on **GLP-2** are offered at the end of this subsection.
- Infusion experiments with neurotensin in rats suggest a potential trophic effect on the small intestine but not the colon.[13]
- The physiological role of **gastrin** in human gut adaptation is still unclear but must be considered as **hypergastrinemia has been described after a major intestinal resection.** The gastric hyperplasia, which is associated with acid-induced inhibition, is mediated via gastrin but it is debatable whether this induces to malignancy. It has been suggested that it may not be gastrin itself but its intermediaries, such as **glycine-extended gastrin**, that are trophic.[14]
- At physiological doses in man, **peptide YY**[15] increases small bowel transit time and reduces stimulated intestinal secretion. Peptide YY serum levels are high in patients with a retained colon and low in patients with a jejunostomy, thus it may be responsible for part of the functional adaptation that occurs in patients with a retained colon. **According to up-to-date information, peptide YY is unlikely to be responsible for any structural changes, as it does not induce gut growth in rats fed only with parenteral nutrition.**
- **Growth factors and cytokines** are extracellular signaling proteins or peptides, the cytokines being generally considered as local mediators in cell-to-cell communication while the growth factors were originally defined on the basis of their stimulation of growth or cell division. **EGF** acts on multiple organs by several multiple actions, including influencing gastric acid secretion, gut growth and repair.
- The **mucosal integrity peptides** include **TGF-α and pancreatic secretory trypsin inhibitor**, which are constitutively expressed in the mucosa throughout the gastrointestinal tract and function to maintain normal mucosal integrity. The major distribution of TGF-α is in the superficial (non-

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[13] Wood, J.G. et al. Neurotensin stimulates growth of small intestine in rats. Am J Physiol , 255: G813-G817 (1988)

[14] Mice that overexpress glycine-extended glycine show a large increase in colonic mucosa thickness and colonic proliferation [Koch, T.J. Overexpression of glycine-extended gastrin in transgenic mice results in increased colonic proliferation. J Clin Invest 103:1119-1126 (1999)]

[15] **Peptide YY, like GLP-2, is produced by the L cells of the ileum and colon**; it slows gastric emptying and small bowel transit and may be responsible for the "ileal" and "colonic" brakes [Nightingale, JMD et al. Disturbed gastric emptying in the short bowel syndrome. Evidence for a "colonic brake" Gut 34: 1171-1176 (1993)]

proliferative) zones. It may therefore be that its major role is to **maintain cell migration and differentiation as opposed to proliferation.**[16]

- The **rapid-response peptides** are the trefoil peptide family (e.g. **spasmolytic polypeptide**); their production is rapidly unregulated at sites of damage and is likely to be of **particular importance in the early stages of mucosal repair. KGF, originally known as FGF-7**, has been demonstrated to markedly stimulate proliferation of hepatocytes and epithelial cells throughout the rat gastrointestinal tract, and can alter crypt branching. Moreover, KGF, like EGF, also stimulates mucus production, but unlike EGF does not stimulate cell migration and is not cytoprotective.[17]

GLP-2 as therapy for the short bowel syndrome

Recently, Jeppesen and his co-workers[18] presented results of a pilot study using GLP-2 in 8 patients with functional short bowel syndrome. **After an initial, extensive balance study**, GLP-2 was administered for 35 days by a twice-daily subcutaneous injection. **Balance studies** in these patients were then repeated and GLP-2 was found to have resulted in **significantly greater intestinal absorption of energy, water, and nitrogen.** Patients also demonstrated increases in lean body mass, body weight, and reduced gastric emptying. The authors concluded that **GLP-2 improves intestinal absorption and nutrition status in short bowel patients with impaired postprandial GLP-2 secretion in which the terminal ileum and colon have been removed.** The opportunities and constraints offered by the results of this study were recently discussed.[19] It was concluded that the results of this pilot trial were modest. GLP-2 would not be considered cost-effective. As Jeppesen et al. note, **a much greater beneficial effect of GLP-2 might be realized using a more optimal dose and duration of therapy.**

II. Clinically Relevant Findings from Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

- **There are no CMC issues.** As mentioned in the Chemistry Review by Dr. Maria E. Ysern, somatropin (rDNA origin) for injection is an approved drug, under NDA 20-604 for treatment of AIDS wasting or cachexia. It is further noted that the sponsor's claim for categorical exclusion for the preparation and submission of an Environmental Assessment is adequate. This is because the approval of the current

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[16] **TGF-α "knock-out" mice** have an increased susceptibility to injurious agents to the colon [Egger, B. et al. Mice lacking transforming growth factor α have an increased susceptibility to dextran sulfate-induced colitis. Gastroenterology 113: 825-832 (1997)] but they do not have an increased susceptibility to indomethacin-induced small intestinal injury [Macdonald, C.E. et al Transforming growth factor α knockout mice have smaller small intestines, larger large intestines, but no increased sensitivity to NSAID-induced small intestinal injury. Gut 42 (suppl. 1): A3 (1998)]

[17] Playford, R.J. et al. Effects of **keratinocyte growth factor (KGF)** on gut growth and repair. J. Pathol. 184: 316-322 (1998)

[18] Jeppesen, P. B. et al **Glucagon-like Peptide 2** improves Nutrient Absorption and Nutritional Status in Short-Bowel Patients With No Colon. Gastroenterology 120: 806-815 (2001)

[19] Warner, B. W. Editorial: **GLP-2 as therapy for the short bowel syndrome.** Gastroenterology 120:1041-1048 (2001)

application, for a new indication (short bowel syndrome, NDA 21-597) will not increase the use of the active moiety, somatropin.

- **There will not be a Pharmacology/Toxicology review for the current application.** Pharmacology and Toxicology data were reviewed By Dr. David H. Hertig, a Pharmacologist from HFD-510 (review dated February 13, 1996). The reviewer noted that a battery of in vitro and in vivo tests had been carried out with rh-GH. These tests included acute toxicity studies in mice, rats, and monkeys; subchronic/chronic toxicity s.c. studies for 4, 13, and 52 weeks in rats and s.c. studies for 4, 13, and 52 weeks in monkeys; Segment I, II, and III rat and Segment II rabbit reproductive tests; mutagenicity and special toxicity tests including irritation, sensitization, and antigenicity. In general, rh-GH [m] was well tolerated in acute and subchronic and chronic toxicity studies with **findings being mainly extensions of the pharmacological properties of growth hormone.** From the standpoint of Pharmacology, the application under NDA 21-597 is **approvable** [Dr. Jasti Choudary, Pharmacologist Team Leader]. It is worth noting that **carcinogenicity studies have not been done with the drug. This is because of the expected immune response from the animals.**

- It has been shown that increased polyamine synthesis results in intestinal growth and maturation and that luminal nutrients promote the synthesis and release of certain peptides that stimulate ODC activity, resulting in intestinal growth. **In rodent models, both GH and IGF-1 have been shown to increase small bowel growth after resection.[20] GH mediates its trophic effects primarily through IGF-1.** IGF-1, but not GH, has also been reported to increase mucosal DNA and protein levels in the jejunal mucosa of rats to reverse TPN-induced mucosal atrophy.[21] **The combination of IGF-1 and glutamine was also shown in two studies in rats to synergistically increase plasma IGF-1 levels, intestinal DNA, and villus growth of the resected small bowel.[22]** But other rodent studies do not support this observation.[23] An additional important observation is that GH-infused, TPN-fed rats have reduced responsiveness to endogenous IGF-1 over time. [24] These observations, and some findings in humans, question the sustained effects of GH (see clinical section).

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[20] Lund PK. Molecular basis of intestinal adaptation: the role of the **insulin-like growth factor system**. Ann NY Acad Sci 859: 18-36 (1998)

[21] Peterson, et al. GH elevates serum IGF-1 levels but does not alter mucosal atrophy in parenterally fed rats. Am J Physiol 272: G1100-G1108 (1997)

[22] Gu Y et al. Effects of **growth hormone and glutamine supplemented parenteral nutrition** on intestinal adaptation in short bowel rats. Clin Nutr 20: 159-166 (2001)

[23] Vanderhoof JA, et al. **Growth hormone and glutamine** do not stimulate intestinal adaptation following massive small bowel resection in the rat. J Pediatr Gastroenterol Nutr 25: 327-331 (1997)

[24] Lund PK et al (locus cited) (1998)--

- A study by Snibson et al.[25] showed that overall, GH synergistically promotes carcinogen-induced hepatocarcinogenesis in both sexes of GH-transgenic mice by stimulating tumor cell proliferation.

- In reality, the role of growth hormone in carcinogenesis is unclear, but **it raises serum concentrations of insulin-like growth factor (IGF)-1, which is mitogenic** and **antiapoptotic**, and results from in-vitro and animal studies suggest that GH may raise the risk of hyperplasia and malignancy.[26]

- A very recent study in rats suggests that the combination of glutamine and GH may synergistically reduce bacterial translocation over time in sepsis.[27]

III. Human Pharmacokinetics and Pharmacodynamics

There will not be a separate Biopharm review because the sponsor has not submitted/presented a separate Biopharmaceutics section for review. The material that follows on Serostim® (rDNA human growth hormone for injection; rh-GH) was provided by Dr. Suliman Al-Fayoumi, an FDA reviewer in the Biopharmaceutics Division.

- The absolute bioavailability of rh-GH following s.c. administration was 70 to 90%.
- Apparent half-life of rh-GH after s.c. administration was significantly prolonged (3.94 ± 3.44 h) relative to that obtained after i.v. administration (0.58 ± 0.08 h), which indicates that **s.c. absorption is slow and rate-limiting.**
- No accumulation was observed following multiple dose administration of doses of 6 mg/d for 6 weeks. However, the **pharmacological markers** determined in the study (**IGF-1 and IGFBP-3**) were significantly higher at 6 weeks relative to the first dose.
- The steady state volume of distribution of rh-GH in healthy subjects is 12.0 ± 1.08 L.
- The liver plays an important role in the elimination of rh-GH. Nevertheless, rh-GH is primarily eliminated via kidneys where it undergoes glomerular filtration then it is cleaved within the renal cells and the peptides and amino acids are subsequently reabsorbed into the systemic circulation.
- Published reports indicate that patients with chronic renal impairment tend to have decreased rh-GH clearance relative to normal healthy subjects. Similarly, patients with severe hepatic impairment have been reported to exhibit reduced rh-GH clearance.
- Available evidence suggests that rh-GH clearance is similar between adults and children. However, only a limited number of pediatric patients were included in the sponsor's clinical trials submitted in NDA 21-597.

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[25] Snibson KJ et al. Overexpressed growth hormone (GH) synergistically promotes carcinogen-initiated liver tumour growth by promoting cellular proliferation in emerging hepatocellular neoplasms in female and male GH-transgenic mice. Liver 21(2): 149-158 (2001)

[26] [Ogilvy-Stuart AL. Safety of growth hormone after treatment of a childhood malignancy. Horm Res 44 (Suppl 3): 73-79 (1995); Ng ST et al. Growth hormone treatment induces primary gland hyperplasia in aging primates. Nat Med 3: 1141-1144 (1997)]

[27] Jung Sung-Eun, et al. Combined Administration of Glutamine and growth Hormone Synergistically Reduces Bacterial Translocation in Sepsis. J Korean Med sci 18: 17-22 (2003)

- Both, the labeling for Saizen® [somatropin (rDNA for injection)] and that for Serostim® [somatropin (rDNA origin) for injection] state that elderly patients are more sensitive to growth hormone action, and may be more prone to develop adverse reactions. Thus, dose selection for an elderly patient should be cautious, **usually starting at the low end of the dosing range.**
- Formal in vitro and in vivo drug-drug interaction studies have not been conducted to evaluate the drug-drug interaction potential for rh-GH. Recent published results suggest that rh-GH induces UDPGT and CYP3A enzyme systems.
- As previously mentioned, **GH mediates its trophic effects primarily through insulin-like growth factor-1 (IGF-1).** In rodent models, GH and IGF-1 have been shown to increase small bowel growth after resection. **IGF-1 and its receptors are expressed locally through the human and rodent small bowel. Endogenous GH administration increases serum IGF-1 levels as well as IGF-1 levels in the small intestine.**

IV. Description of Clinical Data and Sources

A. Overall Data

The present submission for Serostim® for the indication treatment of short bowel syndrome (Orphan Drug Designation 94-803), is being reviewed under NDA 21-597. The drug, somatropin (rDNA origin) for injection, is already approved for the indication treatment of AIDS wasting (NDA 20-604). The current submission consists of a summary, revised package insert (Attachment 1), minutes to FDA meetings (Attachment 2), patents information, debarment certification, user fee documents, and statement on environmental assessment. **In support of their application, the sponsor submitted results from one pivotal trial (Study IMP20317).** The Clinical Study Report includes information on ethics, investigators and study administrative structure, study objectives, details of results of investigational plan (study protocol), efficacy evaluation, safety evaluation, with discussion and overall conclusions, a list of references and appendices.

B. Tables Listing the Clinical Trials

In this instance, there is no need for a Table listing the clinical trials. The core of the submission consists of a clinical and statistical study report from Protocol IMP20317: **"Randomized, double-blind, controlled, parallel-group evaluation of the relative efficacy and safety of recombinant human growth hormone and glutamine, single and as a co-therapy, in the improvement of residual gut absorptive function in patients with short bowel syndrome."**
The trial enrolled 47 patients. Of these, 6 were discontinued [intercurrent illness, n=5; withdrew consent, n=1]. A total of **41 patients** was randomized into 3 groups [Group A, n=16; Group B, n=16; Group C, n=9; see below for identity of these 3 groups]. The trial was conducted at two clinical sites, **Site 1** [n= 38 patients] at the Brigham and Women's Hospital, Boston MA and **Site 2** [n= 3 patients], at the University of Nebraska, Omaha, NE.

C. **Post-marketing Experience**

There is no marketing experience with rh-GH for short bowel syndrome because the sponsor is seeking a new indication for this drug in the United States. Also, **the indication is not approved outside of the United States.**

However, the sponsor's Serostim® was approved in ***1996*** for the **treatment of AIDS wasting or cachexia.**[28] Under the Adverse Reactions Section, the currently approved package insert includes information stating that, **in placebo-controlled clinical trials, the most common adverse reactions judged to be associated with Serostim® were musculoskeletal discomfort and increased tissue turgor (swelling, particularly of the hands and feet).** These symptoms were generally rated by investigators as mild to moderate in severity and **usually subsided with continued treatment.** Discontinuations as a result of these events were rare. After a description of adverse events by body system, the following paragraph is included in the package insert. The types and incidences of adverse events reported in an open-label, extension trial in a single, foreign trial, for up to one year, were not different from, or greater in frequency, than those observed in the primary, placebo-controlled, clinical trials.

Finally, the following pertinent information is included in the currently approved package insert. **"During post-marketing surveillance, cases of new onset glucose intolerance, diabetes mellitus and exacerbations of pre-existing diabetes mellitus have been reported in patients receiving Serostim®.** Some patients developed diabetic ketoacidosis and diabetic coma. In some patients, these conditions improved when Serostim® was discontinued while in others, the glucose intolerance persisted. **Some patients necessitated initiation or adjustment of antidiabetic treatment while on Serostim®."**

According to the sponsor, the adverse event profile seen in the Short Bowel Syndrome patient population is similar to that described above.

NOTE: A consult has been sent to ODS to confirm the post-marketing safety profile of the drug. Addressed in this consult will be issues such as off-label use in general and AEs related to the use of the drug in SBS as an off-label indication.

D. **Literature Review**

Literature publications used during the review included papers on the effect of growth hormone, other hormones, or peptides in animal models of short bowel syndrome, studies in humans and reviews. Among the latter, a very recent

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[28] Under Dosage and Administration, the currently approved Package Insert indicates that Serostim® [somatropin (rDNA origin) for injection] should be administered to AIDS wasting patients subcutaneously daily at bedtime according to the following dosage recommendations : (information simplified by reviewer)

Weight Range (Kg)	SC Daily Dose (mg)
> 55	6
45-55	5
35-45	4

publication in Gastroenterology (**AGA Technical review on Short bowel Syndrome** and Intestinal transplantation)[29] and a book on **Intestinal Failure**[30] were particularly useful.

In addition, because of some inconsistent reports in the literature on the role of growth hormone in the treatment of short bowel syndrome, the sponsor was asked to identify which of the published trials have used the Serono formulation of rh-GH. A succinct account of the sponsor's May 2, 2003 to the Agency, is given below.

- Publications on the potential specific effects of somatropin on the remnant bowel were provided in sponsor' s Attachment 1. Several scientific publications suggest that **GH can exert an enterotrophic effect on the gut mucosa, an effect that may occur mainly by improving the life span of mature enterocytes and subsequently to improve the function of these enterocytes to digest nutrients, an effect that seems to be GH specific.**
- According to the sponsor, the entire list of 9 publications referenced in the May 2, 2003 submission, with the exception of the article and editorial by J. Scolapio (Ref. 6 in Table 2 of the current review) and the article by J. Szkudlarek et al.[31] is supportive of their application (the use of growth hormone for the treatment of short bowel syndrome).
  Since Serono was not the sponsor of any of the reported studies, **Serono does not have the source documents for these publications.**

- The sponsor noted that there has been one oral presentation of the data from the Clinical Trial submitted in NDA 21-597 at the American Society of Parenteral and Enteral Nutrition (ASPEN) meeting in San Antonio TX, on January 21, 2003. The data were presented by Theresa A. Byrne, DSc, one of the co-investigators in the NDA clinical trial.

V. Clinical Review Methods

A. How the Review was Conducted

Based on what the sponsor has requested in the proposed labeling, this reviewer updated his information on the subject of short bowel syndrome. As he has been consultant to HFD-510 (DMEDP) and has participated in pre-NDA-related matters, he is already familiar with some of the issues discussed at the IND level. The reviewer then examined and listed all the evidence presented by the sponsor in support of their request. The materials reviewed included all 8 volumes that constitute the submission, with emphasis on the Clinical Study Report that is the pivotal support of the application. Also considered were available reviews and results of interactions with all other pertinent disciplines (chemistry,

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[29] Buchman AL, et al. [locus cited, under Footnote 7] (2003)

[30] Nightingale, JMD, Editor. Intestinal Failure, GMM, San Francisco, CA (2001)

[31] Szkudlarek, J. et al. Effect of **high dose growth hormone with glutamine and no change in diet** on intestinal absorption in short bowel patients: a randomized, double-blind, crossover, placebo-controlled study. Gut 47: 199-205 (2000).

pharmacology/toxicology, biopharmaceutics, and endocrinology). These interactions were aimed at identifying issues, if they existed, already recognized by this multidisciplinary approach.

The review begins with a title page, identifying the sponsor, the drug product, and dates of submission. This information is followed by a concise Executive Summary, listing the main recommendations for regulatory action and the main issues identified in the review. The main objective of this part of the review is to provide the reader with a concise preliminary picture of the study purpose, execution, emerging issues identified (or re-identified), major findings and conclusions and efficacy and safety evaluations that led to the reviewer's recommendations for regulatory action. The organization of the review and a road map to its sections are found in a detailed Table of Contents. These sections correspond in general with the **"Guideline for the Format and Content of the Clinical and Statistical Sections of an Application" (CDER, FDA, July 1988).** Throughout the review, the reviewer's abstracting, paraphrasing or summarization of the material submitted by the sponsor as well reviewer-generated opinions and discussions are identified and these are to be differentiated from text taken directly from that submitted by the sponsor (usually shown in quotes) or from publications.

B. Overview of Materials Consulted in Review

As stated above, information from other disciplines was consulted in review. But the most important contribution came from publications related to the efficacy of growth hormone in the proposed indication, **treatment of short bowel syndrome.** Because **literature data are inconsistent** and because there is need to determine if the efficacy endpoints used in the clinical trials submitted by the sponsor in support of their application are adequate (clinically meaningful), the pertinent literature information is summarized in Table 2. The emphasis is on **clinically meaningful** ***nutrition endpoints,*** considered by the experts as the most important. It is to be noted that although glutamine is one of the components of the proposed triple co-therapy, **evaluations of the effect of glutamine alone are not the subject of the current submission or review.** Therefore, information on the effects of glutamine alone are not included in Table 2 and will be briefly discussed later on in the review.

The conclusions from the publications included in Table 2 arrived at by the authors of those publications are summarized next.

Ref. 1.: GH administration accelerated protein gain and in stable adults patients receiving aggressive nutritional therapy without a significant increase in body fat or a disproportionate expansion of ECW. GH therapy accelerated nutrition repletion and, may shorten the convalescence of the malnourished patient requiring a major surgical procedure.

Ref. 2.: The ability of GH to enhance amino-acid uptake from the gut lumen provides energy and precursors for protein synthesis in the gut mucosa, as well as additional substrate for anabolism in other organs.

Ref. 3: **GH + GLN + DIET** offers a potential method for providing cost-effective rehabilitation of surgical patients who have the short bowel syndrome or other complex problem of the gastrointestinal tract. This therapeutic combination

also may be useful to enhance bowel function in patients with other gastrointestinal diseases and those requiring extensive intestinal operations, including transplantation.

Ref. 4: **The combined administration of GH, GLN, and a modified diet enhanced nutrient absorption from the remnant bowel after massive intestinal resection.** These changes occurred in a group of patients that previously failed to adapt to the provision of enteral nutrients. According to the authors, this therapy may offer an alternative to L-T dependence on TPN for patients with severe SBS.

Ref. 5: **8 weeks of low-dose rhGH treatment leads to increases in body weight, lean body mass, and fat-free mass in patients with SBS, correlated to increases in IGF-1 levels** [**NOTE:** this publication was also the subject of an editorial " Can the Intestine Adapt to a Changing Environment? By J. S. Thompson. Gastroenterology 113:1402-1405 (1997)].

Ref. 6: Although treatment with GH, GLN, and HCLF (high CHO-low fat) diet for 3 weeks resulted in modest improvements in electrolyte absorption and delayed gastric emptying, **there were no improvements in small bowel morphology, stool losses, or macronutrient absorption.**

Ref. 7: **Combined high-dose GH and GLN administered for 4 weeks, did not improve absorption of fatty acids or EFA status in SBS patients. No changes in body weight or composition were seen when comparing treatment to placebo periods. The increase in LBM measured by DEXA scan, comparing treatment and baseline periods, was not accompanied by an increase in the 24-h urinary creatinine excretion and suspected to be associated with an accumulation of extracellular fluids.**

Ref. 8: Although larger prospective, randomized, double-blind, controlled studies are underway to differentiate the effects of the components of this therapeutic approach, this study recognizes the **heterogeneity of this patient population** and help to identify patients most likely to respond to the described regimen. The regimen consisted of medications, a specific diet with supplements, and a behavior modification program. It is worth reiterating that the medications dosages included standard antidiarrheal and antacid agents, prescribed at recommended. **In addition, the patients received GH** [**Serono Laboratories**, Norwell, MA and Eli Lilly, Indianapolis, IND, USA] **at an average dose of 0.09 mg/kg/d**. GH was discontinued upon discharge from the inpatient facility. All patients consumed a specific oral diet, with the percent CHO, fat, and protein and the type of fluids dependent upon the presence or absence of colon. While within the guidelines of the specific diet prescriptions, given foods were often adjusted based upon patient specific sensitivities, determined from the 24-h intake and output records, most likely to respond to the described noninvasive regimen. The authors of this publication note that **while the majority of the patients responded to the intervention with a significant reduction or the elimination of PN, others, despite aggressive intervention and monitoring, experienced minimal to no change in PN requirements. These patients should be considered for either intestinal transplantation or other therapeutic approaches.**

Ref. 9: 3 weeks of low-dose (**subcutaneously administered 0.05 mg/kg/d**) GH significantly improved intestinal absorption in Home Parenteral Nutrition (HPN)-dependent SBS patients who were on a hyperphagic western diet [**NOTE:** This publication also was the subject of the Editorial **"Tales From the Crypt"** by J. S. Scolapio. Gastroenterology124: 561-564 (2003)].

C. Overview of Methods Used to Evaluate Data Quality and Integrity

As part of the NDA submission, the sponsor presented documentation of the data processing section of the study workbook which contained the following sections: Protocol, CRF (a clean and an annotated copy). Panel Schemas, Form Schemas, Page Layouts, Validation Specifications (including Rules, Derivations and Final Validation Report), Data Entry Guide, General Assumptions, Data processing Notes, Correspondence, Audits and Quality Control. All data were subjected to electronic validation programs. A Clintrial™ DBA Report was generated to confirm that all records from all panels had been merged from the Update Table into the Data Table. **Trials were conducted in accordance with accepted ethical standards.**

- The sponsor explains that the follow-up data for 3 patients' database were completed and locked on 22 JULY 2002 and were selected for a 100% audit of all data points.
- All variables for these 3 subjects were visually checked for agreement with the final CRFs by two-person-teams according to standard operating procedures. With a general audit result of 0.0, the data passed the criteria of Cato Research Ltd. QC review for release (<1:2,500).
- The database was unlocked on 23 JULY, 2002 to correct and verify 2 outstanding queries entered into the comments log that were found at the time of the database lock; the database was re-locked on the same day.
- During a statistical review, it was found that there was a page that was not entered. The sponsor decided to enter the omitted page post lock. The database was unlocked again on 08 August 2002, to enter, verify, validate and merge the page that had not been entered, then re-locked on the same day.
- According to the sponsor, no other trends or other questionable issues are known to be outstanding that would affect the planned quality for the clinical trial.

Table 2

Overview of Study Endpoints Used to Evaluate the Effect of GH in the treatment of SBS

Study No.	Study Population	Main Features/ Dose of GH	Efficacy Endpoints	Summary of Results Comments
1.	Stable, nutritionally compromised postoperative patients receiving standard nutritional support (hypercaloric diet) for **severe gastrointestinal dysfunction** **SND = Specialized Nutrition Diet**	Comparative, open-label **n = 14** The SND provided ca. 50 kcal/kg/d during an initial 7-day equilibrium period. 4 patients then continued on SND; 10 received, in addition, **GH 0.14 mg/kg/d [recombinant methionyl-GH (Protropin, Genentech, South San Francisco, CA)]**	Evaluated on Day 7 of the equilibrium period and again 3 weeks after treatment • **Components of Body Weight, which included body fat, mineral content, lean (nonfat and non-mineral-containing tissue) mass, total body water, extracellular water (ECW), and body protein.** • **Daily and cumulative nutrient balance and substrate oxidation studies determined the distribution, efficiency, and utilization of calories for protein, fat, and carbohydrate deposition.**	• The GH-treated patients **gained minimal BF** but had significantly more LBM (4.311 +/- 0.6 kg vs 1.988 +/- 0.2 kg, p< or = 0.03) and more protein (1.417 +/- 0.3 kg vs. 0.086 +/- kg, p< or = 0.03) than did the SND-treated patients. • **The increase in lean mass was not associated with an inappropriate expansion of ECW.** In contrast, patients receiving SND tended to deposit a greater proportion of body weight as ECW and significantly more fat than did GH-treated patients (1.004 +/- 0.3 kg vs. 0.129 +/- 0.2 kg, p<0.05). • **GH administration altered substrate oxidation** (respiratory quotient = 0.94 +/- 0.02 GH vs. 1.17 +/- 0.05 SND, p< or 0.0002) and the use of available energy, resulting in a 66% increase in the efficacy of protein deposition (13.37 +/- 0.8 g/1000 kcal vs. 8.04 g +/- 3.06 g/1000 kcal, p< or = 0.04).
Byrne TA et al. Anabolic therapy with growth hormone accelerates protein gain in surgical patients requiring nutritional rehabilitation . Ann Surg 218(4):400-416 (1993)				
2.	Adult healthy patients admitted to the VAH in Gainesville, Florida for abdominal operations such as Roux-en-Y diversion (harvested jejunum), right hemicolectomy for cecal or ascending colon lesions (harvested ileum) . Control jejunum was obtained from patients in whom normal jejunum was resected en block with other tissues.	Randomized, open-label **n = 12** • For 3 days before surgery: **a)** daily subcutaneous dose of **low-dose hormone (0.1 mg/kg)** **b)** **high dose GH (0.2 mg/kg)** **Human methionyl recombinant GH [Genentech, Inc. (San Francisco, CA, USA)]** c) No Tx (control) for 3 days before surgery. All patients were consuming a **regular diet** and received nothing by mouth for 24h before operation	• Brush border membrane vesicles (BBMVs) prepared by differential centrifugation. • Carrier-mediated transport of specific amino acids measured by rapid mixing/filtration technique • Influence of carrier-mediated transport of glutamine, leucine, alanine, arginine, methyl α-aminoisobutyric acid and glucose by BBMVs as measured by a rapid mixing/filtration technique.	• Treatment with **low-dose GH** resulted in a statistically ***insignificant*** increase in amino-acid transport rates in jejunal and ileal BBMVs. • **High-dose GH** resulted in a generalized **20% -to-70% stimulation of amino-acid transport** , whereas glucose transport was not affected.. • **The effects of GH were similar in ileum and jejunum.** • Kinetic analysis of the transport of **glutamine (the most abundant a-a in the body and the principal gut fuel)** and the essential a-a leucine revealed that the increase in transport was caused by a 50% increase in carrier V_{max} **consistent with an increase in the number of functional carriers in the brush border membrane.** • Pooled analysis of transport velocities demonstrated that the **total rate of a-a uptake from the gut lumen was increased significantly by 35% in GH-treated patients.**

Inoue Y. et al. Growth Hormone Enhances Amino Acid Uptake by the Human Small Intestine Ann Surg 219(6): 715-724 (1994)				
3.	Patients who had **previously undergone extensive bowel resection** for trauma, mesenteric infarction, or inflammatory bowel disease with or without colonic resection. All patients were **chronically dependent on specialized nutritional support.** All patients were able to tolerate *ad libitum* oral diet, **but without parenteral support they were unable to adequately maintain hydration and/or nutritional status.**	Initially, 17 studies were performed in **15 TPN-dependent short bowel patients** over 3 to 4 weeks in the clinical research center; the first week served as a control period, and during the next 1 to 3 weeks, the specific treatment was administered and evaluated. Throughout the study, food of known composition was provided. The treatment was expanded to **47 adults** (25 men, 22 women) with short bowel syndrome, depending on TPN for 6 (+- 1) years. After 28 days of therapy, the patients were discharged on only GLN **GH: 0.14 mg/kg/d [recombinant methionyl GH, Protopin, Genentech, Inc., San Francisco,CA]** **GLN : supplemental parenteral and /or enteral L-GLN (given at an average dose of 0.6 g/kg/d; Ajinomoto USA, Raleigh, NC)** + DIET.	• The aim of the study was to initially determine if GH or nutrients, given alone or together, **could enhance absorption from the remnant small bowel** after massive intestinal resection. • **Throughout the study all stool was collected and analyzed to determine absorption across the remaining bowel.** • **The effect of a high-carbohydrate, low-fat diet (DIET), the amino acid glutamine (GLN) and GH administered alone or in combination with the other therapies (GH + GLN + DIET) was evaluated.**	• The initial **balance studies** indicated improvement in absorption of protein by 39% and a 33% decrease in stool output with the GH+GLN+DIET. In the L-T study, **40% of the group remain off TPN** and **an additional 40% have reduced their TPN requirements,** with follow up averaging a year and the longest being over 5 years. • The authors speculate that this therapeutic combination (GH + GLN + DIET) **may be useful to enhance bowel function** in patients with other gastrointestinal diseases and those requiring extensive intestinal operations, including transplantation.
Byrne, TA. A New treatment for Patients with Short -Bowel Syndrome: Growth Hormone, Glutamine, and a Modified Diet. Ann Surg 222 (3): 243-255 (1995)				

4.	**10 patients (5 females, 5 males)** with severe SBS who had undergone extensive small bowel resection with or without colonic resection, who were ambulatory and clinically stable. Other characteristics of the study population were as described above.	Patients were admitted to the Clinical Research Center for a 28-day period. The first week served as a control period when nutritional (enteral and parenteral) and medical management simulated usual home therapy. Thereafter, 8 pts. received exogenous GH, supplemental GLN, and a modified high-CHO, high-fiber diet.; 2 pts. were treated with the modified diet alone. The GH was a **recombinant methionyl-GH [Protoprin, Genentech Inc.) at a dose 0.14 mg/kg/d.]** GLN was administered at an average parenteral dose of 0.42g/kg/d or given as L-glu powder, at the enteral dose of 0.63 g/kg/d.	**The efficiency of net nutrient absorption (percent absorbed)** for total calories, protein, fat, CHO, water, and sodium was calculated from the measured nutrient intake and stool losses.	• **Treatment with diet alone did not influence nutrient absorption or stool output.** • 3 weeks Tx with GH, GLN, and a modified diet **increased total caloric absorption** from 60.1% to 74.3 % (p< or = 0.003), **protein absorption** from 48.8 to 63.0% (p< or = 0.006), **and CHO absorption** from 60.0 to 81.5 % (p < or = 0.02). • **Fat absorption did not change** (61.0 to 60.3%) • **There was also a significant increase of water and sodium absorption.** • **The above-described absorptive changes resulted in a decrease in stool output (1,783 g/d control period vs. 1,308 g/d third week of treatment, p< or = 0.05)**
Byrne, TA, et al. Growth Hormone, Glutamine, and a Modified Diet) Enhance Nutrient Absorption in Patients With Severe Short -Bowel Syndrome. J Par Ent Nutr 19 (4): 296-302 (1995)				
5.	**10 patients (3F, 7M)** with SBS for more than 1 year because of Crohn's disease. Some pts. had some blood biochemistry abnormalities. All had normal fasting serum glucose concentrations. All exhibited normal 24-h GH profiles, with maximum peak values of > 5 milliunits/L. Daily fecal/stomal outputs	This was a placebo-controlled, randomized, double blind, crossover clinical trial. **10 pts.** were treated with daily subcutaneous doses of **rhGH/placebo (0.5 international units /kg^{-1} per week^{-1} = 0.024 mg/kg^{-1} per day^{-1} Source of GH: Genotropin Kabi Pharmacia, Stockholm, Sweden)** The low-dose rhGH/placebo was administered daily.	**Absorptive capacity and biochemical parameters** were investigated in a metabolic ward before treatment and during first and last week of treatment. Body composition was determined by DEXA-Scan (Lunar DPX, Scanexport Medical, Helsingborg, Sweden), impedance analysis, and whole body potassium counting.	• This **well-designed and apparently well- executed study** is of interest. The authors set to investigate the effects of low dose rhGH (from a source different from that from the sponsor of the present NDA) on **body composition and absorptive capacity in patients with SBS from Crohn's disease.** • Low-dose rh-GH **doubled serum concentrations of IGF-1** and increased body weight, lean body mass, and total body potassium by 5%. • **Fat-free mass and total body water increased by 6% (p = 0.008).** • **Increased in IGF-1 levels correlated with increase in fat-free mass** (r = 0.77, p< 0.02). • **No significant changes in absorptive capacity of water, energy, or protein were detected.**

	were 2.9 kg (range, 0.9 to 5.8 kg). All required oral or parenteral fluid substitution in combination with electrolytes, vitamins, and minerals.	subcutaneously during 8 weeks, separated by a washout period of at least 12 weeks.		
Ellegard, L. Low-Dose Recombinant Human Growth Hormone Increases Body Weight and Lean Body Mass in Patients with Short Bowel Syndrome. Ann Surg 225 (1): 88-96 (1997)				
6.	**8 patients (6 men and 2 women)** with SBS who were dependent on L-T **HPN (home parenteral nutrition)** for an average of 12.9 years, with mean residual small bowel length of 71 cm.. All patients were able to eat food by mouth but were unable to maintain hydration or adequate nutrition (or both) without parenteral nutrition support.	**D-B, PL-controlled, randomized, 6-week, crossover.** Pts. were admitted to Mayo Clinic's GCRC For 4 days on 3 separate occasions, 21 days apart. Active treatment: **GH (0.14 mg. kg^{-1}. d^{-1}), [Eli Lilly Co., Indianapolis, IN] and GLN (0.63 g. kg^{-1}. d^{-1}) and a high CHO-low fat (HCLF) diet for 21 days.**	**The weight, BMR, nutrient and electrolyte balance , serum insulin-like growth factor 1 (IGF-1) levels, D-xylose absorption, morphology and DNA proliferation of small intestinal mucosa, and gastrointestinal transit were evaluated** Treatments were compared by paired *t* test.	• **Rh-GH *transiently* increased body weight, significantly but modestly increased the absorption of sodium and potassium and decreased gastric emptying.** • **The assimilation of macronutrients, stool volumes and morphometry of small bowel mucosa were not statistically different in the 2 treatment arms.**
Scolapio, JS et al. Effect of Growth Hormone, Glutamine, and Diet on Adaptation in Short - Bowel Syndrome: A randomized, Controlled Study. Gastroenterology 113: 1074-1081 (1997)				
7.	**8 patients (7women, 1 man)** with SBS and **intestinal failure depending on home parenteral nutrition for 3 to 11 years and with 1 to 11 years to last surgical procedure.** **Residual small**	**Double-blind, placebo-controlled, randomized, crossover.** Active treatment . consisted of subcutaneous **rh-GH [0.14 mg/kg/d; Norditropin, Novo-Nordisk AS, Bagsvaerd, Denmark] divided into 2 daily injections, oral L-**	• **Body weight and composition.** measured by dual energy X-ray absorptiometry (Nordland XR36, Nordland Corp., Wis., USA) • **Urinary creatinine excretion** measured at 505 nm as a pikrat-creatinine complex using a standard Hospital analytical technique (method of Jaffe).	• In this study, the combination high-dose GH and glutamine **did not increase body weight, lean body mass** (LBM), **fat mass** (FM) and **bone mass significantly compared to placebo treatment.** • However, **body weight increased** 1.03 kg (1.7%, $p < 0.05$), LBM 2.93 kg (8.7%, $p < 0.001$) **and FM decreased** 2.41 kg (10.6%, $p < 0.001$) in comparison with baseline. • **24-h urine creatinine excretion did not differ between study periods.** • **No changes in intestinal absorption of FAs were seen and no changes in EFAs measured in plasma phospholipids were observed.**

	bowel length was 30 to 150 cm and 4 patients had a part of colon in function (28%, 43%, 86%, and 86%).	**glutamine (30 g/d; Ajinomoto, Kawasaki City, Japan) divided into 6 doses dissolved in a beverage of the patients' choice, and parenteral GLN as GLN-enriched infusions (17% of N as GLN; Glavamin, Pharmacia-UpJohn, Sweden).** The other group was randomized to placebo treatment. Each treatment period lasted 28 days. At home, patients consumed their habitual diets.	• **Dietary and Fecal analyses.** • **The dietary and fecal FAs** were determined by combined GLC and MSW. Intestinal FA absorption was calculated as the difference between the ingested and excreted FAs. • **FA composition of plasma phospholipids.** The FA methyl esters were analyzed by GLC.	• **Only 1 of 8 patients, who did not receive parenteral lipids, had a Holman index above 0.2, indicative of EFA deficiency.** • **All patients developed peripheral edema.**
Jeppesen PB. Effect of High-Dose growth Hormone and Glutamine on Body Composition, Urine Creatinine Excretion, Fatty Acid Absorption and Essential Fatty Acids Status in Short Bowel Patients Scan J Gastroenterol 36:48-54 (2001)				
8.	**Sixty one (61) stable adult patients with anatomical SBS,** defined as <= 200 cm of remnant small bowel. The length of time from small bowel resection was 4 (+- 5) years. In addition to SBS, 6 pts. also had **chronic radiation enteritis.** **Of the 61 pts, 49 were dependent upon PN at the time of admission** and 12 were referred with the intent of preventing the initiation or resumption of this mode of support.	**Open-label, uncontrolled.** All pts. adhered to a standardized bowel rehabilitation regimen throughout the in-house period (4 to 6 weeks) and were then monitored and adhered to the prescribed regimen throughout the follow-up period (6 and 12 months).The regimen consisted of medications, a specific diet with supplements, and a behavior modification program.. **GH [Serono Laboratories, Norwell, MA and Eli Lilly, Indianapolis, IND USA] was given at the dose of 0.09 mg/kg/d.**	**Vitamin, trace elements levels, and liver and kidney function were assessed upon admission and then reassessed at 6 and 12 months after discharge.** **Throughout the entire in-house period, body weight and all parenteral and enteral intake and output of urine, stool and emesis were recorded daily.** **Serum electrolytes were typically assessed one to two times per week.** **These same parameters were monitored throughout the follow-up period with the frequency dependent upon the clinical course of the patient..**	• Of the 61 pts., 49 were dependent upon PN, infusing on average 6 (+- 1) days per week, 2.2 ± 1 L per infusion, at the time of admission. **Of these 49, 20 were weaned completely from PN and remained off for an average of 1 year following admission to the in-home program;** 25 pts. experienced a reduction in PN requirements and 4 had no change in PN. • 19 of the 20 pts. weaned completely off of PN, maintained their weight within 10% of their admission or ideal body weight range; 8 of these were able to gain weight (2% to 17% increase from admission weight) off of PN, most notably, 3 pts. with jejunal -ileal lengths of 12 to 17 cm anastomosed to a portion of colon. • Of the 25 pts. who experienced a reduction in PN, 21 maintained their weight within 10% of their admission or ideal body weight range. **Despite an initial positive response to the bowel rehabilitation regimen, 4 of these pts. lost greater than 10% of their weight; 3 of these 4 pts. were eventually referred for intestinal transplantation.**

		Oral GLN [Cambridge Nutraceuticals, Boston, Mass, USA] was provided at a dose 30 g /d (5 g/ 6x per day)		• **The 4 pts. who experienced no change in their PN requirements following a standardized bowel rehabilitation regimen were also referred for intestinal transplantation.** • The complications associated with the bowel rehabilitation regimen included : (1) mild fluid retention, which occurred in the majority of the patients . and was attributed to the administration of GH, and treated, if indicated, with a diuretic, and (2) an increase in gas and bloating, related to the changes in the diet, particularly the CHO content.
Byrne TA et al. Bowel rehabilitation: an alternative to long-term parenteral nutrition and intestinal transplantation for some patients with short bowel syndrome. Transp Proc 34: 887-890 (2002)				
9.	**12 patients from the register of HPN-dependent patients with SBS.** All had undergone extensive resection of the small bowel without any surgical resection of the stomach, duodenum or pancreas. Usual medications such as PPIs, loperamide, fluoroquinolones, and oral supplements (vitamin E, D, Ca, K, Mg salts) were not changed during the study.	**Prospective randomized, double-blind, placebo-controlled, crossover.** All pts. were on an **unrestricted hyperphagic diet..** **Patients received daily low-dose GH [0.05 mg . kg $^{-1}$. day^{-1}] , corresponding to 0.15 IU kg $^{-1}$./ day^{-1} [Genotropin, Pharmacia and Upjohn AB, Stockholm, Sweden] administered by subcutaneous injection daily at 8am.**	Immediately before the first treatment period (baseline) and at the conclusion of each treatment period (day21), a **nutrition status (body weight, body mass index, skinfold thickness, bioelectric impedance analysis) assessment was performed.** **At the same time , a series of blood tests, including hemogram, glucose, insulin, insulin-like growth factor 1 (IGF-1), IGF binding protein 3 (IGFBP-3), and GH binding protein (GHBP, soluble form of GH receptor) serum levels as well as plasma glutamine and citrulline amino acid levels, was performed on blood samples taken in a postabsorptive state (7am).** During the third week of each Tx period, pts. were admitted for 5 days and 4 nights (days 17 to 21)to study **intestinal macronutrient absorption (main judgment criteria).** **During the first day of hospitalization (day 17), a D-xylose absorption test was performed.** **Thus, a minimum 23-day washout period actually elapsed between the evaluation of test medication and placebo treatments.**	• **Treatment with GH increased intestinal absorption of** - **energy** (15% ± 5%, $p < 0.002$) - **nitrogen** (14% ± 6%, $p < 0.04$) - **CHOs** (10% ± 4%, $p < 0.04$) **and** - **fat** (12% ± 8%, NS). • According to the authors' calculations, the increased food absorption represented 37% ± 16% of total parenteral energy delivery. • He following parameters **increased:** - **Body weight** ($p < 0.003$) - **lean body mass** ($p < 0.006$) - **D-xylose absorption** ($p < 0.02$) - **insulin-like growth factor 1** ($p < 0.002$) **and** - **insulin-like growth factor binding protein 3** ($p < 0.002$) whereas uptake of GH binding protein decreased ($p < 0.01$) , without any apparent major adverse effect.
Seguy d et al. Low-Dose Growth Hormone in Adult Home Parenteral Nutrition-Dependent Short Bowel Syndrome Patients: A Positive Study. Gastroenterology 124: 293-302 (2003)				

efficacy and safety of rh-GH and glutamine, **singly and as co-therapy**, in the **improvement of residual gut absorptive function in patients with short bowel syndrome.**

This study was reviewed in detail.

In addition, although the sponsor has not submitted any additional data as supportive, the reviewer elected to assess and summarize information published in the literature that is pertinent to the application (Table 2) to address certain issues. These issues include proof of principle (**does GH have an effect -in any way or fashion- in the treatment of SBS patients**?). Emphasis was put on publications, if any, that tested the sponsor's formulation of the hormone.

C. Detailed Review of Trials by Indication

The sponsor submitted results of a single trial, for a single, new indication. This trial is entitled "***Randomized, Double-Blind, Controlled, Parallel-Group Evaluation of the Relative Efficacy of Recombinant Human growth Hormone and Glutamine, Singly and as Cotherapy, in the Improvement of Residual Gut Absorptive Function in Patients with Short Bowel Syndrome".*** The Clinical Study Report (Protocol No. IMP20317) is reviewed in detail below.

- The study was initiated on 23 July 1998 and completed on 27 June 2002.
- There were two Principal Investigators : a) David Lautz, MD [Brigham and Women's Hospital, Boston MA], with three Sub-investigators and Nutritional Restart Center, Wellesley, MA as the study site and b) Kishore R. Iyer, M.B., B.S., F.R.C.S. [University of Nebraska, Omaha, NE] with one sub-investigator and the University of Nebraska as the study site.
- The primary objective of the study was to evaluate **the change in intravenous parenteral nutrition (IPN) requirements** measured during Week 2 (last week of baseline period) to that seen at Week 6 (last week of Treatment Period) in adult, IPN-dependent, SBS subjects receiving a specialized oral diet (SOD) supplemented with glutamine (GLN), Serostim® recombinant human growth hormone (rh-GH) with a SOD, or rh-GH with a SOD supplemented with GLN.
- The overall study design was that of a randomized, double-blind, placebo-controlled, parallel-group, 3-arm, Phase III clinical trial.
- After screening and following completion of a 2-week Baseline Period , the Treatment Period consisted of 4 weeks, after which subjects were discharged on a SOD supplemented with either GLN or GLN Placebo; subjects were reevaluated as outpatients 12 weeks later.
- **The study population consisted of 41 randomized patients** (age range : 20 to 75 y; age categories : < 65y, n = 33; >= 65y, n = 8; 32 Caucasian, 9 Non-Caucasian; 29 females and 12 males). **The study population (Table 3) was adequate for this type of study.**

Table 3
Study IMP20317
Characteristics of the Study population

INCLUSION CRITERIA	REASONS FOR EXCLUSION
• M or F, between 18 and 75y of age	• Body mass index grater than 28
• Diagnosis of SBS with less than or equal to 200 cm small bowel	• Pregnancy or lactation • Ongoing, chronic infectious disease
• Eat at least some solid food on a regular basis, but require at least 3000 cal. per week of IPN for nutritional support	• History of cancer within 5y of entry into the Baseline Period (non-melanoma skin cancer or in situ carcinoma of the cervix are not reasons for exclusion)
• Have: - body mass index equal to or greater than 17 - undergone bowel resection surgery at least 6 mo. prior to entering the trial and have an intact stomach and duodenum and one or more of the following: a) at least 30% of the colon remaining functional and at least 15 cm of jejunum or ileum remaining intact b) less than 30% of the colon remaining functional but having at least 90 cm of jejunum or ileum remaining intact c) less than or equal to 3L per day of stool output d) an acceptable level of liver function, with a total serum bilirubin concentration less than 3 times the upper limit of normal, and renal function, with a serum creatinine concentration less than or equal to 3 mg/dL e) the ability to understand the requirements of the study, to provide written informed consent and to abide by the study restrictions and agree to complete the required assessment in the follow-up period.	• History of mental deficiency or illness that might compromise with the requirements of the study. [History of psychiatric eating disorder or drug or alcohol abuse were reasons for exclusion] • Sustained hypertension (arterial pressure of >= 160/100 mm Hg or more on 2 successive measurements) • Secretory bowel disease, as demonstrated by a stool output of greater than or equal to 800 mL per 24-h period when there has been no oral intake of food for 24h • Clinically serious neurological disfunction • Established diagnosis of diabetes mellitus • Hypoxemic pulmonary disease (i.e. resting pAO_2 <= 75 torr) • Unstable ischemic heart disease or uncompensated cardiac failure • Any condition requiring either daily systemic glucocorticoids exceeding a dose equivalent to 10 mg/d prednisone or significant immunosuppressant therapy (e.g. active inflammatory bowel disease, collagen-vascular disease, autoimmune disorder, or radiation enteritis) • History of carpal tunnel syndrome unless surgical release has been performed • Participation in any study involving investigational drugs within 30 days prior to entry into this trial • Have received rhGH or any other type of growth factor that may affect intestinal absorption
- For women participating in this trial, manifest or give assent to adequate criteria to ensure that the patient does not become pregnant during the trial	
- For pts. with known hypertension or other cardiovascular disorder, be both compensated and stabilized on a regular therapeutic regimen	

- The methods/procedures/approaches to remove patients from therapy were adequate.

- **DOSE SELECTION/TIMING OF DOSING**

  The sponsor states that the dosage of rh-GH chosen for this study was based upon previous experience in SBS patients. Doses ranging from 0.07 to 0.14 mg/kg/d have been shown to be effective in decreasing IPN-dependence in SBS patients (publications by T. A. Byrne, D.W. Wilmore, who commented on results of IMP20317 at the June 25,2003 AC). **A dose of 0.10 mg/kg/d was selected because of its "good safety and efficacy profile"**. The GLN supplementation was selected on the basis of past experience in SBS patients and suggestions from the Agency during the pre-IND meeting on 19 October 1994.

  Each patient was scheduled to receive a daily subcutaneous injection of **0.10 mg/kg rh-GH** or **rh-GH placebo** (to a maximum dose of 8 mg/d) for 4 weeks, calculated using a step-wise dosing procedure depending on patient's weight (ranging from 4 mg/d for a patient whose weight was 35 to 44.9 kg to 8 mg kg/d for a >=75 kg patient.

  Each patient received a daily oral supplement of GLN (30 g /d) or GLN placebo (27 g/d) divided into 6 single dose packets that were each mixed with water or Crystal Light beverage according to the patient's preference. Patients consumed the beverages with meals or snacks at 2 -to 3-h intervals during the day. The volume of the beverage could be varied according to the patient's tolerance.[32]

  NOTE: All study participants received an oral diet individualized to meet nutritional needs. It is important to note that modifications to the diet throughout the treatment period were necessary to maintain adequate nutrition status. Dr. D. Price, the FDA Statistician reviewer, noted the following: **"due to changes to the diet after randomization and the potentially complex relationship between diet and total IPN volume, an unbiased statistical analysis adjusting for the diet effect is not possible."**

  However, data on the diet and nutritional status of patients serve to provide clinicians with a descriptive clarification of the nature and strength of the relationship between diet and IPN utilization over time. Additional pertinent discussions and information on the diet issue are included in Section X of the current review.

- **RANDOMIZATION/BLINDING**
  - The randomization scheme and codes were submitted in sponsor's Appendix 16.1.7 (volume 1, page 263 through 266).
  - The proposed randomization scheme was appropriate The plan called for random assignment of subjects in a 2:2:1 ratio at each site to one of the 3 treatment arms (*i.e.,* Group A, rh-GH + SOD; Group B, rh-GH + SOD[GLN]; and Group C, rh-GH placebo + SOD[GLN]. The block size was 5.

[32] In the event of a patient's transient intolerance to oral intake, it was allowable for the dose to be delayed for up to 2 h until the patient was able to drink it.

- **The randomization process was properly executed.** Subjects were randomly assigned using PROC PLAN.[33] Patient randomization codes were maintained in sealed envelopes in the medical monitor's locked file.[34]
- **The study qualifies as being double-blinded. The methods to conceal the identity of the test medication from participating physicians and patients were all adequate. The injectable clinical trial material (CTM), rh-GH or rh-GH placebo, was identical in appearance and packaging.[35] The oral supplement (GLN or GLN placebo) was identical in volume, appearance, and packaging.[36]**

- PRIOR AND CONCOMITANT THERAPY/COMPLIANCE
  The procedures to handle prior and concomitant medications, especially those that may be potentially confounding, were all adequate.
  Equally adequate were the procedures to determine treatment compliance.

- PRIMARY EFFICACY PARAMETER
  The primary efficacy parameter was the change from Week 2 to Week 6 in the total volume of IPN required by each patient for nutritional support. The sponsor states that following discussion with the DMEDP, **IPN volume was selected to achieve an accurate analysis of efficacy since it is less variable than IPN calories.**
  NOTE: An important issue that needs to be addressed is whether **changes in IPN volume** per week --rather than **measurements of adequate parameters to assess clinical/biochemical/nutritional status--** is a valid/important/relevant primary efficacy parameter to determine efficacy of the drug in the SBS indication that the sponsor is requesting.
  This issue, which is a pivotal determinant when assessing approvability of the drug for the sought indication, is discussed in many sections of the current review. This issue is also one of the subjects of the June 25, 2003 GI Advisory Committee discussions. The current review continues on the certainly debatable assumption that **change in IPN volume *is* a valid/relevant/clinically important primary efficacy parameter.**

  Definition of Total IPN volume (administered per week)
  - As prospectively stipulated, total IPN volume is the sum of:
    a) IPN volume *plus*
    b) supplemental lipid emulsion (SLE) *plus*
    c) intravenous hydration fluid administered each week.

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[33] According to the information provided by the sponsor, the seed for subjects 101-135 at Site 01 was 55784. The seed for subjects 201-203 at Site 01 was 55785. The seed for subjects 301-303 at Site 02 was 55787.but only 3 subjects in total were randomized at Site 2.

[34] **There were no laboratory measurements performed that would have unblinded the study.**

[35] Each vial of test medication contained a two-part label consisting of a portion permanently attached to the vial and a tear-off portion that was attached to the patient's CRF [The and the ones below are all adequate procedures].

[36] These packets had tear-off portions as above.

- IPN and SLE requirements were captured on a daily basis during Week 2 through 6.

- **SECONDARY EFFICACY PARAMETERS**

There were two (2) secondary parameters of efficacy:

1) **Mean change in Total IPN calories (calories per week) from Week 2 to 6.** Total calories are (adequately) defined as the sum of kilocalories for CHO, protein, and fat in the IPN.

2) **Mean change in IPN or SLE frequency (days per week) from Week 2 to 6. Frequency** is defined as the number of days per week of administration of IPN or, if no IPN, administration of SLE where the amount of SLE provides greater than 200 kcal.[37]

In addition, the sponsor attempted to evaluate the persistence of observed treatment effects. To accomplish this, the change in weekly volume of IPN used during Week 2 versus Week 6 was compared with the change in weekly volume requirements during Week 6 versus Week 18 (last week of the Follow-up Period).[38] But, as we will see later, these data are not very helpful.

Furthermore, the sponsor analyzed other related efficacy parameters in an attempt to examine the consistency of effects over time. This was done through a repeated-measures analysis of all primary, secondary, and other efficacy parameters. Such an analysis used all the data from Week 2 through Week 6. In addition, **hydration fluid intake, urine output, and stool output for all treatment groups for Week 2 and Week 6 were compared.** Because such an evaluation may provide some evidence of fluid balance, the reviewer elected to examine data for the last three parameters.

TEST MEDICATION

This was recombinant human growth hormone (Serostim®); subcutaneous injection at a dose of 0.10 mg/kg/d.[39]
Also made use of was rh-GH placebo; subcutaneous injection; 0.10 mg/kg/d.[40]

DURATION OF TREATMENT

GROUP A: rh-GH + SOD for 4 weeks followed by SOD for 12 weeks.

GROUP B: rh-GH + SOD [GLN] for 4 weeks followed by SOD [GLN] for 12 weeks.

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[37] IPN and SLE requirements for each patient were recorded daily during Week 2 through Week 6.
[38] For Week 18, summary data only for IPN frequency, volume, and calories were provided in the CRF on the basis of **contact with the patient's local physician**.
[39] Lot numbers TC0409, MMK641A2, and MON668B.
[40] Lot Numbers TC0396 and PLM99-34.

GROUP C: rh-GH placebo + SOD[GLN] for 4 weeks followed by SOD[GLN] for 12 weeks.

It is important to note that the "active treatment", either growth hormone in co-therapy with active glutamine (Group B) or growth hormone alone (Group A) is only given for 4 weeks. **This approach does not test long-term effects of the recombinant human growth hormone.**

CRITERIA FOR EVALUATION OF SAFETY

The procedures to gather, process, analyze and report trial emerging adverse events, whether clinical or laboratory abnormalities, were all adequate.

STATISTICS

Determination of Sample Size

The sample size calculation was based on the number of patients (i.e. 17) studied by Byrne[41].

Patients in the Byrne study received rh-GH + SOD [GLN] and were evaluated within 6 months of the end of treatment.

Based on this experience, a total of 40 patients [Group A, n = 16, Group B, n = 16, and Group C, n = 8] was needed to yield 80% power for the overall F test ($\alpha = 0.05$) from a one-way ANOVA. This determination was made on the following assumptions:

- That the difference in the decrease of IPN volume between Group B (rh-GH + SOD [GLN]) and Group C, the control (rh-GH placebo + SOD [GLN] is **6.6 L per week** ***and***
- That the decrease in IPN volume between Group A (rh-GH + SOD] and Group C (rh-GH placebo + SOD [GLN) is **6.6 L per week** ***and***
- That the pooled root mean squared error is **5.5 L per week.**

NOTE: According to the Clinical Report, the original plan was to enroll 5 additional patients to ensure that at least 40 patients completed the trial.

The Clinical report states that analysis of covariance of the change in total volume from Week 2 to Week 6, with Week 2 as the covariate and with the treatment effect was used to compare the primary efficacy parameter for the treatment arms. **This statistical approach is acceptable.**

The secondary efficacy parameters were evaluated through pair-wise comparisons of the least squares means of the two rh-GH groups, Group A (rh-GH + SOD); Group B (rh-GH + SOD [GLN]) ***to*** the GLN-supplemented diet group, Group C: (rh-GH placebo + SOD [GLN]) by using the Dunnett-Hsu t-test.

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[41] [Byrne, TA. Et al. Advances in the management off patients with intestinal failure. Transplt Proc 28:2683-2690 (1996)]

Effects of Covariates

Statistical models of the effects of other covariates on the primary and secondary parameters were also assessed. Covariates that were assessed include, but were not necessarily limited to: age, sex, race, weight (this included weight history), time since diagnosis of SBS, time since last resection (< 12 months or >= 12 months), length of residual jejunum-ileum, presence of an intact colon, and IPN history (this included weekly IPN volume, calories, and frequency).[42]

The Clinical Report states that site effects were included in the above models if multiple sites were used and the site effect was statistically significant in the corresponding analysis excluding the covariate. Covariates were assessed individually.[43]

The safety analyses were conducted using the safety population. The latter was defined as 41 patients randomized in the trial who had postbaseline assessments. If all randomized patients had at least one postbaseline assessment, then the safety population is identical to the ITT population [n = 41].[44]

RESULTS

Disposition of Subjects

- Of the 47 patients considered for study participation, 6 discontinued before randomization [5 due to intercurrent illness and 1 because the patient withdrew informed consent].
- Of the 41 patients enrolled into the trial, 38 were randomized at Site 01, the other three at Site 02, with the distribution summarized in Table 4.

Table 4
Study IMP20317
Summary of Patient Accrual
Number of Patients Randomized per Site and Treatment Arm

SITE	GROUP A (rh-GH + SOD)	GROUP B (rh-GH + SOD [GLN])	GROUP C (SOD [GLN])	Total
01	15	15	8	38
02	1	1	1	3
Subtotal	16[a]	16	9	41

a) One patient (No. 106) was randomized to Group A on 26 October 1998 and discontinued from the trial on 15 November 1998 (Week 5) due to a central line infection that resulted in fungemia. Therefore, the total number of patients completing the Treatment Period, as well as the Follow-Up Period was 15, 16, and 9, for Groups A, B, and C, respectively.

[42] For continuous covariates, the covariate was assessed by using Type I sums of squares.
[43] Model assumptions including the presence of covariate by treatment interactions were to be checked , and analyses were to be adjusted accordingly.
[44] According to the Clinical Report, a formal inferential analysis for safety parameters was not conducted.

NOTE: From the information summarized in Table 4, it is hard to characterize Study IMP20317 as being **multicenter.** This is because of the fact that the bulk of the patients in this study were randomized at one site (Site 01) while the other (Site 02) randomized one single patient per arm. It is clear that Site 2 did not contribute significantly to the data used to assess efficacy and safety of the drug in SBS patients. **Thus, IMP20317 is primarily a single center study.**

Protocol Deviations

The Clinical Report included two Appendices, 16.2.1.1 and 16.2.1.2 listing all patient termination data, organized by site and treatment group, including patient identifier, specific reasons for discontinuation, and the date of discontinuation or termination. It is explained that at the time of discontinuation, the blind was not broken for any subject. The main protocol deviations by treatment arm for the ITT study population, were summarized in sponsor's Table 10-1 (page 103) of the Clinical Report. Most of the protocol deviations consisted of reduced dose of oral CTM for 1 to 7 days, followed by incomplete vital sign assessments, missed 1 to 4 days of subcutaneous CTM administration and missed incomplete vital sign assessments. In the final analysis, **there were no gross imbalances among the 3 treatment arms regarding the protocol deviations.**

Data Sets Analyzed

There were 3 data sets analyzed: a) **ITT** (n = 41), defined as all subjects that were randomized into the trial; b) **Efficacy Evaluable** (n = 40), defined as subjects that completed treatment period assessment (i.e., IPN requirement assessments for 5 of 7 days during Week 2 and Week 6), received at least 80% of scheduled CTM (i.e., 23 doses of subcutaneous CTM and 135 doses of oral supplementation) and those who did not have any protocol violations with a clinical impact; and c) *treatment responders*. Because the reviewer feels **the latter is a very important parameter of efficacy**, the definition of treatment responder is given below.

Treatment Responder Population

This study population includes all subjects who demonstrated a complete response (i.e., **a 100% reduction in total IPN volume**) at Week 6. **Unfortunately, results in this study population were (only) summarized descriptively because each treatment group was not represented by at least 2 subjects.**

SUBJECTS BASELINE CHARACTERISTICS

All in all, the 3 treatment groups were comparable in terms of demographic , disease and other baseline characteristics.

- The treatment groups were comparable (no statistically significant differences among treatment arms) in demographic characteristics. As summarized in sponsor's Table 11-1 of the Clinical Report, **the mean age** for Groups A, B,

and C was 50.5, 52.5, and 45.0 years, respectively. Roughly, **two thirds of the patients were women, mostly Caucasian.** There was a lower proportion of patients of non-Caucasian origin. Although this difference approached statistical significance (p = 0.064) **this imbalance is not expected to influence results.** Likewise, the treatment arms were similar in baseline weight (Group A = 61.4 kg, Group B = 62.1 kg, and Group C = 61.3 kg). Weight was the average of each patient's weight at 1 month and 2 months before screening.

- The underlying conditions resulting in bowel resection represented in all 3 treatment arms were vascular **insufficiency, Crohn's disease, and volvulus. Other categories included patients with strangulated hernia, jejunoileal bypass for morbid obesity and other. There were no gross imbalances among the treatment arms in underlying condition resulting in bowel resection. When considering these comparisons, the number of subjects per group was not sufficient for statistical analysis.**
- Similarly, at baseline, there was no statistically significant difference among the 3 treatment groups with regards to SBS and IPN history (Table 5). Results of evaluations regarding the 6 SBS/IPN-related variables listed in this Table were carefully analyzed because parameters such as **mean length of residual jejunum-ileum , percent of colon intact , mean number of days per week of IPN administration, mean volume IPN per week, and mean IPN calories per week are factors that may influence outcome.**

Table 5
Study IMP20317
Summary of Disease Baseline Characteristics

SBS/IPN Variable	Group A rh-GH+SOD [n = 16]	Group B rh-GH+SOD[GLN] [n = 16]	Group C SOD[GLN] [n = 9]	p-value
Mean number of years since most recent bowel resection	5.1	4.6	3.9	N.S.
Mean length of residual jejunum-ileum [cm]	84.2	68.4	62.3	N.S.
Percent of Colon Intact	67.1	52.6	61.8	N.S.
Mean number of days per week of IPN administration	5.2	5.5	5.9	N.S.
Mean volume IPN per week [L/wk]	13.8	13.0	13.1	N.S.
Mean IPN calories per week [kcal/wk]	11620.8	10403.8	10224.9	N.S.

This Table is based on sponsor's Tables 1.5.1 and 1.6.1 (Section 15.1) and Summary Table 11-3 (page 108) of the Clinical Report. Standard deviations have been omitted for clarity of presentation purposes.

RESULTS OF EFFICACY EVALUATIONS

1. Groups Being Compared

- There were 3 arms in the trial. **The *main test medication arm is B***, which consists of rh-GH, SOD, and GLN (3 co-therapies).
- **Arm C**, consisting of two co-therapies, SOD and GLN (like arm B) but containing **no active rh-GH (instead, it contains rh-GH placebo),** is a suitable control.). For this comparison to be valid and to be able to conclude that the hormone is active in this indication, there must be no significant changes between these two arms (B and C) in SOD as well as GLN. But of course, in Group B, rh-GH is, in reality, given in co-therapy to active glutamine.
- **Also important** is to test the effect of growth hormone (rh-GH) alone (without active glutamine), as in Group A, to the control (Group C).
- Although not apparently tested by the sponsor, another comparison of interest might be that of **B** (the 3 co-therapies) **to A**, a test arm consisting of 2 co-therapies, rh-GH and SOD, but containing no active GLN. Again, if SOD is common (in effects or lack of effects) to both arms, then **this comparison B vs A, may provide an assessment of the effect of glutamine alone.**

In summary, **the question of efficacy of growth hormone, given in co-therapy with active glutamine, is settled by comparing results of Group B to C**. The question of efficacy of growth hormone alone (rh-GH without active glutamine as co-therapy), is settled by comparing results of Group A to C. This is a comparison included in the sponsor's summary Tables of efficacy. But the reviewer is not sure if meaningful conclusions can be drawn from such a comparison. Assuming that SOD is common to both arms, this comparison appears to be testing the effect of 2 variables: rh-GH alone, without active glutamine (in arm A) to that of active GLN (in arm C). If carried out (as the sponsor has) this seems to represent **an active-active comparator situation but, owing to the small number of observations per cell, neither superiority nor non-inferiority hypotheses can be appropriately tested.** Therefore, this comparison, A vs. C, is not discussed in detail in the reviewer's efficacy evaluations.
The question of **glutamine's contribution** might be settled by comparing results of **Group B to A**. This comparison, included in the reviewer's efficacy Tables, was carried by Dr. Dionne Price, FDA statistician.

2. Evaluations of Primary Efficacy Parameter (Table 6)[45]

- For both, the ITT (upper panel of Table 6) and the EE population (lower panel of Table 6), a significant reduction in the Total IPN volume requirement was noted in patients who received rh-GH + SOD[GLN] (Group B) in comparison to the control, that is , those who received SOD + [GLN] (Group C). **The therapeutic gain was 3.9 L/wk.** Whether a reduction in Total IPN volume requirement of 3.9 L/wk is clinically meaningful, is a matter of debate. The important question considered at the June 25, 2003 GI AC is : **the difference between Group B and C is statistically significant. Is this difference also clinically significant?**
- Although the comparison of A to C yielded a therapeutic gain of **-2.1 L/wk** and this difference was statistically significant in ITT Study Population evaluations, **these results were not confirmed in analyses of the E-E Study Population** (therapeutic gain = **-2.0 L/wk**, p-value = N.S.). Based on these results, the reviewer believes that the effect of rh-GH alone (**when administered without active glutamine as co-therapy**) is **, both clinically and statistically weak, borderline. As a consequence,** the results of this study suggest that the **preferred/recommended mode of administration of the hormone is with active glutamine as co-therapy.**
- The other comparison of interest is that of Group B vs Group A. This was carried out by the FDA statistician, Dr. D. Price. In her Statistical Review of NDA 21-597, Dr. Price notes that ascertainment of the relationship between rh-GH alone versus rh-GH in co-therapy with glutamine may provide some insight into the effect of the amino acid. Since , **regardless of the study population evaluated**, the difference between the comparison arms was not statistically significant (Table 6), Dr. Price concluded that **glutamine has little or no effect.** This reviewer agrees that, under the conditions of these experiments, **little if any glutamine contribution has been demonstrated.** Therapeutic gains (decreases) of 1.8 (ITT Study Population) or 1.9 (E-E Study Population) liters per week of Total IPN volume are: a) less impressive than those seen with glutamine plus rh-GH as co-therapies (Group B) and b) not supported by statistical significance.

3. Evaluations of Secondary Efficacy Parameters (Table 7)

In the Clinical Report, the sponsor presented results of evaluations of 2 secondary efficacy parameters, the **mean change in total IPN calories and the mean change in IPN or SLE Frequency** from Week 2 to Week 6, for both secondary evaluation parameters.

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[45] As previously noted, the primary outcome was analyzed utilizing an analysis of covariance model with baseline covariate. Pairwise comparison between the groups of interest were assessed utilizing Dunnett-Hsu test to control Type I error rate at 5%.

Table 6
Study IMP20317
Primary Efficacy Evaluation: Mean Change in Total IPN Volume [L/wk] from Week 2 to Week 6

Treatment Groups			Therapeutic gain [L/wk]//(p-value)		
A rh-GH + SOD	B rh-GH + SOD[GLN]	C SOD[GLN]	B vs C	B vs A	A vs C
I. ITT STUDY POPULATION					
[n = 16]	[n = 16]	[n= 9]			
-5.9	-7.7	-3.8	-3.9 [<0.001][a]	-1.8 [N.S.][b]	-2.1 [0.043][c]
II. EFFICACY-EVALUABLE STUDY POPULATION					
[n = 15]	[n = 16]	[n = 9]			
-5.8	-7.7	-3.8	-3.9 [<0.001][a]	-1.9 [N.S.][b]	-2.0 [N.S.][c]

This Table is based on sponsor's Tables 2.5.1., 2.9.1.1, 2.13.1 and 2.5.2, 2.9.2, and 2.13.2 and Summary Table 11-4 and 11-7 of the Clinical Report.
Standard deviations have been omitted for clarity of presentation purposes.
a.c) These p-values were determined from pairwise comparisons of treatment groups B and A vs. the "control" (Group C) by Dunnett-Hsu t-test following ANCOVA with Week 2 as covariate including baseline by treatment interaction.
b)To extend comparisons to include all pairwise comparisons, the FDA statistician, Dr. D. Price applied a Tukey-Kramer test for this comparison.
NOTE: For Group A, in the E-E Study Population, the number of patients is 15 because results of Patient No. 106 are not included.

Table 7 displays data from evaluations in the ITT population only, because results from evaluations using the E-E Study population were nearly identical to those using the ITT analysis and therefore confirm the conclusions drawn from the latter analyses. As shown in Table 7, after 4 Weeks of treatment, subjects who received rh-GH + SOD[GLN] (Group B, the main test medication arm consisting of rh-Gh given in co-therapy with active glutamine) significantly reduced their Total IPN calorie content (therapeutic gain = -3117.9 kcal/wk) and their weekly frequency of IPN administration (therapeutic gain = -2.2 d/wk) in comparison to the control (Group C, subjects receiving SOD[GLN] without active rh-GH). **There is need to assess the clinical significance of the results with secondary parameters of efficacy, a reduction of 3,117.9 kcal/wk, and a reduction by 2 out of 7 days per week in the need for Total IPN.** Once again, it is important to note that

neither the primary nor the secondary parameters of efficacy measure the patient's nutritional status.
In an approach similar to that for the primary efficacy parameters where additional statistical evaluations by Dr. Price are included in Table 6, results of further statistical evaluations for the secondary efficacy endpoints are included in Table 7.

According to the data displayed in Table 7, the difference between Groups A (rh-GH alone) and C is statistically significant for the secondary parameters of assessment. But the clinical impact of these results, a reduction of 1705.0 kcal per week, but specially, one day less (6 instead of 7 ?) in Total IPN or SLE, suggest a less impressive effect than that obtained when comparing Group B to C. These data from secondary efficacy evaluations support the reviewer's view that although the hormone is active in this indication, **the preferred mode of administration is in co-therapy with active glutamine rather than rh-GH alone..**

Table 7
Study IMP20317
Secondary Efficacy Evaluations
ITT STUDY POPULATION

Treatment Groups			Therapeutic gain //(p-value)		
A rhGH +SOD	B rhGH +SOD[GLN]	C SOD[GLN]	B vs C	B vs A	A vs C
A. Mean Change in Total IPN Calories [kcal/wk]					
[n = 16]	[n = 16]	[n =9]			
-4338.3	-5751.2	-2633.3	-3117.9 [<0.001]	-1412.9 [0.0436]	-1705.0 [0.005]
B. Mean Change in IPN or SLE Frequency [d/wk]					
[n = 16]	[n = 16]	[n = 9]			
-3.0	-4.2	-2.0	-2.2 [<0.001]	-1.2 [0.0478]	-1.0 [0.025]

Source of table: see footnote to Table 6.
a.b.and c) : See footnote to Table 6.

4. **Number of Subjects Weaned off Total IPN (Table 8)**

In their Table 11-6 of the Clinical Report, the sponsor presented a summary of categorical change of frequency of IPN or SLE administration from Week 2 to Week 6 for the ITT Population by Treatment arm. The frequency change was split into 3 categories. The small number of patients per cell in these categories precludes definite conclusions. The reviewer has elected to focus on the 100% reduction category (Table 8).

NOTE: These data seem to be hypothesis-generating. One important issue is the degree of standardization of procedures across patients to determine **when IPN requirement volume is to be decreased** and when is the patient to be weaned off IPN (completely). The sponsor explained that IPN requirements were to be reduced when the patient demonstrated **all 3 of the following**: 1. Ability to hydrate; 2. Ability to maintain serum electrolytes within the limits of normal range with or without the use of enteral electrolyte supplement(s); and 3. Ability to sustain an appropriate body weight.These parameters are hard to standardize. In addition, each of these parameters of evaluation may be subject to different definitions and varied interpretations. To be more valuable, the information should include a) **the proportion of patients that are weaned off IPN**; and b) more importantly, the proportion of those **who remain off IPN long-term**.

Nonetheless, when examining these rather initial data, it is worth mentioning that calculating percentages (proportions) of patients when the total Study Population is so small is not very helpful. From the comparison of Groups B (the main test medication arm, including 3 co-therapies) to the control arm (Group C, which includes 2 co-therapies, SOD and GLN, but no rh-GH), the conclusion may be reached that **rh-GH in co-therapy with SOD and GLN might (eventually) result in more patients that could be weaned off Total IPN. Confirmation of these findings would be important.**

Table 8 Study IMP20317		
COMPLETE RESPONDERS, ITT POPULATION		
Groups		
A **rh-GH + SOD** **[n = 16]**	**B** **rh-Gh + SOD[GLN]** **[n = 16]**	**C** **SOD[GLN]** **[n = 9]**
Complete Wean from IPN, Lipids, and I.V. Hydration		
4	**4**	**1**
Complete Wean from IPN and Lipids (I.V. Hydration Allowed)		
5	**7**	**1**
In the Footnote to Table 11-6 of the Clinical Report, the sponsor explained that the number of subjects with a 100% reduction in IPN or SLE administration is greater than the number of subjects in the TR population because some subjects continued to receive hydration fluid.		

5. **Comparison between the Treatment Period (Week 2 to Week 6) and the Follow-up Period (Week 6 to Week 18)**
   The sponsor presented data (Table 11-9, volume 1, page 118 of the Clinical Report), summarizing the change in weekly volume, calories and frequency of IPN used during Week 6 versus Week 18, adjusting for the change from Week 2 to Week 6 for the ITT Study Population. It is to be noted that this information is not included in Table 8. It should also be noted that residuals from the ANCOVA on the original scale were not normally distributed. As already mentioned, the change in primary and secondary efficacy parameters was analyzed adjusting for the change during the Treatment Period as a covariate. These analyses demonstrated that all groups increased their IPN requirements similarly during the Follow-up Period. An initial interpretation of these data is that **the persistence of treatment effects during the Follow-up Period was similar for all 3 treatment arms**, which, of course, included 2 rh-GH-containi9ng arms. **But additional, more convincing data are needed to demonstrate durability of effects.**

6. **Adjustments for Effects of Covariates on Primary and Secondary Endpoints**
   According to the Clinical Report (volume 1, page 121) covariates that were assessed for the ITT Study Population included: age; sex; **weight;** time since diagnosis of SBS; time since last resection (< 12 months or >= 12

months); **length of residual jejunum-ileum; presence of an intact colon**; and **IPN volume history** (this includes weekly IPN volume, calories, and frequency, the efficacy evaluation parameters assessed in the trial).

- The analyses revealed that the Total Weekly IPN volume results were influenced significantly by patients'
- **weight [p<0.001]**. Subjects with higher body weight experienced greater reductions in total weekly IPN volume than those with lower body weights.
- **length of residual bowel[p = 0.028].** Subjects with longer residual bowel had larger decreases in Total IPN volume than those with shorter residual bowel.
- **IPN volume history [p = 0.044].** Subjects with a history of higher IPN volume requirements experienced greater decreases in IPN volume during the Treatment Period than those with a history of lower IPN volume requirements.
- **race [p = 0.021].** It was found that Caucasians responded to treatment better than non-Caucasians. The sponsor brings attention to the fact that only 9 out of 41 subjects randomized in Study IMP20317 were non-Caucasians.

NOTE : In all cases with a significant covariate, the effect of the ***main test medication arm*** (group B, rh-GH + SOD[GLN]) **remained highly significant.**[46]
According to the Clinical Report, Total IPN calorie results for the ITT Study Population were not influenced by the inclusion of any of the covariates. **Only patients' weight [0.029] influenced the treatment results** for the frequency of administration of IPN or SLE for the ITT Study Population. Covariate analyses for the E-E Study Population yielded results similar to those for the ITT Population.

7. Other

- Drug-Dose, Drug-Concentration, and Relationships to Response were not analyzed because drug concentration data were not collected.
- Drug-Drug and Drug-Disease Interactions were not analyzed statistically. In general the data seemed to indicate that 4 weeks of 0.10 mg/kg/d rh-GH **did not induce hyperglycemia** in subjects with SBS that were dependent on IPN.

[46] In those instances with a significant covariate, **the comparison of Group A (rh-GH alone, without active glutramine as co-therapy) to Group C (The control) remained significant only when weight was used as a covariate.**

D. Efficacy Conclusions

The question of efficacy is settled by comparing the active rh-GH-containing arm, Group B in co-therapy with glutamine (rh-GH + SOD[GLN]) to Group C, the control. Once again, the group B treatment arm includes the recombinant human growth hormone test medication and was administered in co-therapy with two additional components, the specialized/standardized oral diet (SOD) and (active) glutamine [GLN]. Group C is an adequate control because this treatment arm is similar in composition to B with regards to SOD and GLN but contains rh-GH placebo instead of the active hormone. **Therefore, the comparison B vs C is both valid and meaningful.**

Analyses using the **prospectively stipulated primary endpoint of efficacy** demonstrated that the administration of rh-GH in co-therapy with SOD + [GLN] was associated with a significant reduction (**therapeutic gain = 3.9 liters per week**) in the Total IPN volume requirement. *The difference between B and C was highly significant ($p < 0.001$, for both the Intent-To-Treat as well as the Evaluable- for- Efficacy Study Populations).*

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

From the available information, it is reasonable to conclude that overall, there are no major safety concerns with the use of rh-GH in co-therapy with GLN (and SOD) in patients with SBS treated for up to 4 weeks

The reviewer agrees with the sponsor that the safety profile of rh-GH + SOD[GLN] appears to be similar to the safety profile of rh-GH + SOD plus placebo glutamine. It is to be noted that the sponsor **does not propose to revise the currently approved labeling** to include safety data related to the use of the drug in SBS patients. Because of the above-noted information, **the reviewer agrees that this approach is reasonable and acceptable.**

B. Description of Patient Exposure

In section 12.1, page 129 of the Clinical Report, the sponsor summarized the total exposure information. **Total exposure of subjects to rh-GH was a maximum of 28 days at 0.10 mg/kg/d (32 subjects)**[47].

C. Methods and Specific Findings of Safety Review

- During the Baseline Period, 88% of rh-GH +SOD[GLN] (Group B) and 88% of those receiving rh-GH + SOD (Group A) subjects reported at least one Baseline Sign and Symptom (BSS) in comparison to 78% of those in the SOD[GLN] (control Group).
- There were no deaths in this trial.

[47] Total exposure of subjects to rh-GH placebo was a maximum of 28 days at 0.10 mg/kg/d (9 subjects).

- The most frequently reported BSSs included edema, fatigue, and gastrointestinal disorders. The latter **are signs and symptoms of SBS**.
- During the treatment period, all of the subjects receiving rh-GH + SOD[GLN], the main test medication group, as well as all of those treated with rh-GH+SOD (the group containing rh-GH alone, with no glutamine as co-therapy)reported at least one AE as compared with 89% of SOD[GLN] subjects (The Control group).
- The proportion of subjects experiencing at least one treatment-related AE in the rh-GH + SOD[GLN], rh-GH + SOD[48], and SOD[GLN} treatment groups was 88%, 94%, and 22%, respectively. Although 94% vs 22% appear quite different, these percentages are calculated from small number of patients. These results are rather difficult to interpret. However, see below.
- None of the SAE (**none reported in subjects in Group B consisting of rh-GH given in co-therapy with glutamine to patients receiving a specialized oral diet) were considered related to test medication.**
- The proportion of subjects experiencing at least one AE during the Follow-up Period was similar among the 3 treatment groups.
- The treatment emergency rates of other AEs occurring in subjects in the rh-GH + SOD[GLN] or rh-GH + SOD treatment groups was similar to the rates reported in the package insert for Serostim® except for **edema and application (injection) site disorders,** which were reported more often in IMP20317.
- As noted by the sponsor, variations in laboratory values are expected in this subject population due to their underlying conditions and their dependence on parenteral nutrition. The fluctuations in laboratory values were similar across all 3 treatment arms. **No clinically significant pattern was detected.**

D. Adequacy of Safety Testing

Giving the fact that **SBS is an orphan indication** and that rh-GH (***alone***)is already approved for another indication (**treatment of AIDS wasting or cachexia**), the reviewer believes that the safety testing in NDA 21-597 was, all things considered, adequate.

Safety testing was adequate both, with respect to exposure as well as the type of clinical and laboratory assessments that were carried out.

NOTE: For completeness purposes, the reviewer includes here a brief summary of three recent publications on the subject matter of safety when using growth hormone long-term, which should be considered if the drug is approved for the treatment of Short Bowel Syndrome. **This information is mentioned here because, for this proposed indication, the drug may need to be administered for prolonged periods of time, perhaps for the rest of the patient's life. However, it is worth noting that *long-term safety matters with growth hormone require further discussion/consideration.***

[48] One rhGH + SOD subject discontinued from the trial during Week 5 because of fungemia.

- The first is a pre-clinical study aimed to gain a clearer understanding of the interaction between GH and tumor cells in vivo. [49]It was concluded that overall, GH synergistically promotes carcinogen-induced hepatocarcinogenesis in both sexes of GH-transgenic mice by stimulating tumor cell proliferation.
- The other two publications referred to clinical/epidemiologic findings.
  - In the first, Bramnert et al.[50] examined both short-term (1 wk) and long-term (6 months) effects of a **low-dose GH replacement therapy**, in comparison to placebo, **on whole body glucose and lipid metabolism and on muscle composition.** It was concluded that replacement therapy with a low-dose GH in GH-deficient adult subjects is associated with a sustained deterioration of glucose metabolism as a consequence of the lipolytic effect of GH, resulting in enhanced oxidation of lipid substrates. Also, a shift toward more insulin-resistant type II X fibers was seen in muscle **[glucose metabolism should be carefully monitored during long-term GH replacement therapy].**
  - In the second, Swerdlow and co-workers[51], did a cohort study to investigate cancer incidence and mortality in 1848 patients in the UK who were treated during childhood and early adulthood with human pituitary GH during the period from 1959 to 1985. Patients were followed up for cancer incidence to December, 1995 and for mortality to December, 2000. Risk of cancer control was compared with that in the general population, controlling for age, sex, and calendar period. **The authors' findings included a highly raised risk of colorectal cancer.** Their interpretation of their findings was that, although based on small numbers, the risk of colorectal cancer is of some concern and further investigation in other cohorts is needed.
  - Although the above-summarized information is included here for completeness, the reviewer believes that **evidence that GH administration is associated with an increased risk of colorectal cancer needs confirmation.**

VIII. Dosing, Regimen, and Administration Issues

In clinical trial IPM20317, the sole evidence of effectiveness presented by the sponsor, only one dose level of the subcutaneously administered hormone (0.1 mg/kg/d) was tested. Based on results of this trial, the sponsor proposes to revise the DOSAGE AND ADMINISTRATION Section of the labeling to include the following wording: ***"In patients with Short Bowel Syndrome (SBS), Serostim® should be administered at a***

[49] Snibson KJ et al. Overexpressed growth hormone (GH) synergistically promotes carcinogen-initiated liver tumour growth by promoting cellular proliferation in emerging hepatocellular neoplasms in female and male GH-transgenic mice.

[50] Bramnert M et al. Growth Hormone replacement Therapy Induces Insulin Resistance by Activating the Glucose-Fatty Acid Cycle. J Clin Endocrinol Metab 88: 1455-1463 (2003)

[51] Swerdlow AJ et al. Risk of cancer in patients treated with human pituitary growth hormone in the UK, 1959-85: a cohort study. Lancet 360: 273-277 (2002).

dose of 0.1 mg/kg subcutaneously daily to a maximum of 8 mg daily". Based the evidence at hand as well as literature publications made use of throughout the current review, **the reviewer does not believe that the dose has been adequately assessed.**

- In a recently published well-designed clinical trial (Study No. 7 in Table 2 of the current review), the combination **"high-dose" GH (defined as 0.14 mg/kg/d) plus glutamine** did not increase body weight, lean body mass, fat mass, and bone mass significantly compared to placebo treatment.
- An even more recently but also well-designed and apparently well-executed published trial (Study No. 9 in Table 2 of the current review) showed that treatment with **GH at the "low-dose" of 0.05 mg/kg/d** increased intestinal absorption of energy, nitrogen, and fat. In this study, other parameters that increased were body weight, lean body mass, D-xylose absorption, insulin-like growth factor-1 and insulin-like growth factor binding protein 3. This study reported also that uptake of GH binding protein decreased without any apparent adverse event.

NOTE: In spite of the above, and with the evidence at hand, it is not possible to rule out the possibility that the difference in efficacy results seen between the sponsor's and other GH preparations are due to methodological (differences in primary and secondary efficacy endpoints used in the clinical trials and the way the clinical trials were actually executed) rather than differences due to dose. It is worth reiterating that rh-GH, at the subcutaneously administered dose of 0.1 mg/kg/d, was shown to be safe and effective when assessed under the experimental conditions in Study IMP20317. The reviewer believes that if issues such as replicability/generalizability, and adequacy of the primary endpoint of efficacy are resolved, the issue of the dose recommendation might be resolved by the sponsor agreeing to a Phase IV commitment to assess the efficacy of low-dose rh-GH in the treatment of SBS, under a mutually agreeable, well-designed trial.

IX. Use in Special Populations

Although it is always important to address questions regarding use in special populations, short bowel syndrome is an orphan indication. The total number of SBS patients who were totally IPN-dependent who were randomized into one of the 3 arms of Study IMP20317 and received test medication was too small (n = 16). For this and other reasons, evaluation of the use of the drug in special populations is not very helpful.

It is worth noting that the currently approved Package Insert, PHARMACOKINETICS Section, includes information on Pediatric Patients, Gender, those with Renal Insufficiency, and those with Hepatic Insufficiency; but data for race are not available. In addition, in the PRECAUTIONS Section, Information on Pregnancy, Nursing Women, Pediatric Use and Geriatric Use, is already included.

X. ADDITIONAL ISSUES

There are three additional issues, already noted throughout this review, that are worthy of further discussion.

The first is the reduction in Total IPN volume, in liters per week, as the primary endpoint of efficacy. **The second** is the **contribution of glutamine** as co-therapy and **the third** is the role of the specialized diet. After all, the proposed (additional) use in the

INDICATIONS AND USAGE Section of the labeling reads "...*for the treatment of Short Bowel Syndrome in patients receiving specialized nutritional support. Serostim® therapy should be used in conjunction with optimal management of Short Bowel Syndrome".*

- Long-term Total Parenteral Nutrition (TPN) is a supportive rather than curative therapy but **it is life-sustaining and remains the current standard of care for patients with severe SBS.** In addition to extraordinary costs, it is very important to recognize the complications that may accompany TPN . These complications include hepatic dysfunction, progressive renal insufficiency, bone demineralization, catheter sepsis, and numerous nutrient deficiencies. **There is no question that weaning a patient off TPN therapy is a very significant clinical achievement.** But if one were to demand this as an endpoint, **is this expecting too much of the drug?** One question raised by the data in NDA 21-597 is: **in the absence of data demonstrating that patients are weaned off TPN, what is considered a clinically important reduction in Total IPN volume (primary efficacy endpoint) and a reduction in Total IPN calories and IPN or SLE Frequency (secondary efficacy endpoints)?**
- As mentioned in Section I of this review, **glutamine (GLN) exerts important morphological and functional effects on the bowel**. These effects appear to be similar to those of GH. GLN is a major fuel source for both the enterocytes and the colonocytes [52] and **this amino acid is necessary for the maintenance of intestinal structure.** In critically ill patients unable to take adequate enteral nutrition , the addition of GLN to standard TPN solutions prevent TPN-induced gut permeability[53]. Enteral rather than parenteral GLN has also been shown to induce trophic or regenerative effects on the bowel[54]. **But, based on many publications, the effects of GLN in the clinic appear inconsistent.** In addition, based on evaluations by Dr. D. Price, FDA Statistician, in Study IMP20317, actually, **the contribution of glutamine to the effect observed with growth hormone was not substantial. Based on these data, the MTL's recommendation is that, if the aim of the treatment is to achieve the best results, rh-GH should be administered in co-therapy with glutamine rather than alone.**
- The current recommendation is to maintain patients with SBS with residual colon on a high-carbohydrate, low-fat diet. Such a diet results in greater caloric absorption than a high-fat, low-carbohydrate diet because **malabsorbed CHOs are salvaged in the colon,** whereas malabsorbed fatty acids are not. In addition, **fat restriction enhances mineral absorption and decreases oxalate hyperabsorption.** However, in the experience of many investigators, **patients dislike low-fat diets** and **sometimes need to consume fat in order to maintain their weight.** It is worth noting that a high-fat diet did not increase fecal weight in SBS patients with residual colon in comparison to high-CHO diets. Indeed, the evidence supporting a low-fat diet is based on short-term balance studies, **where compliance is demanded,** rather than on body weight

[52] Souba WW, et al. Glutamine metabolism by the intestinal tract. JPEN 9: 608-617 (1985)
[53] VanderHulst RRJ et al. Glutamine and the preservation of gut integrity. Lancet 341: 1363-1365 (1993).
[54] Klimberg VS et al. Prophylactic glutamine protects the intestinal mucosa from radiation injury. Cancer 66: 62-68 (1990); Klimberg VS et al. Oral glutamine accelerates healing of the small intestine and improves outcome after whole abdominal radiation. Arch Surg. 125: 1049-1055 (1990)

response to various dietary prescriptions, **where compliance is questionable**. A well-designed, well-executed trial concluded that **conjugated bile acid replacement therapy should be part of the armamentarium for the treatment of selected patients with the short bowel syndrome.**[55]

- Although further studies are needed before the composition of a standard diet can be recommended (and this may depend upon the patient's nutritional status), **the important issue concerning the use of an SOD in Study IMP20317 is standardization of the nutrient/caloric intake so that it cannot be considered a potentially confounding variable.** This subject matter is further addressed in Dr. Price's statistical review.

XI. Highlights of June 25, 2003 Meeting of GI Advisory Committee to FDA

A. GENERALITIES

The Gastrointestinal Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met June 25, 2003. On this day, the Committee discussed new drug application (NDA) 21-597, Serostim® (somatropin), Serono Inc., for the treatment of Short Bowel Syndrome in patients receiving specialized nutritional support. Welcome and opening comments were provided by Robert Justice, M.D., Director, Division of Gastrointestinal and Coagulation Drug Products

Presentations by Serono Inc., representatives included those by Pamela Williamson Joyce, (VP, RA&QA; Introduction and Regulatory History); Dr. Douglas W. Wilmore, (Harvard; Short Bowel Syndrome (SBS): Unmet Medical Need); and Dr. Joseph Gertner (VP; IMP 20317 Efficacy and Safety: SBS Phase III Clinical Study). The FDA Clinical Summary presentation was given by Dr. Hugo E. Gallo-Torres (Medical Team Leader, GI Drugs). There were two Public Speaker participants, Ms. Brenda Bobitt (an SBS patient) and Dr. Thomas Ziegler (Emory University). The Charge to the Committee was provided by Dr. Robert Justice (Director, HFD-180). Because they are pertinent to the use of rh-GH in SBS patients, comments provided by Drs. Wilmore and Ziegler are briefly summarized below.

B. Dr. D. W. Wilmore's presentation

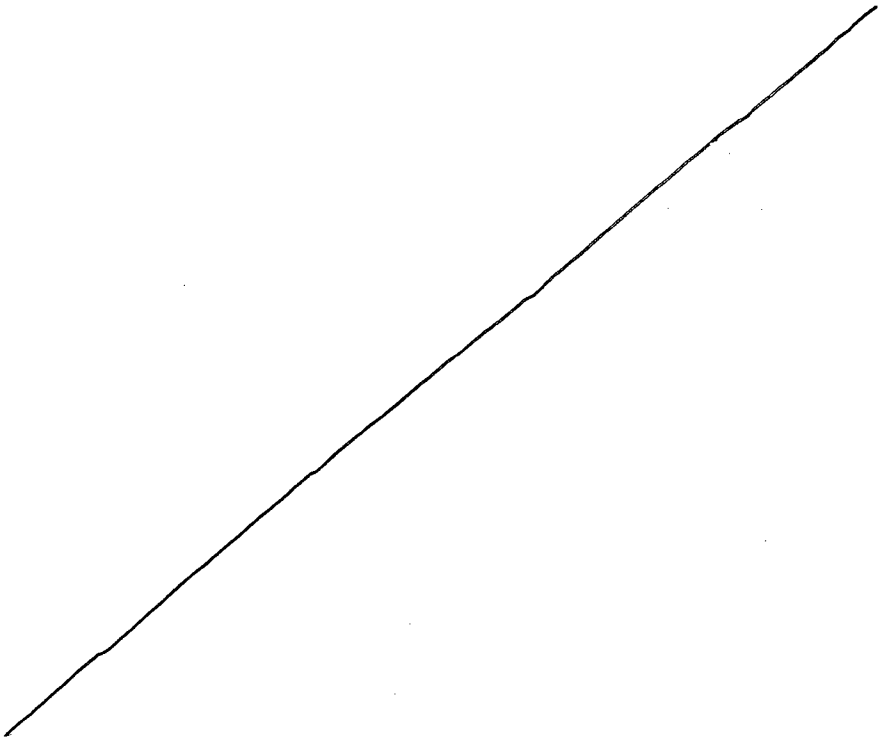
After defining SBS, mentioning its causes and characteristics, Dr. Wilmore gave a historical evolution of the care of patients with this syndrome. There were no mojor therapies before the 1960s, TPN was introduced in 1970, bowel rehabilitation in 1985 and intestinal transplantation in the late 1980s. But there are problems with the current approaches. These problems include the fact that PN does not enhance bowel function, L-T PN is expensive, diminishes quality of life, restricts patients' life style and may be associated with serious complications, while intestinal transplantation remains an evolving therapy with rather limited application. Dr. Wilmore then referred to the concept of ***Intestinal Rehabilitation,*** defined as a program to optimize

[55] Gruy-Kapral C et al. Conjugated Bile Acid Replacement Therapy for Short-Bowel Syndrome. Gastroenterology 116: 15-21 (1999)

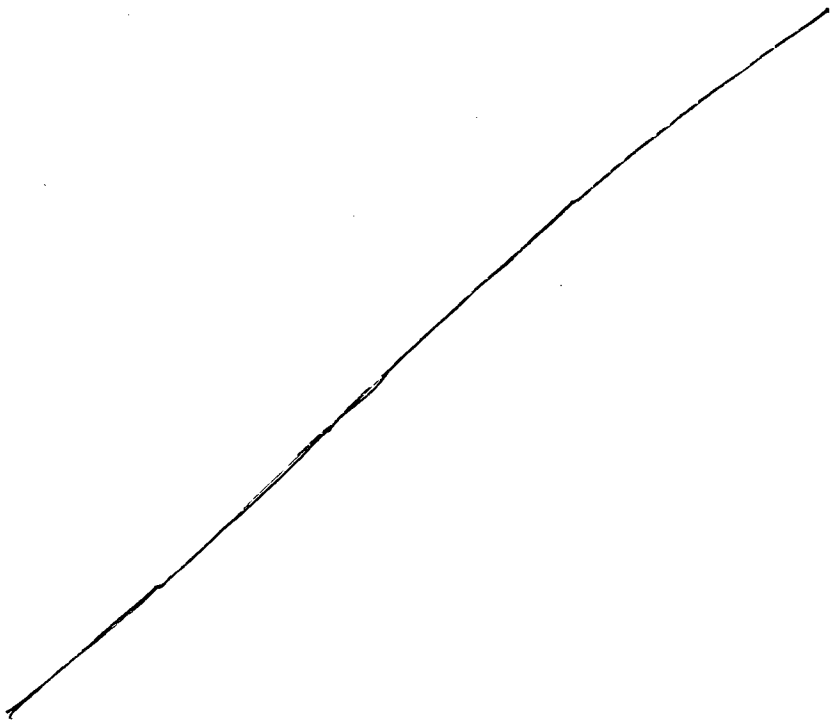
diet, and to provide appropriate nutrient and growth factors to allow increase in the adaptive response. Possible mechanisms of action of GH, the role of glutamine, and pilot studies with GH were described next. These included 15 y experience at Brigman & Women's Hospital with GH in the treatment of SBS and several publications detailing results of this therapeutic approach. Dr. Wilmore concluded that a well-controlled, well-executed study (IMP20317) was needed to confirm the initial (open label) findings and that the proposed therapy has an appropriate benefit/risk profile.

C. Presentation by Dr. Thomas R. Ziegler: Summary

Dr. Ziegler, from the Division of Endocrinology and Metabolism, Emory School of Medicine, in Atlanta, referred to an on-going study with the sponsor's rh-GH in patients with SBS. The study, entitled *"Intestinal Adaptation in Human Short Bowel Syndrome: Potential Molecular Mechanisms and the Influence of Recombinant Growth Hormone Administration"*, is being carried out under



[56] Most of the information included in the current review originates from the 10/10/02 Annual Report.



D. GI AC Responses to Agency Questions

In the materials that follow, each of the 6 questions posed by the Agency is listed. These questions incorporate descriptive Tables, when appropriate. The actual voting by the Committee members is given next. This is in turn followed by a reviewer's NOTE with comments on the subject matter, in an attempt to reflect the salient concerns expressed by the Committee discussants. The reviewer's notes also take into consideration the Serono's response(s) [submission of July 15, 2003]to the comments and recommendations made during the June 25th AC meeting.

Question 1

The primary endpoint of this study was change in Total IPN volume from week 2 to week 6. Pairwise comparisons of results of the primary endpoint yielded statistically significant differences between the recombinant human growth hormone (rh-GH)-containing arms and the control group. Are the findings in the table below clinically meaningful? In your response consider the definition of the primary endpoint and the duration of study treatment.

Changes in Total IPN Volume

Mean Change in Total IPN Volume			Difference in Total IPN Volume [L/wk] (p-value)	
Group A rh-GH (n=16)	Group B rh-GH + GLN (n=16)	Group C GLN (n=9)	Group B vs C	Group A vs C
-5.9	-7.7	-3.8	-3.9 (<0.001)	-2.1 (0.043)

Baseline IPN Requirements:
Group A: 10.3 L/wk
Group B: 10.5 L/wk
Group C: 13.5 L/wk

Vote on Question 1: *Yes = 6* *No = 3*

COMMENTS

- Following lots of deliberations, which included the definition and selection of the primary endpoint and the 4-week duration of study treatment, the Committee answered the most critical FDA question in the positive. There was general agreement that a 3.9 L/wk (and for that matter, even a 2.1 L/wk) ***reduction of the total IPN volume burden,*** shown to be ***statistically significant*** (adjusted p-values) in Study IMP20317, is ***also clinically significant.*** The discussions included the effects of glutamine and the fact that considerably better results were obtained when rh-GH was administered in co-therapy with glutamine rather than alone.

- The reviewer agrees with the sponsor that acceptance of reduction of the total IPN volume burden as the primary efficacy endpoint is consistent with the AGA position [see Reference under Footnote 7 to page 11 of the current review] which states: ***"The goal of the medical therapy is for the patient to resume work and a normal lifestyle, or as normal of one as possible. This is undertaken via the use of specific measures to gradually decrease the requirements for TPN, and at best, to eliminate its need".*** As discussed throughout the current review and during his presentation to the AC, the reviewer believes that some patients receiving rh-GH for four weeks, may be completely weaned from IPN, lipids, and I.V. hydration and this is good. But requiring this as the primary endpoint might be asking too much of the drug.

Question 2

Secondary endpoints were change in Total IPN calories and change in IPN or lipid frequency. Pairwise comparisons of the results of these secondary endpoints yielded statistically significant differences between the rh-GH-containing arms and the control

group. Are the findings in the table below clinically meaningful?

Secondary Efficacy Analysis

Treatment Groups				
Group A rh-GH (n=16)	Group B rh-GH + GLN (n=16)	Group C GLN (n=9)	Group B vs C	Group A vs C
Change in Total IPN Calories [kcal/wk] / (p-value)				
-4338.3	-5751.2	-2633.3	-3117.9 (<0.001)	-1705.0 (0.005)
Change in IPN or Lipid frequency [d/wk] (p-value)				
-3.0	-4.2	-2.0	-2.2 (<0.001)	-1.0 (0.025)

Vote on Question 2: *Yes = 6* *No = 3*

COMMENTS

- The Committee's vote reflects the fact that this question is the flip side of question 1. During the Committee's discussions on question 1 it was made clear that, the secondary endpoints go hand in hand with the primary one. In other words, for a reduction in total IPN volume to be clinically meaningful, it needs to be associated with a concomitant proportionate reduction in infusion time as well as frequency. One of the AC discussants commented that it is important to decrease the amount of time the patient is hooked up to a machine. The more calories one is infusing, the greater the risk of some sort of TPN-associated liver complications. It is not just a mobility issue. Certainly reducing the infusion volume is intrinsical beneficial. The reviewer agrees with the concept that, from the patient's perspective, even a reduction of one infusion per week, as that seen when using rh-GH alone (no glutamine co-therapy) is to be considered clinically significant. It is however important to reiterate that, according to the data in Study IMP20317 and as illustrated in the above-displayed Table, the analysis of results of secondary endpoints just as those of the primary endpoints, demonstrate that rh-GH is twice as effective when given in co-therapy with glutamine rather than alone.

Question 3

The primary endpoint was change in Total IPN volume. Only 1 of the 3 components

(IPN volume) was recorded between week 6 and 18. Is the measurement of IPN volume adequate to demonstrate durability of effect?
If not, what do you recommend as a minimum follow up period?

Vote on Question 3 *Yes = 4* *No = 5*

COMMENTS

It took considerable discussion and clarification of uncertainties about the question to realize that this is a question of durability not maintenance, of effect. It is important to clarify that although the question of durability is a good one, Study IMP20317 was set to assess the efficacy and safety of a 4-week course of rh-GH, either alone or in co-therapy with glutamine in SBS patients. It was not the objective of the trial to determine durability. The reviewer believes that the methods to assess durability post hoc are inadequate due to a number of reasons pointed out during the discussion on the subject matter at the AC meeting. These limitations include the small size of the trial, the primary and secondary parameters of evaluation and the frequency of determination of these parameters, the source of weight loss experienced by patients, the lack of evaluation of clinically meaningful nutrition parameters, among others.
The Committee's recommendation of a minimum follow up period varied from 6 months to two years.

Question 4

The data were primarily derived from a single, nutritional support tertiary care center. Are these data generalizable to the population of short bowel syndrome patients?

Vote on Question 4: **Yes = 2** **No = 7**

COMMENTS

There was considerable discussion and request for Agency clarification regarding the question of one Study (IMP20317) that has not been replicated and the applicability of the findings in one specialized center in Boston to the rest of centers and SBS patients in the United States. The initial voting on this question was 4 Yes and 5 No. Although some Committee discussants felt that there was a need to have the pivotal Clinical Trial reproduced with a confirmatory study, the reviewer believes that the issue of replicability/generalizability has been, to a large extent, satisfactorily addressed .
The following are among the reasons in support of the above-mentioned statement. First, the 41 SBS patients study is the largest ever carried out and this is remarkable if one considers that one is dealing with an orphan indication. Second, from the AC presentations (all parties) and subsequent deliberations, it was clear that the actual design of the protocol, including study population , assessment of endpoints and prospectively stipulated analyses, left little if any doubt that the study was well-designed and, apparently, well-executed; consequently, the data from this trial are valid. Third, the pre-referral treatment was performed by the referring physicians; this was done outside of a residential treatment setting. Fourth, the 41 participating patients were

geographically dispersed across 26 US states and 2 foreign countries; it is important to note that this is a rare condition and that although it would be nice always to have a second confirmatory trial, this is not practical. Fifth, SBS was diagnosed by standard and consistent norms, by now postulated in the AGA Technical Review. Finally, several members of the AC recommended to explore the possibility of continuing education, use of support and training materials, and many other appropriate communication tools, for both, patients and physicians. The reviewer believes that this is a reasonable approach when any new treatment option is made available [see Recommendations for Regulatory Action].

Question 5

Are there specific safety concerns considering the potential for long-term use of rh-GH in the treatment of short bowel syndrome patients?

Vote on Question 5: *Yes = 6* *Abstentions = 3*

COMMENTS

It is important to note that the question refers to long-term, not short-term use. The former would be off-label since the clinical data was of 4-weeks duration only and there is no information that can be used in support of the hormone long-term for the SBS indication. There was near unanimous agreement that there were no safety concerns about the use of the hormone for the 4-weeks sought by the sponsor. The reviewer believes that long-term safety is of concern, mainly because of the lack of information and that long-term safety must be considered in the risk-benefit appraisal. However, it is also important to note that the sponsor is not asking for long-term use, just 4 consecutive weeks.

Question 6

Do the data support the safety and effectiveness of rh-GH alone or in co-therapy with glutamine in patients with short bowel syndrome?
Are there any additional studies that you would recommend, e.g., dose finding?

Vote on Question 6: *Yes = 3* *No = 6*

COMMENTS

As mentioned under the Generalities Subsection of this section of the current review, this question was rephrased after Agency clarification on the several possible answers was provided. It is to be noted that some members of the Committee commented that the data from Study IMP20317 was indeed robust and, as mentioned above, both statistically as well as clinically significant. Others, however, felt that although generally there were data to support safety, especially short-term, the endpoint [lack of evaluation of clinically meaningful nutrition parameters] had not met the criteria for efficacy. One member commented that he thought of

Study IMP20317 as a Phase II trial and that there was need to do a Phase II, definitive Study. As noted in the comments to the questions above, this reviewer does not necessarily agree with these conclusions and recommendations. On the other hand, certain Committee's recommendations may be helpful in formulating the Agency's Regulatory Action. These recommendations included the need to gather follow-up data on multiple time points for at least one year, more information on dose findings and possible repeated administration of the drug, additional information using as primary study endpoint the successful [complete] weaning from IPN, post-marketing surveillance, and patient monitoring. The Educational Programs for both, patients and physicians, including support of a web based program for clinicians as well as patients, already commented above in relation to question 4, were reiterated. But, as far as this reviewer is concerned, the Committee was unclear as to what should be done before approval and what may be requested as part of a Phase IV commitment.

XII. Conclusions

The sponsor of NDA 21-597 has presented evidence from a single, 41-patient study that subcutaneously administered rh-GH, at the daily dose of 0.1 mg/kg for 4 weeks, effectively reduces the total IPN volume requirement in IPN-dependent SBS patients. **This primary endpoint of efficacy [reduction in Total IPN volume requirement per week] is both statistically and clinically significant.** Further results of these studies demonstrated that subcutaneously administered rh-GH, at the daily dose of 0.1 mg/kg for 4 weeks, effectively reduces the Total IPN calories per week and the IPN or lipid frequency (days per week). **These secondary endpoints of efficacy are both statistically as well as clinically significant.** There are no specific safety concerns for the sought length of treatment (daily subcutaneous administration for 4 weeks). However, owing to the very likely and realistic off-label use and primarily due to the lack of information, long-term safety is of concern. Therefore, long-term use must be addressed when considering the benefit /risk equation.

XIII. Recommendations for Regulatory Action

NDA 21-597 is approvable. Before the NDA is approved, deficiencies must be addressed. Attempts to address GI AC concerns should also be made.

A. Deficiencies that must be addressed before approval

1. **Educational Plan**
   The sponsor must provide a comprehensive educational plan for physicians prescribing the drug, ancillary personnel involved in the care of the SBS patient, notably specialized personnel such as **nutritionists** and other health care providers. The plan should include continuing education on all aspects of the clinical condition as well as all aspects of the preferred treatment regimen [rh-GH in co-therapy with glutamine]. The sponsor's plan must include training materials, communication, all kinds of support of these patients and a periodical appraisal of the success of the plan. Potential remedies in the event the Plan is failing should also be prospectively stipulated.
2. **Additional Data in Support of replicability/generalizability**
   To further document short-term efficacy and safety of the drug under different clinical settings but with Protocol designs similar to IMP20317, and in an

attempt to address other issues such a dose-response, the sponsor might elect to analyze literature publications where the results of the trials were similar to those in IMP20317. Note that for this information to be useful, the emphasis should be in studies using not only the Serono rh-GH product but also the proposed Serono regimen. In addition, whenever possible, source documents should be obtained.

3. **Initial Data in Support of Durability of Effect**
   It is to be noted that neither durability nor repeated cycle effects were pre-stipulated objectives of Study IMP20317. It is however of interest to attempt to answer the question of how long does the benefit last after the recommended 4-week continuous daily treatment. An initial answer to this question might be obtained by surveying the status of the patients that were randomized into this trial. The objective of this survey is to assess the ability of these SBS patients to wean off home parenteral nutrition after a successful intestinal rehabilitation program in Study IMP20317. The data to be collected should include information on the daily IPN prescription for 6, 12 and up to 24 months after discharge. The quality and thereby the usefulness of this information, including its potential impact on labeling, is a matter of review.
4. **Additional work in progress**
   The sponsor should be asked to update the information from a recent publication[57] presented at the time of the June 25, 2003 GI AC meeting. This research, which uses the Serono rh-GH, is being carried out by Dr. Jieshou Li of Nanjing, China. A translation of the entire manuscript-including data from 37 patients, 27 n the previous publication, 10 in the update[58]-should be submitted. The information to be submitted should include the demographic data, the small intestinal length of participating patients, with information on the ileo-cecal valve and colon, time since diagnosis of SBS, and the actual treatment per patient [amount and regimen of rh-GH, amount of oral glutamine per kg per day] and other aspects of nutritional support (amount of kcal per day from enteral nutrition, and amount of carbohydrate and fat in the diet). Parameters of evaluation should include nitrogen balance, plasma levels of proteins, intestinal absorptive capacity, and the number of patients who were weaned off parenteral or enteral nutrition completely and were able to live on a well-tolerated high-carbohydrate low-fat diet, so as to get an idea of durability of effect.

B. Phase IV Commitments

No Phase IV commitments are being requested.

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Hugo E. Gallo-Torres, MD, PhD, PNS
Medical Team Leader (GI Drugs)
HFD-180

[57] Zhu W. et al. Rehabilitation therapy for short bowel syndrome. Chin Med 115(5):776-778 (2002)
[58] Zhu W. et al. Effect of recombinant human growth hormone and enteral nutrition on short bowel syndrome. Manuscript in preparation. Co-authors : J. Li and N. Li.

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/s/

Hugo Gallo Torres
8/26/03 11:49:39 AM
MEDICAL OFFICER

Executive Summary Section

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: **October 17, 2003**

TO: **DIVISION FILES: NDA 21-597**
Serostim® [somatropin (rDNA origin)] for injection
Applicant: Serono, Inc.
Rockland, MA 02370

THROUGH : **Robert Justice, MD**
Director
Division of Gastrointestinal/Coagulation Drug Products
HFD-180

FROM: **Hugo E. Gallo-Torres, MD, PhD, PNS**
Medical Team Leader, Gastrointestinal Drugs
Division of Gastrointestinal/Coagulation Drug Products
HFD-180

SUBJECT: **Review of Additional Information in Support of the Recommendation for Approval of NDA 21-597 for the following indication:**
"Treatment of Short Bowel Syndrome in patients receiving specialized nutritional support. Serostim® therapy should be used in conjunction with optimal management of Short Bowel Syndrome."

Included in this memorandum are: a critical review of additional information in support of NDA 21-597 submitted by Serono on August 27, 2003; salient points from discussants partaking in the June 25, 2003 deliberations around the six specific questions posed to the GI AC; and highlights from the first cycle Medical Officer's review, from which an **approvable** recommendation ensued. Since no major issues regarding efficacy or safety remain, and a comprehensive and sound Educational Plan is being set up to begin in the near future, **approval** of Serostim® for the treatment of short bowel syndrome in patients receiving specialized nutritional support is recommended.

Medical Team Leader Review of Additional Information in Support of NDA 21-597

Table of Contents

Medical Team Leader Review of Additional Information in Support of NDA 21-597

I. Executive Summary

Recommendations

A. Recommendation and Conclusion on Approvability

-- NDA 21-597 should be approved.

B. Recommendation for Phase 4 (Post-Marketing) Commitment

-- The sponsor is developing and already setting up an Educational Plan for prescribers, ancillary personnel involved in the care of the SBS patient, such as nurses and nutritionists, and SBS patients themselves. After final documents are accomplished, which include training materials, communication, all kinds of support of these SBS patients and a periodical appraisal of the success of this program, the plan should start within four months of drug approval.

Serostim® [somatropin (rDNA origin)], a form of growth hormone produced by recombinant DNA technology, is already marketed for the treatment of AIDS wasting or cachexia. Through NDA 21-597, Serono, Inc. is seeking approval of the product for the treatment of Short Bowel Syndrome (SBS) in receiving specialized nutritional support. This is a new indication. There are no drugs approved for the treatment of SBS but trophic hormones/peptides and glutamine are part of the physician's armamentarium.

SBS occurs when there is < 200 cm of bowel remaining[1]. The control of gut growth and adaptation is complex. Following a large resection of small intestine, food intake increases (hyperphagia) to cope with malabsorption. Structural and functional adaptation occurs in the ileum after a predominantly jejunal resection. Intestinal failure occurs when there is reduced intestinal absorption so that macronutrients and/or water and electrolyte supplements are needed to maintain health and or growth. There are two common types of patients with short bowel: those with jejunum in continuity with a functioning colon and those with jejunostomy. Patients with SBS, especially those without a colon, present challenging management problems because the latter patients cannot derive energy from the colonic anaerobic bacterial fermentation of CHOs to short-chain fatty acids. By manipulating the diet and maximally utilizing the remaining intestine, some patients can maintain or improve their nutritional status. Patients with SBS are usually managed in a Specialized Unit, but treatment at home is now a real possibility. Home Parenteral Nutrition [HPN] is a sophisticated and costly treatment given for acute or chronic intestinal failure. HPN provides the opportunity for people to live in their own homes.

From the review of the originally submitted evidence, the Medical Reviewer concluded that the

[1] This could be the result of Crohn's disease, volvulus, intestinal obstruction, infarction of the mesenteric artery, thrombosis of the mesenteric artery or vein, etc.

sponsor of NDA 21-597 had presented evidence from a single, 41-patient study that subcutaneously administered rh-GH, at the daily dose of 0.1 mg/kg for 4 weeks, effectively reduces the total IPN volume requirement in IPN-dependent SBS patients. **This primary endpoint of efficacy [reduction in Total IPN volume requirement per week] is statistically significant.** Further results of these studies demonstrated that subcutaneously administered rh-GH, at the daily dose of 0.1 mg/kg for 4 weeks, effectively reduces the Total IPN calories per week and the IPN or lipid frequency (days per week). **These secondary endpoints of efficacy are both statistically significant.** The initial review identified several issues that needed to be addressed, clarified, and eventually resolved before the application is approved. These issues, which included the clinical validity/relevance/importance of the protocol-stipulated primary endpoint of efficacy, replicability, generalizability, further exploration of dosing, durability of effect, and long-term safety, were discussed at the June 25, 2003 meeting of the GI Advisory Committee to the FDA. As discussed in detail in the text of the current review, the Committee members deliberated and voted on six specific questions posed at the Committee. The reviewer believes that the first and foremost AC contribution was the answer to Questions 1 and 2 concluding that, in addition to being statistically significant, the changes in primary as well as secondary evaluation parameters associated with the rh-GH-containing arms of the trial were **clinically significant.**

The division's regulatory action was approvable. The sponsor was asked to further address issues of replicability/generalizability, provide follow-up information on the 41 patients treated in Study IMP20317 in support of durability of effect, and to develop an Educational Plan. The sponsor's responses to these requests are reviewed in the present document. Data from 37 patients given the Serono GH and treated by Drs. Li and Zhu in China are non-contributory because these are follow-up open-label, non-randomized, non-comparative observations are not designed to minimize bias. The statistical meta-review of published literature on SBS uncovered a variety of clinical designs and use of endpoints that could not be linked to the primary efficacy parameter used in the sponsor's pivotal trial. Nonetheless, based on the following, the reviewer believes that replicability/generalizabilty has been demonstrated:. 1) the 41 SBS patients study is the largest ever carried out and this is remarkable if one considers that one is dealing with an orphan indication; 2) it is clear that the actual design of the protocol leaves little if any doubt that the study was well-designed and, apparently, well-executed; 3) the pre-referral treatment was performed by the referring physicians; 4) the 41 participating patients were geographically dispersed across 26 US states; and 5) SBS was diagnosed by standard and consistent norms. The data on durability of effect [Study 24236] are very incomplete and not helpful. Serono is developing and has already begun to set up a Phase IV sound and appropriate Educational Plan.

There are no overt safety concerns for the sought length of treatment (daily subcutaneous administration for 4 weeks). However, owing to the very likely and realistic off-label use and primarily due to the lack of information, long-term use of the drug in these chronically ill patients, must be addressed when considering the benefit /risk equation.

Since no major safety or efficacy issues remain, approval of Serostim® for the treatment of Short Bowel Syndrome in patients receiving specialized nutritional support [NDA 21-597] is recommended

II. Introduction/Background Information

Serostim® [somatropin (rDNA origin) for injection], **abbreviated in this memorandum as rh-GH**, is a **human growth hormone** produced by recombinant DNA technology. Its amino acid sequence and structure [2]are identical to the dominant form of human pituitary growth hormone.[3]

Somatropin (somatotropin) belongs to the class of growth hormones (GH). Somatotropin is a species-specific **anabolic protein** that **promotes somatic growth, stimulates protein synthesis, and regulates carbohydrate and lipid metabolism**. Somatotropin is secreted by the anterior pituitary under the regulation of the hypothalamic hormones, **somatoliberin** and **somatostatin**; it also increases serum levels of **somatomedins.** GHs from various species differ in amino acid sequence, antigenicity, isoelectric point, and in the range of animals in which they can produce biological responses.[4]

The sponsor's Serostim® [somatropin (rDNA origin)] is approved for the **treatment of AIDS wasting or cachexia**. According to the labeling for this product, this is an indication based on analysis of surrogate endpoints in studies of up to **12 weeks in duration.**[5] The sponsor also manufactures another form of GH. The brand name for this form is SAIZEN® [somatropin (rDNA origin) for injection], for subcutaneous or intramuscular injection. SAIZEN® is indicated for the **long-term treatment** of children with growth failure due to inadequate secretion of endogenous growth hormone.

Through **NDA 21-597**, submitted on 31 October, 2002, the sponsor is seeking approval of the product for a **new indication**, ***"treatment of Short Bowel Syndrome in patients receiving specialized nutritional support".*** It is to be noted that the newly proposed indication includes the following additional wording: ***Serostim® therapy should be used in conjunction with optimal management of Short Bowel Syndrome.***

The indication being sought by the sponsor is **short bowel syndrome (SBS),** a condition arising from the loss of the small intestine's ability to compensate and functionally adapt after loss of a significant amount of surface area. [It is well accepted that **resection of > 50% of the small bowel** is associated with symptoms that can often be disabling, socially incapacitating, or even life-threatening].

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[2] Human GH consists of a single polypeptide chain of 191 amino acids having the normal structure of the principal growth stimulating hormone obtained from the anterior lobe of the human pituitary gland.

[3] Serostim® is produced by a mammalian cell line (mouse C127) that has been modified by the addition of the human GH gene. Serostim® is secreted directly through the cell membrane into the cell culture medium for collection and purification. Serostim® is highly purified preparation. **Biological potency is determined by measuring the increase in the body weight induced in hypophysectomized rats.**

[4] There exist human GH, methionyl human GH, bovine somatotropin, porcine somatotropin, among others.

[5] The product information notes that, for patients treated in open-label extension studies, **no significant additional efficacy** was observed beyond 12 weeks. There are no data available from controlled studies for patients that start, stop, and re-start treatment. Concomitant anti-viral therapy is necessary. The Product Information also notes that the continued use of Serostim® treatment should be reevaluated in patients who continue to lose weight in the first two weeks of treatment.

SBS occurs when there is **<200 cm**[6] **of bowel remaining.**[7,8] **Loss of intestinal function can be complete or partial.** ***Intestinal Failure*** is defined as **"reduced gastrointestinal absorption to the extent that macronutrients and/or fluid supplements are required"**, a concept that includes the need for enteral or parenteral supplements to maintain a normal nutritional state.[9] **Intestinal failure** may be described as **acute (usually reversible)** and **chronic (when long-term treatment over weeks, months, or longer is required, especially if continued treatment is needed at home)**. Patients who are unable to increase their oral intake sufficiently or are unable to absorb sufficient energy despite significantly increased intake, are defined as patients with intestinal failure and require **parenteral nutrition support**. A **standardized diet** may be useful for clinically defined functional SBS. For example, one recommendation is to maintain patients with SBS with residual colon on a **high-carbohydrate, low-fat diet.**[10] **But in reality there are insufficient data with regard to what the composition of the so-called standardized diet optimally should be.**

Signs and symptoms of SBS include electrolyte disturbances; deficiencies of calcium, magnesium, zinc, iron, vitamin B_{12}, or fat-soluble vitamin deficiency; malabsorption of carbohydrates, lactose and protein; metabolic acidosis, gastric acid hypersecretion; formation of cholesterol biliary calculi and renal oxalate calculi; and dehydration, steatorrhea, diarrhea, and weight loss. Non-specific approaches[11] to SBS include increasing the absorption of sodium by sipping a sodium-glucose solution, reducing stomal loss by restricting water or low-sodium drinks. If a stoma is situated less than 100 cm along the jejunum, a constant negative sodium balance may necessitate parenteral saline supplements. Gastric antisecretory drugs or a somatostatin analog (**off-label use**) reduce jejunostomy losses in such patients but do not restore a positive sodium balance. Loperamide or codeine phosphate benefit some patients. Magnesium deficiency can usually be corrected by oral magnesium oxide supplements.
It is worth noting that **thorough nutritional management is necessary** in the early stages, as is **replacement of excess fluid and electrolyte losses**. Recommendations regarding the need for parenteral nutrition vary depending on the presence or absence of certain factors: ***the ileocecal valve, jejunum, and functional colon***. **Patients with residual small bowel of 100 cm or less usually require the administration of parenteral nutrition at home [HPN = Home Parenteral Nutrition].**
The other aspect of SBS management consists of ***enhancing the natural intestinal adaptation response***. Although the mechanisms of intestinal adaptation are not entirely understood, they can be grouped into three broad categories: **luminal nutrition, hormonal factors, and pancreatobiliary secretion.** Animal models of SBS have suggested several gut hormones are

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[6] This is an approximate length as most methods of residual intestine measurement (such as radiologic contrast studies, pathology of the resected specimen. and perioperative measurement of unweighted intestine) are not especially accurate. **Because absorption is related to the amount of residual intestine, it is more important to document the amount of remaining, viable intestine.**
[7] Those patients at greatest nutritional risk generally have a duodenostomy or a jejunoileal anastomosis with **<35 cm** of residual small intestine, jejunocolic or ileocolic anastomosis with < 60 cm of residual small intestine, or an end jejunostomy with <115 cm of residual small intestine
[8] Buchman, A.L. et al. AGA Technical Review on Short Bowel Syndrome and Intestinal Transplantation. Gastroenterology 124:1111-1134 (2003)
[9] Malabsorption of a single nutrient, such as vitamin B_{12} or the need for a special diet to exclude a damaging component such as gluten, is not included within this definition.
[10] **Such a diet results in greater caloric absorption than a high-fat, low-carbohydrate diet because malabsorbed carbohydrates are salvaged in the colon whereas malabsorbed fatty acids are not. In addition, fat restriction enhances mineral absorption and decreases oxalate hyperabsorption.**
[11] Lennard-Jones, J.E. Review article: practical management of the short bowel. Aliment. Pharmacol. Ther. 8:563-577 (1994).

involved in post-resection intestinal adaptation. These include enteroglucagon, glucagon peptide II, epidermal growth factor, **growth hormone** ***[the subject of the current review],*** cholecystokinin, gastrin, insulin, and neurotensin.[12] Other therapies to enhance intestinal growth include fiber, **glutamine** ***(one of the components of the co-therapy being proposed by the sponsor)*** and aminoguanidine.

No therapy has been approved for the treatment of SBS.[13]

Following the FDA customary approach, the information submitted in NDA 21-597 was reviewed by the respective **specialty disciplines**. In conclusion, **there are no CMC issues**. Although no Pharmacology/Toxicology review for the current application will be carried out, a February 13, 1996 review by Dr. David H. Hertig (HFD-510), noted that, in general, **rh-GH was well tolerated in acute and sub-chronic and chronic toxicity studies.** The findings were mainly **extensions of the pharmacological properties of GH.**[14] Although there will not be a separate **Biopharm review**, Dr. Suliman Al-Fayoumi, an FDA reviewer in the Biopharm Division has provided insightful remarks, worth reiterating here. The available data indicate that **subcutaneous absorption is slow and rate-limiting.** Although no accumulation was observed following multiple dose administration of doses of 6 mg/d for 6 weeks, the **pharmacological markers** determined in the study (**IGF-1 and IGFBP-3**) were significantly higher at 6 weeks relative to the first dose. rh-GH is primarily eliminated via kidneys where it undergoes glomerular filtration, then it is cleaved within the renal cells and the resulting peptides and amino acids are subsequently reabsorbed into the systemic circulation[15]. Available evidence suggests that rh-GH clearance is similar between adults and children. However, only a limited number of pediatric patients were included in the sponsor's clinical trials submitted in NDA 21-597. Both, the labeling for Saizen® [somatropin (rDNA for injection)] and that for Serostim® [somatropin (rDNA origin) for injection] state that elderly patients are more sensitive to growth hormone action, and may be more prone to develop adverse reactions. Thus, dose selection for an elderly patient should be cautious, **usually starting at the low end of the dosing range.** Formal *in vitro* and *in vivo* drug-drug interaction studies have not been conducted to evaluate the drug-drug interaction potential for rh-GH[16].

The following material on the **Clinical Program** includes summaries of the pivotal trial, with specific conclusions on efficacy, safety, dosing, and special populations. The **pivotal trial** consisted primarily of a 3-arm, 41 patient total, double-blind, randomized study **[Protocol IMP20317]**.This study was set to assess the effect of rh-GH administered in **co-therapy** with **glutamine** and a **specialized oral diet**, in the **improvement of residual gut absorptive function** in patients with short bowel syndrome. Although the trial was designed to be

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[12] Sham J. et al. **Epidermal growth factor** improves nutritional outcome in a rat model of short bowel. J. Pediatric Surg. 37:765-769 (2002)

[13] **Although no therapy has been approved for the treatment of this disease,** some of the hormones, available in the clinic for other indications or available for human use experimentally, are used in the treatment of SBS. **There are, however, little data on the role of either endogenous or exogenous hormones on intestinal adaptation in humans.** Similarly, there are very few studies using peptides to slow intestinal transit (e.g. peptide YY or an analogue) [Lennard-Jones, J.E. Review article: practical management of short bowel. Aliment. Pharmacol. Ther. 8: 563-577 (1994)].

[14] Dr. Jasti Choudary, Pharmacologist Team Leader, has concluded that the current application is **approvable.**

[15] Published reports indicate that patients with chronic renal impairment tend to have decreased rh-GH clearance relative to normal healthy subjects. Similarly, patients with severe hepatic impairment have been reported to exhibit reduced rh-GH clearance.

[16] Recent published results suggest that rh-GH induces UDPGT and CYP3A enzyme systems.

"multicenter" there were only 2 sites involved with patient recruitment and **one site randomized 3 patients only** (1 per treatment arm) while the other randomized a total of 38, in a 2:2:1 ratio. Consequently, **in the final analysis, this was a single-center study.** The protocol stipulated primary efficacy endpoint was the mean change **(decrease)** in Total IPN volume **(measured in liters per week)** from Week 2 to Week 6. In analyses of the Intent-to-Treat Study Population, a **statistically significant reduction in the Total IPN volume requirement** was noted in patients who received rh-GH + SOD[GLN] when compared to those receiving SOD + [GLN] plus rh-GH placebo. The therapeutic gain was **3.9 liters less** per week. Results of this comparison were also supported and confirmed in the statistical analyses of the Evaluable for Efficacy Study Population. Owing to the fact that **no clinical nutrition parameters of efficacy** were made use of in Study IMP20317, there remained questions **regarding the most adequate clinical tool (approach)** to demonstrate **clinically meaningful benefit of the drug** in the treatment of SBS in patients who are dependent on IPN. **There was uncertainty if a reduction of Total IPN volume requirement of 3.9 L/wk is clinically meaningful [This was one of the pivotal questions considered by the GI Advisory Committee on June 25, 2003, see below].**

During the NDA review, it was recognized **that an unquestionably meaningful and convincing clinical endpoint** is the proportion of patients that, as a result of the intervention [administration of rh-GH in co-therapy with GLN in patients receiving SOD] is **weaned completely from IPN. In addition, there is the question of durability. Further clinical significance would be achieved if the patients remain off IPN for at least 1 year** following admission into an in-home program [the matter of **durability of effect** was also discussed at the AC meeting, see below].

All in all, the review on **safety** revealed no overt safety concerns with the use of rh-GH in co-therapy with glutamine and a specialized diet in patients with SBS treated **for up to 4 weeks.**

From the review of the evidence, it was concluded that the safety profile of the **triple co-therapy** (rh-GH+SOD+GLN) appears to be similar to that of rhGH + SOD. As expected, the majority of AEs reported in pivotal trial IMP20317 were related to the underlying clinical situation (SBS patients who were on Total IPN). However, for completeness of information purposes, the reviewer included a brief account of some recently published information from patients that were given GH for long periods of time. [**Safety matters** were also discussed at the AC Meeting, see Section V. Summary/Conclusions, below].

Regarding **dosing,** some uncertainty remained about whether dose levels of GH lower than the proposed 0.1 mg/kg/d are more effective [a question on dose was also asked of the AC, see Section V. Summary/Conclusions, below]. Finally, because the total number of patients who had SBS and were randomized to the rhGH + SOD [GLN] arm **was so small** (n= 16), assessment of the use of the drug in **Special Populations** was not thought to be helpful.

From the initial review of the evidence, the Medical Officer reviewer concluded that several issues, listed below, need to be addressed, clarified and eventually resolved before NDA 21-597 is approved.

1. *Replicability* [results of only one trial of 41 patients (IMP20317) were submitted as part of NDA 21-597];
2. *Generalizability* [in the final analysis, the bulk of the patients in Study IMP20317 originated from one center only, and, due to known variations in the standard of care, **this center may or may not be representative of the general U.S. population**];
3. The *clinical validity/relevance/importance* **of the protocol-stipulated primary endpoint of efficacy [a reduction in the Total intravenous parenteral nutrition (IPN) volume requirements (measured in terms of L/wk)]**.[17]; and
4. ***Further exploration of dosing***[18].

Because of the above-listed questions and uncertainties regarding the efficacy data, the Division requested a meeting of the GI Advisory Committee to FDA[19]. The Gastrointestinal Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met June 25, 2003. On this day, the Committee discussed new drug application (NDA) 21-597, Serostim® (somatropin), Serono Inc., for the treatment of Short Bowel Syndrome in patients receiving specialized nutritional support. Key presentations included those by the following Serono Inc., representatives: Pamela Williamson Joyce, (VP, RA&QA; **Introduction and Regulatory History**); Dr. Douglas W. Wilmore, (Harvard; **Short Bowel Syndrome (SBS): Unmet Medical Need**); and Dr. Joseph Gertner (VP; IMP **20317 Efficacy and Safety: SBS Phase III Clinical Study**). The FDA **Clinical Summary** presentation was given by Dr. Hugo E. Gallo-Torres (Medical Team Leader, GI Drugs). There were two Public Speaker participants, Ms. Brenda Bobitt (an SBS patient) and Dr. Thomas Ziegler (Emory University). The Charge to the Committee was provided by Dr. Robert Justice (Director, HFD-180).

After defining SBS, mentioning its causes and characteristics, Dr. Wilmore gave a historical evolution of the care of patients with this syndrome. He then referred to the concept of ***Intestinal Rehabilitation,*** defined as a program to optimize diet and to provide appropriate nutrient and growth factors to allow increase in the adaptive response.[20] Dr. Wilmore concluded that a well-controlled, well-executed study (IMP20317) was needed to confirm the initial (open label) findings and that the proposed therapy has an appropriate benefit/risk profile.

Dr. Thomas R. Ziegler[21] referred to an on-going study with the sponsor's rh-GH in patients with SBS.[22] The study is set to evaluate the effects of mammalian cell-derived recombinant human

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[17] It was recognized that a clinically meaningful endpoint would be the proportion of patients that, as a result of the proposed intervention [administration of recombinant human growth hormone (rh-GH) in co-therapy with glutamine (GLN) in patients who are receiving a specialized oral diet (SOD)] are **weaned off IPN** and **remain off IPN long-term. But it was also recognized that using the latter as the primary efficacy endpoint may be asking too much of the drug.**

[18] A recent publication reported that **"low-dose"** rh-GH (**0.05 mg/kg/d**) ***increased*** intestinal absorption of energy, nitrogen and fat. In this study, body weight, lean body mass, D-xylose absorption, insulin-like growth factor 1 and insulin-like growth factor binding protein 3 **also increased.** The above summarized results were in contrast to those reported in another well-designed and apparently well-executed trial where **"high-dose"** rh-GH (**0.14 mg/kg/d**) and **glutamine *did not increase*** body weight, lean body mass, fat mass and bone mass significantly compared to placebo treatment.

[19] Detailed highlights of the June 25, 2003 Meeting of GI Advisory Committee to FDA are given in Dr. Gallo-Torres' review of NDA 21-597.

[20] Possible mechanisms of action of GH, the role of glutamine, and pilot studies with GH were described. These included 15 y experience at Brigman & Women's Hospital with GH in the treatment of SBS and several publications detailing with results of this therapeutic approach.

[21] From the Division of Endocrinology and Metabolism, Emory School of Medicine, in Atlanta.

[22] The study, entitled *"Intestinal Adaptation in Human Short Bowel Syndrome: Potential Molecular Mechanisms and the Influence of Recombinant Growth Hormone Administration"*, is being carried out under IND 49,745.

growth hormone, manufactured by Serono Laboratories, on intestinal function[23] and nutritional status in adults with SBS dependent upon parenteral feeding. A total of 30 completed patients is the recruiting goal. Of these, 22 have been randomized to date, 14 completed the trial as planned and 5 have dropped out of the trial. **No serious adverse events have been reported.** Although Dr. Ziegler's presentation generated lots of interest initially[24], it was later concluded that results of this trial are not very helpful from the regulatory viewpoint. This is because the study is testing the effects of administration of **rh-GH alone and not rh-GH in co-therapy with glutamine.** As repeatedly noted/discussed throughout the MO review, the data in NDA 21-597 demonstrated that the best results and thereby **the preferred mode of administration of the hormone for the sought indication, is in co-therapy with glutamine.** In addition, being that a Final Study Report from Dr. Ziegler's study will be available in about 2 years, this study would not contribute to the **timely regulatory action** required in the case of NDA 21-597.

Listed in the materials that follows are each of the 6 questions posed by the Agency and the corresponding votes by the Committee members. Some comments are added in an attempt to reflect the salient concerns expressed by the Committee discussants. The Medical Officer's simplified comments also took into consideration the Serono's response(s) [submission of July 15, 2003] to the comments and recommendations made during the June 25th AC meeting.

Question 1

The primary endpoint of this study was change in Total IPN volume from week 2 to week 6. Pairwise comparisons of results of the primary endpoint yielded statistically significant differences between the recombinant human growth hormone (rh-GH)-containing arms and the control group. Are the findings in the table below clinically meaningful? In your response consider the definition of the primary endpoint and the duration of study treatment.

Table 1
Changes in Total IPN Volume

Mean Change in Total IPN Volume			Difference in Total IPN Volume [L/wk] (p-value)	
Group A rh-GH (n=16)	Group B rh-GH + GLN (n=16)	Group C GLN (n=9)	Group B vs. C	Group A vs. C
-5.9	-7.7	-3.8	-3.9 (<0.001)	-2.1 (0.043)

[23] The gut mucosal data include: a) determination of small bowel and colonic mucosal glutathione levels, b) di-/tripeptide transporter PepT1 protein and mRNA expression, and c) assessment of up-regulated expression of intestinal trefoil factor. This group of investigators is now able to determine intestinal trefoil factor protein in gut mucosa by immunohistochemistry.

[24] **Data from this trial are of great scientific interest.** The study is a critical test of the hypothesis that diet modification alone does not optimize intestinal nutrient absorptive function after massive bowel resection in man. Dr. Ziegler's trial is an excellent investigation of concomitant gut mucosal morphologic, absorptive, and molecular responses over time in short bowel patients. Results of this trial may help to further address issues regarding replicability/generalizabilty; but these issues have now been addressed through data unrelated to Dr. Ziegler's study.

Vote on Question 1: *Yes = 6* *No = 3*

ABBREVIATED COMMENT

- There was general agreement that a **3.9 L/wk** (and for that matter, even a **2.1 L/wk**) ***reduction of the total IPN volume burden,*** shown to be ***statistically significant*** (adjusted p-values) in Study IMP20317, is ***also clinically significant.*** The discussions included the effects of glutamine and the fact that considerably better results were obtained when rh-GH was administered in co-therapy with glutamine rather than alone[25]. As pointed out throughout the initial Medical Officer's review, during his presentation to the AC, and during the current review, the MTL believes that some patients receiving rh-GH for four weeks, may be completely weaned from IPN, lipids, and I.V. hydration and **this is good. But requiring this weaning off IPN as the primary endpoint might be asking too much of the drug.**

Question 2

Secondary endpoints were change in Total IPN calories and change in IPN or lipid frequency. Pairwise comparisons of the results of these secondary endpoints yielded statistically significant differences between the rh-GH-containing arms and the control group. Are the findings in the table below clinically meaningful?

Table 2
Secondary Efficacy Analysis

Treatment Groups				
Group A rh-GH (n=16)	**Group B rh-GH + GLN (n=16)**	**Group C GLN (n=9)**	**Group B vs. C**	**Group A vs. C**
Change in Total IPN Calories			**[kcal/wk] / (p-value)**	
-4338.3	**-5751.2**	**-2633.3**	**-3117.9 (<0.001)**	**-1705.0 (0.005)**
Change in IPN or Lipid frequency			**[d/wk] (p-value)**	
-3.0	**-4.2**	**-2.0**	**-2.2 (<0.001)**	**-1.0 (0.025)**

Vote on Question 2: *Yes = 6* *No = 3*

[25] The reviewer agrees with the sponsor that acceptance of reduction of the total IPN volume burden as the primary efficacy endpoint is consistent with the AGA position [see Reference under Footnote 7 to page 11 of the Medical Officer Review of NDA 21-597] which states: ***"The goal of the medical therapy is for the patient to resume work and a normal lifestyle, or as normal of one as possible. This is undertaken via the use of specific measures to gradually decrease the requirements for TPN, and at best, to eliminate its need".***

ABBREVIATED COMMENT

- The Committee's vote reflects the fact that this question is the flip side of question 1. During the Committee's discussions on question 1 it was made clear that, the secondary endpoints go hand in hand with the primary one. In other words, for a reduction in total IPN volume to be clinically meaningful, it needs to be associated with a concomitant proportionate reduction in infusion time as well as frequency[26]. The reviewer agrees with the concept that, from the patient's perspective, even **a reduction of one infusion per week**, as that seen when using **rh-GH alone** (no glutamine co-therapy) is to be considered clinically significant. **It is however important to reiterate that, according to the data in Study IMP20317 and as illustrated in the above-displayed Table, the analysis of results of secondary endpoints just as those of the primary endpoints, demonstrate that rh-GH is twice as effective when given in co-therapy with glutamine rather than alone. These observations on primary and secondary endpoints of efficacy should be reflected in the labeling.**

Question 3

The primary endpoint was change in Total IPN volume. Only 1 of the 3 components (IPN volume) was recorded between week 6 and 18. Is the measurement of IPN volume adequate to demonstrate durability of effect?
If not, what do you recommend as a minimum follow up period?

Vote on Question 3 *Yes = 4* *No = 5*

ABBREVIATED COMMENT

It took considerable discussion and clarification of uncertainties about the question to realize that this is a question of **durability not maintenance,** of effect. It is important to clarify that although the question of durability is appropriate Study IMP20317 was set to assess the efficacy and safety of a **4-week course of rh-GH**, either alone or in co-therapy with glutamine in SBS patients. **Indeed, it was not the objective of Study IMP20317 to assess durability.** The Committee's recommendation of a minimum follow up period varied from 6 months to two years.

Question 4

The data were primarily derived from a single, nutritional support tertiary care center. Are these data generalizable to the population of short bowel syndrome patients?

Vote on Question 4: **Yes = 2** **No = 7**

ABBREVIATED COMMENT

The initial voting on this question was 4 Yes and 5 No.
There was considerable discussion and request for Agency clarification regarding the question of

[26] One of the AC discussants commented that it is important to decrease the amount of time the patient is hooked up to a machine. The more calories one is infusing, the greater the risk of some sort of TPN-associated liver complications. **It is not just a mobility issue**. Certainly reducing the infusion volume is **intrinsically beneficial**

one Study (IMP20317) that has not been replicated and the applicability of the findings in one specialized center in Boston to the rest of centers and SBS patients in the United States. As noted in Section V. Summary/Conclusions of the current review, the MTL believes that the issue of replicability/generalizability has been, to a large extent, satisfactorily addressed.

Question 5

Are there specific safety concerns considering the potential for long-term use of rh-GH in the treatment of short bowel syndrome patients?

Vote on Question 5: *Yes = 6* *Abstentions = 3*

ABBREVIATED COMMENT

It is important to clarify that there was **near unanimous agreement** that there were no safety concerns about the use of the hormone for the short-term **[4-weeks] sought by the sponsor.** It is important to note that **Question 5 refers to long-term**, not short-term use. The former would be **off-label** since the clinical data were of 4-weeks duration only and there is no information that can be used in support of the hormone long-term for the SBS indication. The reviewer believed that long-term safety is of some concern, mainly because of the **lack of information. It is also reasonable to consider L-T safety** in the risk-benefit appraisal.

Question 6

Do the data support the safety and effectiveness of rh-GH alone or in co-therapy with glutamine in patients with short bowel syndrome?
Are there any additional studies that you would recommend, e.g., dose finding?

Vote on Question 6: *Yes = 3* *No = 6*

ABBREVIATED COMMENT

This question was rephrased after Agency clarification on the several possible answers was provided. Some of the Committee's recommendations seem helpful in formulating the Agency's Regulatory Action. These recommendations included the need to gather follow-up data on multiple time points for at least one year, more information on dose findings and possible repeated administration of the drug. Further recommendations included the gathering of additional information using as primary study endpoint the successful [complete] weaning from IPN, post-marketing surveillance, patient monitoring and the **establishment of Educational Programs for both, patients and physicians**, in addition to support for a web based program for clinicians as well as patients. **But the Committee was unclear as to what should be done before approval and what may be requested as Phase IV commitments.**

There were further pertinent comments, some of which reflected Committee members concerns. Some of the Committee members commented that the data from Study IMP20317 were indeed robust and, as mentioned above, both statistically as well as clinically significant. Others, however, felt that although generally there were data to support safety, especially short-term, the

endpoint of evaluation, [which did not include evaluation of **clinically meaningful nutrition** parameters] had not met the criteria for efficacy. One member commented that he thought of Study IMP20317 as a Phase II trial and that there was need to do a Phase III, definitive Study. As noted in the comments to the questions above, because efficacy has been demonstrated, this reviewer does not necessarily agree that additional clinical trials should be required.

Based on the overall assessment of the available evidence, which also took into consideration deliberations and recommendations around the six questions on efficacy and safety discussed at the June 25, 2003 GI Advisory Committee, the Division concluded that NDA 21-597 was **approvable**.

At a July 23, 2003 meeting, the applicant was informed that the following four deficiencies must be addressed **before approval of this application is granted**[27] **:** 1. Educational Plan; 2. Additional Data in Support of replicability/generalizability; 3. Initial Data in Support of Durability of Effect, and 4. Additional work in progress. At that time, no Phase IV commitments were contemplated. **The need to address GI AC discussions and concerns before approval was emphasized.**

III. Review of Additional Information in Support of NDA 21-597

1. Additional Data in Support of Replicability/Generalizability

A. Data on Additional Patients Treated by Drs. Li and Zhu in China

- In an initial publication[28], presented to the Agency at the time of the 25th June, 2003 Advisory Committee meeting, Dr. Jieshou Li and his co-workers, of Nanjing, China reported results from their observations in **27 SBS patients** to whom a series of measures called **intestinal rehabilitation therapy**[29] was applied. This is **an uncontrolled review of practice and results in their referral institution**. The objective of this trial is to investigate the effect of rehabilitation therapy for SBS on patient nutritional status and intestinal adaptation. The rehabilitation therapy included: 1) correction of electrolytes and acid-base imbalance; 2) nutritional support, consisting of total energy delivered as carbohydrate, amino acid solution and 20% MCT/LCT fat emulsion, and a peptides preparation chosen as enteral diet. Rehabilitation diet was a specialized diet with high protein and dietary fiber but low fat prepared by the dietitian in accordance with the patient's resting energy expenditure; 3) either **glycyl-glutamine powder** (0.6 g/kg)[30] or **alanyl-glutamine solution** (0.3 g/kg). **One week after the initiation of nutritional support, 53.2 μg. kg^{-1}. d^{-1} (equivalent to 8 μ/50 kg . d^{-1}) of growth hormone manufactured by Serono [rh-GH (Saizen, Serono Co., Switzerland)] was injected for 3 weeks**; 4) vitamins and trace elements supplementation; 5) control of

[27] Details on the justification for the need to address each one of these deficiencies before approval of the drug are given in Dr. Hugo Gallo-Torres' Clinical Review **[Section XIII. Recommendations for Regulatory Action].**

[28] Zhu W, Li N, Ren J, Gu J, Jiang J, Li J. Rehabilitation therapy for short bowel syndrome. Chin Med J 115 (5): 776-778 (2002).

[29] This approach to the treatment of SBS mimics that published by Byrne, TA et al [A new treatment for patients with short-bowel syndrome. Growth hormone, glutamine, and a modified diet. Ann Surg 222: 243-254 (1995)].

[30] This powder was taken for years.

diarrhea by Lomotil or Imodium and antacid therapy ; and 6) scheduled **follow-up and detailed dietary instructions to postpone the occurrence of short bowel complications.**

- The study population consisted of SBS patients with an average age of 38.5 y, length of residual small intestine ranging from 15 to 80 cm (average = 46.8 cm). The ileocecal valve was preserved in 14 cases and the rehabilitation therapy was 86 (± 105) days.

- Nutritional parameters were recorded **before** and **after** the treatment. Parameters reflecting the patients' nutritional status included body weight, serum total protein, serum albumin, and hemoglobin concentration. Parameters reflecting the patients' intestinal functions included daily stool frequency, stool nitrogen content (Kjeldahl) and intestinal D-xylose absorption.

Summary results from a total of 37 patients

- The sponsor has submitted data and a brief summary from a manuscript by Dr. Li's group describing their experience in 10 additional patients[31], comprising a total of **37 patients.**
- **Six** of the patients were children < 18 y of age. The remainder were adults aged 18 to 74 y
- Their minimal small intestinal length was 15 cm with ileocecal valve and intact colon in adults.
- 34 patients were treated within 2 y of developing SBS.
- All patients completed treatment. There were not deaths due to malnutrition.
- As summarized in Table 3, at the end of 3 weeks of therapy, there was a significant improvement of parameters reflecting the patients nutritional status (upper panel of Table 3) in the parameters reflecting the patients intestinal function (lower panel of Table 3).
- According to the available information, 13 patients were followed up for more than 1 year and **10 of these were weaned from TPN** [NOTE: this represents 35% of the total study population]; 8 patients were followed up for more than 2 y, among whom **4 were weaned from TPN** [NOTE: this represents 11% of the total study population].

COMMENT

The reviewer's overall conclusion is that data from these studies in China in 37 SBS patients given rh-GH in co-therapy with glutamine, as part of a bowel rehabilitation regimen, lend support to the safety of the Serono's product. The sponsor's main conclusion in that after the treatment, nutritional status of the patients improved markedly, and intestinal absorptive capacity improved. This conclusion seems correct and the information from this trial appears to lend some support to the concept of **generalizability of the treatment**. However, a number of constraints, resulting from the design and execution of the trial, preclude the formulation of definite conclusions on efficacy. These constraints include: lack of randomization and double blinding [two powerful tools to minimize bias], lack of a suitable and relevant control, and the fact that - although the treatment duration was 3 weeks- the sponsor's product was tested at **50 µg/kg/d [less than half the daily dose used in pivotal trial IMP20317].** It might be argued that the parameters of evaluation, listed in detail in Table 3 of the current review, were all of objective nature and all showed statistically significant improvement after 2 to 3 years of treatment with

[31] Zhu W et al. "Effect of recombinant human growth hormone and enteral nutrition on short bowel syndrome", currently under translation and to be submitted for publication soon.

the proposed overall regimen. But in the absence of a suitable and relevant control arm, it is not possible to assess how effective the regimen is. It does seem that, from this available evidence, one may conclude that, in comparison to before the bowel rehabilitation treatment, **the patients are not getting worse**. The effect on total weaning off TPN seems equally weak. This is because, in the final analysis, after 2 to 3 years of treatment, **only 3 out of the total 37 patients weaned off parenteral or enteral nutrition completely** and were able to live on a high-carbohydrate low-fat diet, which, according to the publication, was well tolerated.

Table 3
Study by Dr. J. Li of Nanjing, China
Nutritional Status and Intestinal Function of SBS Patients[a] After 2 to 3 years of Bowel Rehabilitation Therapy, Including rh-GH[b], Glutamine and Dietary Supplements

EVALUATION PARAMETER	BEFORE	AFTER	p-value
I. CHANGES IN PARAMETERS REFLECTING PATIENTS NUTRITIONAL STATUS [n = 37]			
Total protein [g/L]	60[c]	66[d]	<0.001
Albumin [g/L]	37	40	0.001
Hemoglobin [g/L]	102	110	0.012
II. CHANGES IN PARAMETRS REFLECTING PATIENTS INTESTINAL FUNCTION [n = 29]			
Stool Frequency [# per day]	3.1	1.3	0.002
Stool Nitrogen [g/d]	4.5	2.1	0.036
D-xylose absorption rate [mmol/L]	0.77	1.12	0.004

a) STUDY POPULATION

Volvulus	15
Intestinal Obstruction	9
Infarction of the Mesenteric Artery	7
Thrombosis of the Mesenteric Artery or Vein	4
Crohn's Disease	2
Total	n = 37

b) 50 µg/kg/d [Saizen, Serono Co., Switzerland]
c,d) These figures have been rounded off and the ± SEM deleted for simplification of presentation purpose.

B. Statistical Meta-Review of Published Literature on SBS

To further address the issue of replicability/generalizability, the sponsor review all relevant published literature on the use of GH [any source] in SBS[32]. The summarized results of all such publications were tabulated [pages 3 of the Introduction/Analysis/Conclusions subsection] and a 7-page Table under the Tabulations of studies subsection in the August 27, 2003, submission to NDA 21-597.

It is worth noting that, with one exception, the information from literature publications presented by the sponsor is the same than that included in Table 2 of the MTL's review of NDA 21-597. The one exception is the sponsor's inclusion of results of the study by J. Szkudlarek (see below). In the sponsor's document, the observation subheadings, include a brief study design, number of subjects comprising the treated groups and control groups (if any), primary/secondary endpoints if specified or simply endpoints if these are not so classified, the mean for each endpoint where available, and the significance of the observed change. The latter is given either by comparison to placebo (for placebo-controlled trials0 or by comparison with the baseline value, for uncontrolled trials.

Scope of the Sponsor's Review

- 13 studies and reports [total n = 214 subjects] are listed.
- 3/13 studies [Scolapio, Szkudlarek, and Seguy] are double-blind, controlled studies [Total n = 28 patients]. These are the most important studies of interest. For these trials, the significant level for experimental vs. placebo comparison for all intergroup endpoints is presented. An additional double-blind, controlled study [Ellegard] was summarized separately because although this was a placebo-controlled study, no between-group comparisons were reported.
- The remaining 9 studies [total n = 176 patients] are not placebo-controlled. Therefore, in the sponsor's analysis, the changes due to treatment were expressed as intra-group changes before and after treatment.
- Based on the MTL's review of the initial submission under NDA 21-597, it is not surprising from a group of exploratory trials conducted at a variety of centers in several countries to find that there was no consensus on the dose or manufacturer's brand of GH to be used. However, **only one of the studies**, not included in the present subsection of the current review but reviewed in utmost detail in subsection A., above, **that of Zhu et al., used rh-GH manufactured by Serono.**
- As noted by the sponsor, wide spread of endpoints were chosen in these studies. In addition, there was not a clearly identifiable "translation" from functional endpoints to the clinical endpoints used in Study IMP 20317. For these reasons, the sponsor made no attempt to perform a formal meta-analysis. Rather, in their submission, they refer to the process and the document as a **meta-review** of available study data. The sponsor states that this position was supported by distinguished experts in the field whom Serono consulted on this issue.

Summary Results of Double-blind, Placebo-controlled Studies (Table 4)

- The endpoints in these studies included body weight, basal metabolic rate, absorption of nutrients and d-xylose, and lean body mass. In general, the parameters evaluated reflected

[32] All accessible, Medline-indexed, studies dealing with the use of rh-GH in adults with SBS were examined. Individual case reports were not included.

either the patient's nutritional status or the patient's bowel function. But none of these studies included the **change in Total IPN volume**, the primary efficacy endpoint used in pivotal study IMP20317.

- Nonetheless, combining closely overlapping endpoints gave a total of 15 endpoints. **Table 5** shows whether an endpoint was statistically significantly improved [("YES") or not ("NO") or not examined [("__")] in each of these 3 trials. The following summarizes results of the 3 trials:
  a) In the Scolapio et al study, rh-GH [0.14 mg/kg/d, source other than Serono's] given for 3 weeks in a 6-week crossover study, ***transiently increased body weight,*** significantly but modestly increased the absorption of sodium and potassium and decreased gastric emptying. In this study, the assimilation of macronutrients, stool volumes and morphometry of small bowel mucosa were not statistically different in the two treatment arms [rh-GH vs. placebo].
  b) In the study by Szkudlarek et al, in which test medication was given for 4 weeks [28 days], none of the parameters evaluated showed a statistically significant difference between "high dose" rh-GH [0.12 mg/kg/d] and placebo.
  c) In the study by Seguy et al, rh-GH [0.05 mg/kg/d, Genotropin, manufactured by Pharmacia and Upjohn AB, Stockholm, Sweden], administered for 3 weeks, was statistically significant different from placebo in all evaluation. Parameters.
  d) Finally, in Ellegard's study, when compared to results obtained before treatment, 8 weeks of low-dose rh-GH [0.024 mg/kg/d; source: Genotropin, ———] doubled serum concentrations of IGF-1 and increased body weight, lean body mass, and total body potassium by 5%. Fat-free mass and total body water increased by 6% [$p = 0.008$]. The increase in IGF-1 levels correlated with the increase in fat-free mass [$r = 0.77$, $p < 0.02$]. However, in this study, no significant changes in absorptive capacity of water, energy, or protein, were detected.

Summary results of not placebo controlled studies

Some of these studies were randomized, but open-label. Other studies were comparative but open-label A fair amount of these data originated from Dr. Wilmore's experimental site in Boston but the first author of the various publications is TA Byrne, who, together with Dr. Wilmore, summarized her experiences with rh-GH in SBS patients during the June 25, 2003, GI Advisory Committee meeting.

All in all, the not placebo controlled studies comprise a total of 176 SBS patients. The sponsor's analyses were expressed as **intra-group changes occurring after treatment in comparison to baseline** [before treatment]. It is worth noting that this is the same approach used in Dr. Zhu et al [discussed in detail above] and in the analysis of results from the Ellegard et al. study. Results of this double-blind, randomized trail are summarized in Table 4 of the current review.

Table 4

Overview of Study Endpoints Used to Evaluate the Effect of GH in the treatment of SBS

Study No.	Study Population	Main Features/ Dose of GH	Efficacy Endpoints	Summary of Results Comments
1.	**8 patients (6 men and 2 women)** with SBS who were dependent on L-T **HPN (home parenteral nutrition)** for an average of 12.9 years, with mean residual small bowel length of 71 cm. All patients were able to eat food by mouth but were unable to maintain hydration or adequate nutrition (or both) without parenteral nutrition support.	**D-B, PL-controlled, randomized, 6-week, crossover.** Pts. were admitted to [redacted] for 4 days on 3 separate occasions, 21 days apart. Active treatment: **GH (0.14 mg. kg^{-1}. d^{-1}), and GLN (0.63 g. kg^{-1}. d^{-1}) and a high CHO-low fat (HCLF) diet for 21 days.**	**The weight, BMR, nutrient and electrolyte balance , serum insulin-like growth factor 1 (ILGF-1) levels, D-xylose absorption, morphology and DNA proliferation of small intestinal mucosa, and gastrointestinal transit were evaluated** Treatments were compared by paired *t* test.	rh-GH: • ***transiently*** increased body • **significantly but modestly** increased the absorption of sodium and potassium and • decreased gastric emptying The following were not statistically different in the 2 treatment arms: • **assimilation of macronutrients** • **stool volumes and** • **morphometry of small bowel mucosa**
Scolapio, JS et al. Effect of Growth Hormone, Glutamine, and Diet on Adaptation in Short - Bowel Syndrome: A randomized, Controlled Study. Gastroenterology 113: 1074-1081 (1997)				
2.	8 SBS patients (7 females, 1 male). The SBS was due to Crohn's disease in 6 pts. and to mesenteric infarction in 2. Duration of HPN ranged from 3 to 11 y. The length of the small intestine varied from 30 to 150 cm. 4 patients had no colon In the remaining 4, the proportion of colon left ranged from 28 to 86 %.	Randomized, crossover, two-arm study of GH + GLN vs. placebo. Test medication or placebo given for 28 days rh-GH (0.14 mg/kg/d; Norditropin, Novo-Nordisk, [redacted] divided into 2 daily injections Oral L-GLN (30 g/d: [redacted] divided into 6 doses dissolved in a beverage of the patient's choice and Parenteral GLN as GLN-enriched infusions (17% of N as GLN, [redacted]	Not clearly specified. Patients were admitted to the authors' Department on 3 occasions for balanced studies: **prior to the start of treatment (baseline) and five days after completion of each treatment period** Dietary energy, carbohydrate, and fat were maintained "as usual" According to the publication, in this study, all patients had side effects that "are known to occur during treatment with high doses of growth hormone" [depending on the patient, these included weight increase, fluid retention, peripheral edema, need for diuretics, need for analgesics, opiates, and development of gynecomastia in one patient]	rh-GH with glutamine did not improved intestinal absorption of • **energy** [baseline, placebo treatment, mean: 46%, 48%, 46% of oral intake, respectively] • **carbohydrate** [71%, 70%, 71%] • **fat** [20%, 15%, 18%] • **nitrogen** [27%, 18%, 19%] • **sodium** [-16%, -16%, -36%] • **potassium** [43%, 47%, 33%] • **calcium** [-16%, -16%, -15%] • **magnesium** [-3%, 4%, 2%] or • **weight gain** [37%, 39%, 31%]
Szkudlarek J et al. Effect of high dose growth hormone with glutamine and no change in diet on intestinal absorption in short bowel patients: a randomized, double blind, crossover, placebo controlled study. Gut; 47: 199-205 (2000).				

3.	**12 patients from the register of HPN-dependent patients with SBS.** All had undergone extensive resection of the small bowel without any surgical resection of the stomach, duodenum or pancreas. Usual medications such as PPIs, loperamide, fluoroquinolones, and oral supplements (vitamin E, D, Ca, K, Mg salts) were not changed during the study.	**Prospective randomized, double-blind, placebo-controlled, crossover.** All pts. were on an **unrestricted hyperphagic diet..** **Patients received daily low-dose GH [0.05 mg . kg $^{-1}$. day^{-1}] , corresponding to 0.15 IU kg $^{-1}$./ day^{-1}) [Genotropin. ——— ——— administered by subcutaneous injection daily at 8am.**	Immediately before the first treatment period (baseline) and at the conclusion of each treatment period (day21), a **nutrition status (body weight, body mass index, skinfold thickness, bioelectric impedance analysis) assessment was performed.** **At the same time , a series of blood tests, including hemogram, glucose, insulin, insulin-like growth factor 1 (IGF-1), IGF binding protein 3 (IGFBP-3), and GH binding protein (GHBP, soluble form of GH receptor) serum levels as well as plasma glutamine and citrulline amino acid levels, was performed on blood samples taken in a postabsorptive state (7am).** During the third week of each Tx period, pts. were admitted for 5 days and 4 nights (days 17 to 21) to study **intestinal macronutrient absorption (main judgment criteria).** **During the first day of hospitalization (day 17), a d-xylose absorption test was performed.** **Thus, a minimum 23-day washout period actually elapsed between the evaluation of test medication and placebo treatments.**	**Treatment with rh-GH increased intestinal absorption of:** **- energy** (15% ± 5%, $p < 0.002$) **- nitrogen** (14% ± 6%, $p < 0.04$) **- CHOs** (10% ± 4%, $p < 0.04$) **and** **- fat** (12% ± 8%, NS). According to the authors' calculations, the increased food absorption represented 37% ± 16% of total parenteral energy delivery. The following parameters **increased:** **- body weight** ($p < 0.003$) **- lean body mass** ($p < 0.006$) **- d-xylose absorption** ($p < 0.02$) **- insulin-like growth factor 1** ($p < 0.002$) **and** **- insulin-like growth factor binding protein 3** ($p < 0.002$) whereas uptake of GH binding protein decreased ($p < 0.01$) , without any apparent major adverse effect.
Seguy d et al. Low-Dose Growth Hormone in Adult Home Parenteral Nutrition-Dependent Short Bowel Syndrome Patients: A Positive Study. Gastroenterology 124: 293-302 (2003)				

4.	10 patients (3F, 7M) with SBS for more than 1 year because of Crohn's disease. Some pts. had some blood biochemistry abnormalities. All had normal fasting serum glucose concentrations. All exhibited normal 24-h GH profiles, with maximum peak values of > 5 milliunits/L. Daily fecal/stomal outputs were 2.9 kg (range, 0.9 to 5.8 kg). All required oral or parenteral fluid substitution in combination with electrolytes, vitamins, and minerals.	This was a placebo-controlled, randomized, double blind, crossover clinical trial. **10 pts.** were treated with daily subcutaneous doses of **rhGH/placebo (0.5 international units /kg^{-1} per week^{-1} = 0.024 mg/kg^{-1} per day^{-1} Source of GH: Genotropin** The low-dose rhGH/placebo was administered daily, subcutaneously during 8 weeks, separated by a washout period of at least 12 weeks.	**Absorptive capacity and biochemical parameters** were investigated in a metabolic ward **before** treatment and during **first** and **last week** of treatment. Body composition was determined by DEXA-Scan , impedance analysis, and whole body potassium counting. Between group comparisons [rh-GH vs. Placebo] were not reported.	• This well-designed and apparently well- executed study is of interest. The authors set to investigate the effects of low dose rhGH (from a source different from that used by the sponsor of the present NDA) on body composition and absorptive capacity in patients with SBS from Crohn's disease. • Low-dose rh-GH doubled serum concentrations of IGF-1 and increased body weight, lean body mass, and total body potassium by 5%. • Fat-free mass and total body water increased by 6% ($p = 0.008$). • Increased in IGF-1 levels correlated with increase in fat-free mass ($r = 0.77$, $p < 0.02$). • No significant changes in absorptive capacity of water, energy, or protein were detected.

Ellegard, L. Low-Dose Recombinant Human Growth Hormone Increases Body Weight and Lean Body Mass in Patients with Short Bowel Syndrome. Ann Surg 225 (1): 88-96 (1997)

Table 5

Results of three randomized, double-blind, placebo-control trials examining the effect of growth hormone, given in co-therapy with glutamine, on 15 selected endpoints of efficacy

Author	Scolapio et al	Szkudlarek et al.	Seguy et al.
Dose of growth hormone tested	0.14 mg/kg/d	0.12 mg/kg/d	0.05 mg/kg/d
Duration of treatment [weeks]	3	4	3
Evaluation Parameter			
Body weight	YES	NO	YES
Lean Body mass	—	—	YES
Basal metabolic rate	NO	—	—
Insulin-like growth factor-1 [IGF-1]	YES	—	YES
Energy absorption	—	—	YES
Carbohydrate absorption	—	—	YES
Stool weight	—	NO	—
Stool sodium	YES	NO	—
Stool potassium	YES	NO	—
Stool magnesium	NO	NO	—
Stool fat or fat absorption	NO	—	YES
Stool nitrogen or nitrogen balance	NO	—	YES
Stool calcium	—	NO	—
Urinary nitrogen	NO	—	—
d-xylose absorption	NO	—	YES

This Table is based on sponsor's Table 1 in their August 27, 2003 submission to NDA 21-597, with major modifications.

These publications were previously reviewed. For completeness, summary results of these not placebo controlled trials are included below. The **Ref. number [1., 2., 3., 4., and 8.] identifies the Study No. in Table 2 [page 21 through 26]** of the MTL's review of NDA 21-597, where details are given on study population, mean features of the trial, dose of administered rh-GH, length of administration of test medication, efficacy endpoints and a summary comments of results.

Ref. 1.[33]: GH administration **accelerated protein gain** and in stable adults patients receiving aggressive nutritional therapy without a significant increase in body fat or a disproportionate expansion of ECW. **GH therapy accelerated nutrition repletion** and, may shorten the convalescence of the malnourished patient requiring a major surgical procedure.

[33] Byrne TA et al. Anabolic therapy with growth hormone accelerates protein gain in surgical patients requiring nutritional rehabilitation. Ann Surg 218(4):400-416 (1993)

Ref. 2.[34]: The ability of GH to **enhance amino-acid uptake from the gut** lumen provides energy and precursors for protein synthesis in the gut mucosa, as well as additional substrate for anabolism in other organs.

Ref. 3.[35]: **GH + GLN + DIET** offers a potential method for providing **cost-effective rehabilitation of surgical patients** who have the short bowel syndrome or other complex problem of the gastrointestinal tract. This therapeutic combination also may be useful to enhance bowel function in patients with other gastrointestinal diseases and those requiring extensive intestinal operations, including transplantation.

Ref. 4.[36]: **The combined administration of GH, GLN, and a modified diet enhanced nutrient absorption from the remnant bowel after massive intestinal resection.** These changes occurred in a group of patients that previously failed to adapt to the provision of enteral nutrients. According to the authors, this therapy may offer an alternative to L-T dependence on TPN for patients with severe SBS.

Ref. 8.[37]: Although larger prospective, randomized, double-blind, controlled studies are underway to differentiate the effects of the components of this therapeutic approach, this study recognizes the **heterogeneity of this patient population** and help to identify patients most likely to respond to the described regimen. The regimen consisted of medications, a specific diet with supplements, and a behavior modification program. It is worth reiterating that the medications dosages included standard antidiarrheal and antacid agents, prescribed at recommended doses. **In addition, in this study, the patients received GH [Serono Laboratories**, Norwell, MA and Eli Lilly, Indianapolis, IND, USA] **at an average dose of 0.09 mg/kg/d**. GH was discontinued upon discharge from the inpatient facility. All patients consumed **a specific oral diet**, with the percent CHO, fat, and protein and the type of fluids dependent upon the presence or absence of colon. While within the guidelines of the specific diet prescriptions, **given foods were often adjusted** based upon patient specific sensitivities, determined from the 24-h intake and output records, most likely to respond to the described noninvasive regimen.

The authors of this publication note that **while the majority of the patients responded to the intervention with a significant reduction or the elimination of PN, others, despite aggressive intervention and monitoring, experienced minimal to no change in PN requirements. These patients should be considered for either intestinal transplantation or other therapeutic approaches.**

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[34] Inoue Y. et al. Growth Hormone Enhances Amino Acid Uptake by the Human Small Intestine Ann Surg 219(6): 715-724 (1994)
[35] Byrne, TA. A New treatment for Patients with Short -Bowel Syndrome: Growth Hormone, Glutamine, and a Modified Diet. Ann Surg 222 (3): 243-255 (1995)
[36] Byrne, TA, et al. Growth Hormone, Glutamine, and a Modified Diet) Enhance Nutrient Absorption in Patients With Severe Short -Bowel Syndrome. J Par Ent Nutr 19 (4): 296-302 (1995)
[37] Byrne TA et al. Bowel rehabilitation: an alternative to long-term parenteral nutrition and intestinal transplantation for some patients with short bowel syndrome. Transpl Proc 34: 887-890 (2002)

COMMENTS ON THE STATISTICAL META-REVIEW OF PUBLISHED LITERATURE ON SBS

The sponsor carried out this meta-review to further address the issue of replicability/generalizability. Included in this review were all relevant published literature on the use of GH [any source] in SBS. This information is very much the same included in Table 2 of the first cycle clinical review of NDA 21-597. A total of 13 studies and reports [total n = 214] are listed. As shown in Table 4, 3 [of 13] studies {Scolapio, Szkudlarek, and Seguy] [total n = 28] are double-blind, and controlled. The Ellegard study [No. 4 in Table 4] was summarized separately because although this was a placebo-controlled study, no between-group comparisons were reported. The remaining 9 studies [total n = 176] are not placebo-controlled [commented upon in the text of the current review].

From the data displayed in Table 4 it is clear that none of these studies included the change in Total IPN volume, the primary efficacy endpoint used in pivotal study IMP20317. For the analysis of the placebo-controlled studies, the sponsor obtained a total of **15 closely overlapping endpoints** [Table 5 of the current review] and these data were assessed for statistical significance. For completeness, the reviewer has included in this Table the length of administration [3 to 4 weeks] and the dose of test medication [0.05 to 0.014 mg/kg/d]. In the Scolapio study, rh-GH [0.14 mg/kg/d, source other than Serono's] given for 3 weeks in a 6-week crossover trial, transiently increased body weight, significantly but modestly increased the absorption of sodium and potassium and decreased gastric emptying. In this study, the assimilation of macronutrients, stool volumes and morphometry of small bowel mucosa were not statistically different in the two treatment arms [rh-GH vs. placebo]. In the study by Szkudlarek et al., in which test medication was given for 4 weeks [28 days], none of the parameters evaluated showed a statistically significant difference between "high dose" rh-GH [0.12 mg/kg/d] and placebo. In the study by Seguy et al. rh-GH [0.05 mg/kg/d, Pharmacia and Upjohn], administered for 3 weeks, was statistically significant different from placebo in all evaluation parameters. Finally, in Ellegard's study, when compared to results obtained before treatment, 8 weeks of "low-dose" rh-GH [0.024 mg/kg/d, [redacted], doubled serum concentration of IGF-1, and increased body weight, lean body mass, and total potassium by 5%. Fat-free mass and total body water increased by 6% [$p = 0.008$]. The increase in IGF-1 levels correlated with the increase in fat-free mass [$r = 0.77$, $p < 0.02$]. However, in this study, no significant changes in absorptive capacity of water, energy, or protein, were detected.

In summary, the data available in the literature consist of many exploratory trials conducted in a variety of centers in several countries, with no consensus on brand or dose of rh-GH tested. The reviewer believes that, with the evidence at hand, it is not possible to rule out the possibility that the difference in efficacy results seen between the sponsor's and other GH preparations and commented upon during the first Clinical review cycle, are due to methodological (differences in primary and secondary efficacy endpoints used in the clinical trials and the way the clinical trials were actually executed) rather than differences due to dose. It is worth reiterating that rh-GH, at the subcutaneously administered dose of 0.1 mg/kg/d, was shown to be safe and effective when assessed under the experimental conditions in pivotal Study IMP20317.

2. Initial Data in Support of Durability of Effect

One of the issues discussed at the June 25, 2003, GI Advisory Committee meeting was that of **durability of effect** The Committee was almost equally split [No = 5, Yes = 4] with regard to its answer to the question of whether the measurement of IPN volume [**alone**], which the sponsor had commented on, was adequate to demonstrate durability of effect.. It was also noted that some Committee members confused durability of effect with **maintenance of effect.** As previously noted, neither durability nor repeated cycle effects were pre-stipulated objectives of Study IMP20317. In addition, the sponsor is not asking for approval of the treatment for more than 4 weeks, the duration of pivotal trial IMP20317. Nevertheless, it seems of interest to attempt to answer the question of **how long does the benefit last after the recommended 4-week continuous daily treatment**. An initial answer to this question might be obtained by surveying the status of the patients that were randomized into the critical study. The objective of such survey would be to assess the ability of these SBS patients to wean off home parenteral nutrition [HPN] after a successful intestinal rehabilitation program in Study IMP20317.The sponsor has initiated such a survey and provided information on these results. This subsection of the current review deals with the evaluation of these data.

Follow-up information on the 41 patients treated in Study IMP20317

This survey study is being carried out under **Protocol 24236** [IND 48,750]. In addition to the protocol, which is reviewed below, the following three documents are provided in sponsor's Attachment 1 of their August 27, 2003 submission:

1. A blank Patient Information [Case Record Form];
2. Summary Tables which will be completed and sent to the Agency once a sufficient number of Patient Information Forms have been received by the sponsor; and
3. Completed Patient Information Forms completed and received by the sponsor to date. The sponsor states that additional forms will be submitted to FDA promptly upon receipt at Serono.

SUMMARY OF PROTOCOL 24236

- **Title:** Follow-up to a randomized, double-blind, controlled, parallel-group evaluation of the relative efficacy and safety of recombinant human growth hormone and glutamine, singly and as cotherapy, in the improvement of residual gut absorptive function in patients with short bowel syndrome. Date of protocol: 16 July 2003.

Principal Investigator : **Theresa Byrne, D.Sc. Nutritional Restart Center, Wellesley, MA 02481**

Study Director : _____

- **This is a follow-up to the antecedent study, IMP20317.** The study is designed to collect retrospective data on the L-T outcome of all patients who participated in the study. The follow-up data will help assess safety parameters and the durability of the study treatments. The goal is to access specified medical data for all of the patients that completed the above

referenced study. In the antecedent study, patients were referred to the Principal Investigators by PCPs or Specialist Physicians nationally and internationally. Following informed consent that grants access to patients' medical records, this information will be gathered using standardized questionnaire forms completed by each patient's PCP or Specialist physician, with input from the homecare agency or specialized pharmacy which filled each patient's IPN prescription; patient participation is not otherwise required.

- **The following relevant information is included in Protocol 24236.** The antecedent study evaluated the efficacy and safety of the administration of subcutaneous rh-GH and oral GLN singly and as co-therapy in patients with SBS who were dependent on IPN for nutritional support. The 6-week in-patient study period was comprised of a 2-week Baseline Period and a 4-week Treatment Period. A follow-up visit was conducted during Week 18, 3 months after completion of the treatment regimen. The primary efficacy parameter was the change from Week 2 to Week 6 in the total volume of IPN per week required by each subject for nutritional support. Total IPN volume was defined as the sum of the volumes of IPN, supplemental lipid emulsion (SLE), and intravenous hydration fluid administered each week. The secondary efficacy variables included change in total calories (calories/week) and IPN frequency (d/wk) from Week 2 to Week 6. Total calories were defined as the sum of kilocalories for carbohydrate, protein, and fat in the IPN and SLE administered per week and the kilocalories in the intravenous hydration fluid. Frequency was defined as the number of days of administration of IPN or, if no IPN, administration of SLE where the amount of SLE provides greater than 200 kilocalories. In IMP20317, there were no significant demographic differences among the three treatment groups in age, sex, or weight. The subject resection history and IPN history (frequency, volume, and calories) were also similar across all three treatment groups. After 4 weeks of treatment, subjects who received rh-GH+SOD[GLN] (Serostim® recombinant-human Growth Hormone and a Specialized Oral Diet supplemented with glutamine) and those who received rh-GH+SOD significantly reduced their IPN volume requirements ($p<0.001$ for rh-GH+SOD[GLN] and $p=0.043$ for rh-GH+SOD), their IPN calorie content ($p<0.001$ for rh-GH+SOD[GLN] and $p=0.005$ for rh-GH+SOD), and their weekly frequency of IPN administration ($p<0.001$ for rh-GH+SOD[GLN] and $p=0.025$ for rh-GH+SOD). Overall, there are few safety concerns **with** the use of rhGH and GLN in patients with SBS treated for up to 16 weeks. The safety profile of rhGH+SOD[GLN] is similar to the safety profile of rhGH+SOD. During the Baseline Period, 88% of rhGH+SOD subjects, 88% of rhGH+SOD[GLN] subjects, and 78% of SOD[GLN] subjects reported baseline signs and symptoms (BSS). During the Treatment Period, 100% of rhGH+SOD-treated subjects and 100% of rhGH+SOD[GLN]-treated subjects reported at least one AE, whereas 89% of the SOD[GLN]-treated subjects reported at least one AE. During the Follow-up Period, 75% of rhGH+SOD subjects, 81% of rhGH+SOD[GLN] subjects, and 78% of SOD[GLN] subjects experienced at least one AE. Comparison of the number of AEs before and during treatment demonstrates that this subject population experiences numerous BSSs and AEs due to their underlying conditions and parenteral nutrition complications. Four (25%) of the subjects receiving rhGH+SOD and one (11%) of the subjects receiving SOD[GLN] experienced an SAE during the Treatment Period. None of the subjects who received the rhGH+SOD[GLN] experienced SAEs during the Treatment Period. During the Follow-up Period, 5 (31%) rhGH+SOD subjects, 3 (19%)

rhGH+SOD[GLN] subjects, and 3 (33%) SOD[GLN] subjects experienced an SAE. There were no deaths in this study. Protocol 24236 also contains the following conclusion from the results of Study IMP20317. The GH-treated groups evidenced robust reductions in mean total IPN volume (rh-GH+SOD –5.7 L/wk, rh-GH+SOD[GLN], -7.7 L/wk), total IPN caloric content (, -4338 and –5751 kcal/wk), and frequency of IPN or SLE administration (,-3.0 and –4.2 d/wk) which were clinically significant when compared with the SOD[GLN] group which showed mean reductions in volume of –3.84 L/wk, total IPN caloric content of -2633 kcal/wk), and frequency of IPN or SLE administration of 2.0 d/wk). The collective efficacy data demonstrate that rh-GH treatment combined with a SOD is effective.

OBJECTIVES OF STUDY 24236

- To obtain extended safety data and data on the durability of Serostim® for the treatment of Short Bowel Syndrome at 6, 12, 18, and 24 months post therapy and currently. Total (IPN) volume at 6 and 12, 18 and 24 months, and current volume will be collected.

- To obtain safety information and information on the overall well-being of the patient post therapy by collecting events of hospitalization, infections, thrombosis, liver and biliary disease.

- The STUDY POPULATION consists of all available and eligible patients that will be included in this follow-up study. Each patient must have:
  - successfully completed the antecedent study.
  - voluntarily provided written informed consent and a patient authorization in accordance with ICH GCP, the Declaration of Helsinki, HIPAA and local regulatory requirements, prior to any study-related activities, with the understanding that the subject may withdraw consent at any time without prejudice to her future medical care.
  - his/her Case Report Form/questionnaire (CRF) completed, received and accepted by Serono.

- To be eligible for inclusion into this study, each patient must fulfil the following criteria: successful completion of the antecedent study to the time of discharge from the in-patient facility and have given written informed consent and authorization.
- Subject Information Leaflets/Informed Consent and Authorization Forms will be based on a master document provided by Serono, and must be approved by Serono before submission to the IRB/IEC. Any changes requested by the IRB/IEC must be approved by Serono before the documents are used.

- Each potentially eligible patient will be informed of the study objectives and overall requirements. Prior to accessing any patient information the Investigator will explain the study fully to each patient by providing the Patient Information Leaflet/Informed Consent and Authorization Form. If the patient is willing to allow their medical records to be reviewed, he/she will be requested to give written informed consent after being given sufficient time to consider his/her participation and the opportunity to ask for further details. Due to wide geographic dispersal of the subjects, the investigator will provide a signed and dated consent form for review by each patient with his/her PCP or Specialist physician. The Informed Consent and Authorization Form will be signed and personally dated by both the

patient and the patient's PCP or Specialist Physician. A copy of the signed form will be provided to the patient and a copy may be retained by the PCP/Specialist Physician; the original retained with the completed CRF/Questionnaire by the Principal Investigator. Although nursing staff may be involved in describing the study to a patient, the PCP/Specialist Physician must participate in discussions with the patient and sign and personally date the Informed Consent and Authorization Form prior to completing the CRF/Questionnaire.

- The subsequent follow-up information gathered through patient medical records will be requested from PCP Specialist Physician and/or specialist pharmacy or Homecare Company upon receiving patient consent:
  □ Daily TPN constituents at 6, 12, 18 and 24 months post therapy and currently. Dates within 2 months of these time points are acceptable. TPN constituents consist of the average of the following measures, if possible averaged over one week and ordinarily obtained from the patient's TPN prescription covering the period in question:
  □ Daily total volume of fluids containing nutritional carbohydrate, amino acid solution, and lipid emulsion
  □ Daily total caloric content of the above
  □ Number of treatments (infusion of TPN fluids) administered over the week
  □ Daily volume of non-TPN hydration fluid averaged over the week
  □ Health status of patient. The items noted will be the following:
  □ Mortality □ Body weight □ Specific directed inquiries will be made at 6 month intervals regarding □ Hospitalization □ Line Infection □ Thrombosis □ Liver Disease □ Biliary Disease

- There is no PRIMARY ENDPOINT TEST OF HYPOTHESIS. As this is a follow-up to a completed antecedent study, there is no formal statistical hypothesis to be assessed. No formal statistical tests to be performed. Only the descriptive statistics will be summarized for each of treatment groups (i.e., SOD[GLN], rh-GH+SOD, rh-GH+SOD[GLN]) and overall. As this is a follow-up to the completed antecedent study, no statistical estimation of the sample size was performed.

- Baseline data for the entire study are defined as the last available data prior to the initiation of the antecedent study, i.e., those values obtained on Week 2 or just prior to Week 2 of the antecedent study. The baseline data for this follow-up study are defined as the data collected at date of admission for this follow-up study.
- The statistics including mean, standard deviation, median and range for each of continuous baseline parameters will be descriptively summarized by treatment group and overall. The frequency count for each of categorical baseline parameters will be tabulated by treatment group and overall.
- The Populations to be analyzed are all patients who are enrolled into this follow-up study. They will all be included in the analysis. No imputation methods will be used.
- For EFFICACY ANALYSIS, the Endpoints to be descriptively summarized by treatment group and overall are:
  □ PN volume at 6, 12, 18 and 24 months post therapy and currently.
  □ Total caloric content.

- The total number of infusions of PN fluids administered per week
- Body weight
- Whether or not patient is receiving one or more intravenous infusions for hydration per week at each date-point.

- In addition, for each of the above endpoints, the changes from baseline (from antecedent study) to each time point and the change from the baseline (from this follow-up study) to each time point will be descriptively summarized by treatment group and overall. Patient survey data including consent status (see above) will be descriptively presented by treatment group and overall. Although no safety data will be collected and analyzed in this follow-up study, the patient health status including mortality during the month of the week of evaluation will be noted.

NOTE: All aspects of the proposed Protocol, described in detail above, are adequate. Also adequate are the listed obligations of the Principal Investigator, and **all applicable regulatory requirements, such as** IRB/Ethics Committee, identification of documentation required prior to initiation and documentation required during the study. It is noted that the **Respondent, Home Health Care Company or Primary Care Physician** will be responsible for the accuracy of the data entered in the CRFs/questionnaire. Upon completion all CRFs will be forwarded to Serono.

Also adequate for the proposed study are issues related to MONITORING /AUDITING/ INSPECTING[38]. The protocol explains that on one or more occasions the study site may be inspected by a regulatory agency, often after completion of the Study clinical activities.

- Protocol 24236 provides a list of 27 pertinent references and the World Medical Association Declaration of Helsinki.

SUMMARY RESULTS OF STUDY 24236

- For completeness, it is important to reiterate the patient's status at randomization into trial IMP20317. **SUBJECTS BASELINE CHARACTERISTICS**
  All in all, the 3 treatment groups were comparable in terms of demographic, disease and other baseline characteristics.
- The treatment groups were comparable (no statistically significant differences among treatment arms) in demographic characteristics[39].
- The underlying conditions resulting in bowel resection represented in all three treatment arms were vascular insufficiency, Crohn's disease, and volvulus. Other categories included patients with strangulated hernia, jejunoileal bypass for morbid obesity and other. There were no gross imbalances among the treatment arms in underlying condition resulting in bowel

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[38] **Prior to study start, the Investigator will be informed of the anticipated frequency of the monitoring visits. He/she will also receive a notification prior to each monitoring visit during the course of the study. It is expected that the Investigator and/or his/her sub-investigator(s) and other appropriate staff are available on the day of the visit in case any questions might arise.**
On one or more occasions the study site may be audited by either Serono or by a third party on behalf of Serono. The Investigator will be informed in advance of such a visit

[39] As summarized in sponsor's Table 11-1 of the Clinical Report, **the mean age** for Groups A, B, and C was 50.5, 52.5, and 45.0 years, respectively. Roughly, **two thirds of the patients were women, mostly Caucasian.** There was a lower proportion of patients of non-Caucasian origin. Although this difference approached statistical significance (p = 0.064) **this imbalance is not expected to influence results.** Likewise, the treatment arms were similar in baseline weight (Group A = 61.4 kg, Group B = 62.1 kg. and Group C = 61.3 kg). Weight was the average of each patient's weight at 1 month and 2 months before screening.

resection. When considering these comparisons, the number of subjects per group was not sufficient for statistical analysis.

- Similarly, at baseline, there was no statistically significant difference among the 3 treatment groups with regards to SBS and IPN history (Table 6). Results of evaluations regarding the 6 SBS/IPN-related variables listed in this Table were carefully analyzed because parameters such as **mean length of residual jejunum-ileum , percent of colon intact , mean number of days per week of IPN administration, mean volume IPN per week, and mean IPN calories per week are factors that may influence outcome.**

Table 6
Study IMP20317
Summary of Disease Baseline Characteristics

SBS/IPN Variable	Group A rh-GH+SOD [n = 16]	Group B rh-GH+SOD[GLN] [n = 16]	Group C SOD[GLN] [n = 9]	p-value
Mean number of years since most recent bowel resection	5.1	4.6	3.9	N.S.
Mean length of residual jejunum-ileum [cm]	84.2	68.4	62.3	N.S.
Percent of Colon Intact	67.1	52.6	61.8	N.S.
Mean number of days per week of IPN administration	5.2	5.5	5.9	N.S.
Mean volume IPN per week [L/wk]	13.8	13.0	13.1	N.S.
Mean IPN calories per week [kcal/wk]	11620.8	10403.8	10224.9	N.S.

This Table is based on sponsor's Tables 1.5.1 and 1.6.1 (Section 15.1) and Summary Table 11-3 (page 108) of the Clinical Report. Standard deviations have been omitted for clarity of presentation purposes.

- Two documents, The Follow-up Survey Status Report (Table 7) and the Comments Log (Table 8) provide information on the progress of the study overall. In conjunction, the two Tables give a summary of the current results of the study procedures. These procedures consist of contacting patients to obtain informed consent, mailing forms to treating physicians and home healthcare companies that request information, retrieving these forms and carry out completion of case record forms. In Table 8, under the subheading comments, a number of reasons are listed that illustrate why, in the final analysis, **the sponsor's overall approach to demonstrate durability of effect was not very successful.**

Table 7
Study 24236
Follow-up Survey Status Report

Pt. #	Initials	Date of Contact	Received Consent	MD packet mailed	MD Contacted	Home Care Co. Faxed	HC Contacted
101		8/7/03	8/11/03	8/12/03	8/18/03	8/12/03	8/15; 8/19
102		8/14-LM	8/15/03	8/15/03		8/15/03	8/19; 8/21
103		8/14/03	8/22/03	8/22/03		8/22/03	
104		8/8/03	8/12/03	8/12/03	8/18/03	NA	NA
105		8/14-E-mailed	Yes-e-mail				
106		NA	No	-	-	-	-
107		NA	8/11/03	8/12/03	8/18; 8/21	8/11/03	NA
108		8/14/03	Yes-verbal				
109		8/14/03	Yes-verbal	8/22/03		NA	
110		8/14/03	8/21/03	8/21/03		NA	NA
111		8/14/03	No-declined	-	-	-	-
112		8/14, 8/21-LM					
113		8/15/03	Yes-verbal				
114		8/14-No ans.	8/15/03	8/15	8/21/03	8/15/03	8/19; 8/21
115		8/18/03	Yes- verbal				
116		8/14-LM, 8/21	Yes-verbal				
117		NA	No	-		-	
118		8/15/03	8/20/03	8/20/03	8/22/03	8/21/03	8/20/03
119		8/18 w/ dtr	No	-	-	-	-
120		8/14-LM; 8/21	Yes-verbal				
121		8/18/03	?				
122		NA	8/11/03	8/12/03	8/18/03	8/12/03	8/15/03
123		NA	8/11/03	8/12/03	8/18; 8/21	8/11/03	8/14, 19, 21
124		8/14	Yes-verbal				
125		8/18/03	No-declined	-	-	-	-
126		8/14	Yes-verbal				
127		Attempted					
128		8/8/03 w/ dtr	No	-		-	
129		Attempted					
130		8/11/03	Yes-verbal				
131		Attempted					
132		8/14/03	8/18/03	8/18/03	8/21/03	8/18/03	8/21/03
133		8/6/03	8/15/03	8/15/03	8/21/03	NA	NA
134		8/14	No				
135		NA	8/8/03	8/11/03	8/18/03	8/13/03	8/15/03
201		8/15, 8/21-LM					
202		Attempted					
203		Attempted					

*Pt. was excluded and did not complete the 12-week follow-up.

LM=Left message

Table 8
Study 24236
Comments Log

Entry Date DD-MM-YY	Patient #/ Initials	Comments	Initials
13-08-03	202/ —	Attempted to contact patient, phone number is not in service and no further information is available.	SS
13-08-03	203/—	Attempted to contact patient, phone number is not in service and no further information is available.	SS
13-08-03	131/—	Attempted to contact patient. Address and phone number are incorrect and current resident has no further information.	MK
15-08-03	122/—	Spoke with pharmacist at homecare company. Due to time constraints, he is unwilling to complete survey.	MK
18-08-03	127/—	Pt is unavailable to consent because she is currently in ——— recovering from surgery.	MK
19-08-03	129 —	Patient's number has been changed to a non-published number.	SS
21-08-03	107/ —	Pt.'s MD will be away until ———	SS
21-08-03	114/—	Pt.'s MD has been out sick for two weeks.	SS
21-08-03	123/ —	Home care company may not be able to obtain records in archive.	SS
22-08-03	132/—	Pt.'s MD is willing to complete the survey but it will take a few weeks.	SS

Summary of Results from 22 patients participating in Study Survey 24,236

The sponsor states that during the summer of 2003 attempts were made to contact all 41 patients discharged from the original study to obtain updated information on their health status and on their **current requirements for parenteral nutrition**. The information obtained thus reflects the study patients' clinical progress as **community-living patients** receiving routine care for their SBS. In addition to the information displayed in Tables 7 and 8, the status of these inquiries as of the beginning of October, 2003 was displayed in a number of Tables included in the sponsor's

submission. In summary, **data on 22 living patients** were received and form the basis of the current report. Four of these patients were from the specialized oral diet supplemented with glutamine (SOD[GLN]) group, 10 from the growth hormone (GH) plus SOD group and eight from the GH plus SOD[GLN] group. Due to the small sample size, only descriptive, as distinct from inferential statistics were presented in the sponsor's report.

Because of the above-mentioned limitations, the MTL decided that the information submitted by the sponsor can only be **presented and commented upon in descriptive terms**. Therefore, materials under the following six subheadings, including selected Tables chosen for illustration purposes are presented: 1. Patient Disposition, 2. Demographics, 3. Medical Status, 4. TPN Infusion Data; 5. Body Weight, and 6. Current Information. These data are followed by 7. Sponsor's Conclusions. The MTL's Overall Summary/Conclusions, which include comments provided by Dr. D. Price, FDA Statistician, come after the sponsor's conclusions.

1. Study 24236: Patient Disposition

This information is displayed in Table 9. In summary, of the 41 patients initially randomized into IMP20317 trial[40], one dropped out because of a serious adverse event. Trial IMP20317 was completed by 40 patients. This **[n = 40] is the starting study population**. Of these 40 patients, 15 did not participate in Study 24236 for reasons that included: a) could not be reached [n = 5]; b) were deceased [n = 3][41] and c) refused consent [n = 7]. As a consequence, data were obtained from **22 patients** who gave informed consent. Information on 3 additional patients is pending.

Table 9
Study 24236
Patient Disposition

Total # of patients randomized, n = 41	# of patients
Ineligible [Dropped out due to AE[a]]	1
Completed Trial	40
Could not be reached	5
Deceased [Died post-study]	3
Refused/Unable to provide Informed Consent at this time[b]	7
Consent Obtained	25
Data Obtained	22
Data pending	3

a) Patient 106 terminated due to a serious AE and did not complete the 6 week inpatient period. b) 1 pt. recovering from surgery.

[40] At entry into the original study IMP20317, there were 9, 16 and 16 patients randomized into the three treatment groups of interest, respectively [see Table 6].

[41] Patients deaths, ——— = Massive bleeding S/P Multiple Organ Transplant
——— 2 = Internal Hemorrhage
——— = S/P Blood Clot to Spleen

2. Study 24 236: Demographics (Table 10)

This Table summarizes demographic information [age, body weight and sex] on the 22 patients from whom data are available. The number of patients per follow-up arm were:

4 [out of the initially randomized **9**] in the (SOD [GLN]) group

10 [out of the initially randomized **16**] in the (rh-GH + SOD) group

8 [out of the initially randomized **16**] in the (rh-GH + SOD [GLN])

Of note, follow-up information was obtained from only half of the group of patients [8 0f 16] that had given the best efficacy results in Study IMP20317, that is, the treatment arm consisting of the recombinant human growth hormone in co-therapy with glutamine and who, in addition, were receiving a specialized oral diet **(rh-GH + SOD [GLN]).** Because of the small number of observations, there are constraints when attempting to interpret these findings. **In the final analysis, the data derived from these post-hoc observations appear to be of limited value.**

Table 10
Study 24236
Demographic Characteristics

Characteristic	Statistics	SOD [GLN] (n=4)	rhGH+SOD (n=10)	rhGH+SOD [GLN] (n=8)
Age (yrs)	n	4	10	8
	Mean (SD)	52.3 (15.6)	53.9 (15.8)	47.3 (15.7)
	Median	46.5	55.0	52.0
	Range	(41.0, 75.0)	(31.0, 73.0)	(20.0, 65.0)
Body weight (kg)	n	4	10	8
	Mean (SD)	63.2 (12.3)	66.8 (11.4)	62.1 (14.1)
	Median	66.7	65.4	60.1
	Range	(45.8, 73.7)	(50.1, 83.6)	(47.3, 87.3)
Sex, n (%)	Male	2 (50.0)	1 (10.0)	2 (25.0)
	Female	2 (50.0)	9 (90.0)	6 (75.0)

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* Based on the patient at discharge (the end of treatment period in the 20317 study).

3. Study 24236: Medical Status

The sponsor presented this information in a series of 4 Tables [Numbers 2,3,4, and 5 of this Section of the Clinical Report]. Included in these Tables is a summary of the responses to questionnaire at 6, 12, 18, and 24 months post study discharge, respectively. The parameters listed in these Tables include: a) hospitalization, and whether the patient was treated for an

infection or a thrombotic event; b) >3x the upper limit of normal of liver function tests [total bilirubin, alkaline phosphatase, AST, ALT; c) any liver dysfunction; d) whether TPN was infused and e) whether I.V. hydration was required. The answers, listed for each of the 3 treatment arms of the initial clinical trial [IMP20317], were captured in 3 categories for "statistical purposes": **Yes, No, and Unknown.**

The information on **Medical Status** can be descriptively summarized as follows. A number of patients were listed as requiring hospitalization in each six-month period of the follow-up survey. The reviewer agrees with the sponsor that these findings reflect **the morbidity associated with intravenous cannulation and intermittent parenteral nutrition**. The sponsor notes that at no follow-up visit was more than one patient recorded as being hospitalized while off TPN. It is further claimed that the number of patients on TPN at each follow-up time point who were recorded as being hospitalized ranged from 2 to 3, and the number recorded as being hospitalized while off TPN was either zero or one. But **no firm conclusions, just speculations**, can be drawn from these findings. To illustrate the constraints when interpreting the data displayed in the sponsor's Tables, the reviewer has chosen to display the **24-month follow-up data**. From the evidence submitted and presented in Table 11, it is clear that, the information at hand **is too incomplete**. This is especially true for the group of patients that, at trial IMP 20317, was randomized to rh-GH alone. The follow-up data from this arm show that, for all of the Medical Status-related parameters -except TPN Infused [Unknown = 10%]- displayed in Table 11, **the category Unknown ranged from 40 to 60%.**

4. Study 24236: TPN Infusion Data (Tables 11 and 12)

Information as to whether or not a patient required TPN infusion at any time point of the follow-up survey is contained in a series of Tables submitted by the sponsor, from which, the 24-month data displayed in Table 11 of the current review, was chosen to illustrate certain. Data recorded for the SOD[GLN] and growth hormone plus SOD groups reflect information from only one third and about one half of the originally treated patients in those groups, respectively. One patient in the SOD[GLN] group, five in the GH plus SOD group, and four in the GH plus SOD[GLN] group had no requirement for total parenteral nutrition (TPN) at six months, a picture similar to that seen at the end of the original observation following the 4-week treatment period. As seen in Table 11, changes at the 24-month time point were modest.

The mean and median TPN volumes infused at each time point during the follow-up period are presented in Table 12. These data cannot be seen as supportive of durability of effect. Although the mean weekly requirements for TPN between discharge and month 24 decreased in the rh-GH plus SOD group and in the SOD[GLN] group, this requirement actually increased in the GH plus SOD[GLN] group. The mean increase in weekly TPN volume from discharge to month 24 was 262.4 ml in the seven patients in this group for whom month 24 data are available. The sponsor notes that the median change in TPN volume for this group was zero.

Table 11
Study 24236

Patient Follow-up Data at 24-Month

Parameter	Statistics	SOD [GLN] (n=4)	rhGH+SOD (n=10)	rhGH+SOD [GLN] (n=8)
Hospitalized? n (%)	Yes	0	1 (10.0)	4 (50.0)
	No	2 (50.0)	3 (30.0)	2 (25.0)
	Unknown	2 (50.0)	6 (60.0)	2 (25.0)
Treated for a line infection(s)? n (%)	Yes	0	1 (10.0)	3 (37.5)
	No	2 (50.0)	4 (40.0)	3 (37.5)
	Unknown	2 (50.0)	5 (50.0)	2 (25.0)
Treated for a thrombotic event(s)? n (%)	Yes	0	0	0
	No	2 (50.0)	4 (40.0)	6 (75.0)
	Unknown	2 (50.0)	6 (60.0)	2 (25.0)
Total bilirubin >3x the upper normal limit? n (%)	Yes	0	0	1 (12.5)
	No	3 (75.0)	6 (60.0)	5 (62.5)
	Unknown	1 (25.0)	4 (40.0)	2 (25.0)
Alkaline phosphatase >3x the upper normal limit? n (%)	Yes	1 (25.0)	0	1 (12.5)
	No	2 (50.0)	6 (60.0)	5 (62.5)
	Unknown	1 (25.0)	4 (40.0)	2 (25.0)
AST >3x the upper normal limit? n (%)	Yes	1 (25.0)	0	1 (12.5)
	No	2 (50.0)	6 (60.0)	5 (62.5)
	Unknown	1 (25.0)	4 (40.0)	2 (25.0)
ALT >3x the upper normal limit? n (%)	Yes	1 (25.0)	0	1 (12.5)
	No	2 (50.0)	6 (60.0)	5 (62.5)
	Unknown	1 (25.0)	4 (40.0)	2 (25.0)
Any liver dysfunction*? n (%)	Yes	1 (25.0)	0	1 (12.5)
	No	2 (50.0)	6 (60.0)	5 (62.5)
	Unknown	1 (25.0)	4 (40.0)	2 (25.0)
TPN infused? n (%)	Yes	1 (25.0)	4 (40.0)	5 (62.5)
	No	2 (50.0)	5 (50.0)	3 (37.5)
	Unknown	1 (25.0)	1 (10.0)	0
IV hydration required? n (%)	Yes	0	3 (30.0)	4 (50.0)
	No	3 (75.0)	3 (30.0)	3 (37.5)
	Unknown	1 (25.0)	4 (40.0)	1 (12.5)

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* patient is considered having liver dysfunction if the patient had any of the specified abnormalities in total bilirubin, alkalin phosphatase, AST or ALT.

Table 12

Study 24236

TPN Infusion Data: Volume (ml/week)

Time Point	Statistics	SOD [GLN] (n=4)	rhGH+SOD (n=10)	rhGH+SOD [GLN] (n=8)
Discharge*	n	4	10	8
	Mean (SD)	4537.5 (4029.3)	2005.0 (2153.9)	1490.6 (2318.6)
	Median	4200.0	1650.0	0.0
	Range	(0.0, 9750.0)	(0.0, 6000.0)	(0.0, 6000.0)
6-Month Follow-up	n	2	7	6
	Mean (SD)	600.0 (848.5)	607.1 (1039.4)	585.3 (934.3)
	Median	600.0	0.0	0.0
	Range	(0.0, 1200.0)	(0.0, 2250.0)	(0.0, 2112.0)
12-Month Follow-up	n	3	7	7
	Mean (SD)	500.0 (866.0)	818.6 (1045.8)	644.6 (867.2)
	Median	0.0	0.0	0.0
	Range	(0.0, 1500.0)	(0.0, 2250.0)	(0.0, 2112.0)
18-Month Follow-up	n	3	7	7
	Mean (SD)	500.0 (866.0)	854.3 (1105.4)	966.0 (995.9)
	Median	0.0	0.0	1000.0
	Range	(0.0, 1500.0)	(0.0, 2500.0)	(0.0, 2250.0)
24-Month Follow-up	n	3	8	7
	Mean (SD)	500.0 (866.0)	747.5 (1067.1)	1108.9 (1070.5)
	Median	0.0	0.0	1400.0
	Range	(0.0, 1500.0)	(0.0, 2500.0)	(0.0, 2250.0)
Change from Discharge to 6-Month Follow-up	n	2	7	6
	Mean (SD)	-1200.0 (1697.1)	-1364.3 (1616.2)	-402.2 (1665.3)
	Median	-1200.0	-800.0	0.0
	Range	(-2400.0, 0.0)	(-4000.0, 0.0)	(-2525.0, 2112.0)
Change from Discharge to 12-Month Follow-up	n	3	7	7
	Mean (SD)	-3950.0 (4136.1)	-1152.9 (1896.9)	-201.9 (1609.9)
	Median	-3600.0	-800.0	0.0
	Range	(-8250.0, 0.0)	(-4000.0, 1480.0)	(-2525.0, 2112.0)
Change from Discharge to 18-Month Follow-up	n	3	7	7
	Mean (SD)	-3950.0 (4136.1)	-1117.1 (1886.1)	119.6 (1861.8)
	Median	-3600.0	-800.0	0.0
	Range	(-8250.0, 0.0)	(-4000.0, 1480.0)	(-2525.0, 2250.0)
Change from Discharge to 24-Month Follow-up	n	3	8	7
	Mean (SD)	-3950.0 (4136.1)	-1290.0 (1813.3)	262.4 (1975.5)
	Median	-3600.0	-1150.0	0.0
	Range	(-8250.0, 0.0)	(-4000.0, 1480.0)	(-2525.0, 2250.0)

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* Discharge was the last available data from the treatment phase of the 20317 study.

In addition to the changes in volume (ml/week) related to TPN Infusion, the sponsor presented a series of Tables displaying the changes in the following other parameters: calories (kcal/week), carbohydrate (g/week), protein (g/week) and fat (g/week). Because this information is incomplete in that for none of the periods of observation there were 22 total number of patients accounted for, none of these Tables is reproduced in the current review. Included below is some descriptive information provided in the sponsor's clinical report.

- The results on **total TPN calories** were similar to those summarized above for the volume related to TPN infusion except that patients in the rh-GH plus SOD[GLN] group showed a decrease **in weekly caloric requirements**, to be set against the above-mentioned increase in required volume. Once again, the median change in TPN infusate volume for this group was zero. The data in the sponsor's clinical report covered the major nutrients infused as TPN, **carbohydrate, protein, and fat**, respectively. As expected, these data reflect the total volume of infusate, as listed in Table 12 of the current review.
- In additional Tables, the sponsor presented the change in numbers of TPN infusions required per week at 6 month intervals from discharge to month 24. The mean number increased only slightly in the rh-GH plus SOD [GLN] group, who had had the strongest reduction in frequency during the residential phase of study IMP20317. The mean change in this group was zero. Also observed was a slight decrease in infusion frequency in the 3 patients from the original SOD[GLN] group for whom data could be obtained.

5. Study 24236: Body Weight

Although some comments on these data are provided here, the information on body weight emanated only from a small number of available patients [7, 8 10 and 13 at 6, 12, 18 and 24 months, respectively]. The information of the change in weight from discharge to 24-month follow-up emanated from only 13 patients. Nonetheless, the sponsor states that all groups of patients showed reduction in body weight between discharge and month 24. The degree of reduction was more marked in the groups which had been treated with growth hormone. These were the groups in which weight had increased most sharply between pre-trial screening and discharge, i.e. while they were receiving the test medication. For patients with available data, mean weight increased by 3.4 kg between screening and discharge in the rh-GH plus SOD group and by 4.2 kg in the rh-GH plus SOD[GLN] group. To a considerable extent, therefore, body weight decreased between discharge and the 24 months follow-up, but as previously mentioned the number of patients in whom these observations were made was small.

6. Study 24236: Current Information

Under this heading, the sponsor presented a Table (# 13) showing that three out of four patients in the original SOD[GLN] group were not requiring TPN at the most recent assessment. This contrasts with two of four in this group off TPN at 24 months and one out of four at six months of follow-up. The reasons for the apparent decline in TPN requirements in this small subset of the original control group are not clear. With regard to the patients in the originally rh-GH treated groups the Table showed that six out of 10 from the rh-GH plus SOD group and four of eight from the rh-GH plus SOD[GLN] group were not requiring TPN at the time of the most

recent observation. Once again, this information is incomplete because it accounts for only 22 of the initially randomized 41 patients

7. Study 24236: Sponsor's Conclusions

"Data from the follow-up survey must be interpreted with caution because of the relatively low numbers of responses available. However, data obtained during the follow-up survey indicated that the clinical course followed by patients discharged from the treatment trial remained relatively stable over more than 2 years of observation. Two patients who were taking no TPN at the time of discharge had to have TPN resumed during the period of follow-up observation. Two patients who were discharged on TPN were discontinued from TPN. Eight patients who were taking no TPN at the time of discharge remained off TPN throughout the two-year follow-up period. In addition, those patients who had a reduction of TPN at the end of the clinical trial but who weren't completely weaned, continued to reduce their TPN requirements during the two year follow-up survey period

"The reduction in TPN requirements during the initial clinical trial was significantly greater in the GH-treated groups, especially the GH plus SOD[GLN] group. Thereafter, infusion requirements appeared to be relatively stable during two years of follow-up. The benefits of GH treatment, with or without glutamine, for the treatment of SBS is soundly demonstrated and greatly supported with the follow-up survey information."

8. Study 24236: Reviewer's Summary/Conclusions

It is to be noted that the Summary/Conclusions were formulated with input from Dr. D. Price, FDA statistician.

- Serono Pharmaceuticals has submitted follow-up information on 22 of the 41 subjects from pivotal Study IMP 20,317. Of the 22 subjects, 8 had been initially randomized to the co-therapy of glutamine and rh-GH, 10 to rh-GH alone, and 4 to glutamine [alone]. The follow-up survey was designed to collect information on TPN requirements through 2 years. Due to the **limited number of subjects**, Serono provided descriptive statistics for the follow-up data. Of note, the raw data were not provided to the Agency. Therefore, discussion of the data is only based on the descriptive Tables provided by the sponsor.

- Follow-up data were collected for the **primary measure of TPN requirement**. A mean reduction in TPN requirements from discharge to 6 months was noted for each treatment group. According to the sponsor, discharge corresponded to the last day of the administration of the test medication. Similarly, there was a reduction in requirements from discharge to 12 months for each treatment group. However, there was a mean increase in TPN requirements of 120 ml/week from discharge to 18 months in the co-therapy group. The mean increase was also apparent from discharge to 24 months. As noted by the sponsor, the median change in requirements for the same group was zero.

- Information on the weekly TPN caloric intake and TPN frequency was also collected. Each of the three treatment groups exhibited a mean reduction in weekly TPN calories from discharge to 6, 12, 18, and 24 months, respectively.
- In addition, a mean increase in the frequency of infusions per week was noted in the rh-GH alone and co-therapy groups from discharge to 12, 18, and 24 months respectively

The reviewers agree with the sponsor that "data from the follow-up survey must be interpreted with caution because of the relatively low numbers of responses available." Indeed, no firm or meaningful conclusions can be drawn from these incomplete data.

3. Post-approval Educational Plan

From the Medical Officer's initial review of NDA 21-597, discussions at the June 25, 2003 GI Advisory Committee, and further interactions between the Agency and the sponsor, it became clear that, to further address the issue of generalizability, an Educational Plan was needed. The sponsor was asked to provide a comprehensive educational plan for physicians prescribing the drug, ancillary personnel involved in the care of the SBS patient, notably specialized personnel such as **nutritionists** and other health care providers and SBS patients themselves so that they better understand their clinical condition and they learn the general approaches to the treatment and particularly the use of growth hormone alone or in co-therapy with glutamine, more effectively. The sponsor's plan must include training materials, communication, all kinds of support of these SBS patients and a periodical appraisal of the success of the plan. Potential remedies in the event the Plan is failing should also be prospectively stipulated.

In response to this requirement for approval, Serono has created a set of proposed educational materials for Agency review. These **DRAFT** materials are the subject matter of this section of the current review. Following a summary presentation of the sponsor's materials, reviewer's comments are given. These remarks include comments provided by Ms. Jeanine Best[42] in a Consult Review dated October 6, 2003.

The contents of the DRAFT Serostim®/SBS Educational Plan consists of the following 6 components. In the present review, most of these materials are incorporated in the form of Appendices.

- Executive Summary
- Educational Plan for Healthcare Providers
- Educational Plan for Patients
- Educational Program Evaluation Form for Healthcare Providers
- Draft Serostim®/SBS Treatment Guidelines
- Draft Serostim®/SBS Patient Handbook Outline

[42] Patient Product Information Specialist, Division of Surveillance, Research, and Communication Support, HFD-410.

a. Sponsor's Executive Summary

- An important objective is to ensure appropriate education of prescribers on the role and optimal use of Serostim® and diet (**with or without glutamine**) in the reduction of PN requirements in PN-dependent patients with SBS.
- Current data suggest that the most likely prescribers are from the universe of **Gastroenterologists and General Surgeons**, as well as **current or recent prescribers of PN.**
- The data also suggest that any given prescriber may have, at most, a few SBS patients in their practice at any given time.
- The challenge is to reach the right prescriber at the right time with information that will allow him/her to prescribe a diet/Serostim® regimen to appropriate patients and achieve an optimal outcome.
- The Serono plan for accomplishing the above includes reaching the universe of prescribers with an announcement of the availability of Serostim® for SBS along with a business reply card (BRC) for those interested in receiving the educational packet. In addition, the educational packet will be mailed proactively (no BRC required) to prescribers of PN and Serostim® (for SBS). **This is possible because Serostim® will be distributed only through a secured distribution network of pharmacies.** It ensures every prescriber will have received the materials.
- In addition, every Serostim® patient will be sent a patient brochure with their Serostim® in the event they had not received one previously from their prescriber.
- Within 4 to 6 weeks of a Serostim® prescription, prescribers will be contacted to provide an evaluation of the educational materials received.
- Feedback will be used to further refine the educational plan and content

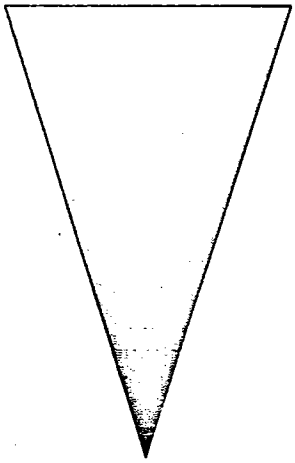
COMMENT

All in all, the Educational Plan is sound and acceptable, although some refinements [not necessarily major] may be helpful (see specific under specified subsections). The Educational Plan should include all issues related to the provision of nutritional support and the use of rh-GH alone or in co-therapy with glutamine in patients receiving a specialized diet. In addition to the patient et al., all members of the nutrition support team [clinicians, dietitians, nurses and pharmacists] should be involved with this Educational Plan. The treatment of SBS patients must be, somehow, recognized as a new specialty in its own right. Although a key feature of the so-called "Intestinal Failure Unit" is the ability to provide safe, effective, long-term parenteral nutrition, it is now recognized that some patients can also be treated by giving extra or special nutrients via the intestine. During the last 30 years, there have been many advances in knowledge on the subject matter treatment of SBS. The advantages of weaning patient off TPN, the sooner the better, are now obvious. Other advances include a better understanding on the sites of nutrient absorption, dilution of nutrients by digestive secretions, fluid and electrolyte fluxes, effect of malabsorption on the colon and adaptation of the residual small intestine after a partial resection. It seems that the sponsor's DRAFT Educational Plan is comprehensive and nearly complete although minor adjustments might be needed.

b. Educational Plan for Healthcare Providers

This part of the Program consists of the following components which are either briefly commented upon below or provided as Appendices to the present review: Identify Members of Target Audience [likely universe of prescribers and Serostim® prescribers], Fully Developed Educational Materials, Educate [includes First Wave and Second Wave] and an Educational Plan for Patients [includes Development of Educational Materials and Call Center]. These are all adequate and acceptable.

Identify Members of Target Audience



Likely universe of prescribers (SBS):

1) Purchased lists of board-certified Gastroenterologists and General Surgeons,

2) Membership lists of American Society of Parenteral and Enteral Nutrition (ASPEN) and the Society for Surgery of Alimentary Tract, and

3) Physicians who have recently prescribed PN.

Serostim® prescribers (SBS):

Physicians who prescribe Serostim for PN patients who have diagnostic codes that include SBS.

Fully Develop Educational Materials

1) Convene panel of experts to develop draft treatment guidelines and review/comment on materials throughout their development

a) Participants of panel include: i. T. Byrne MS, RD, D.Sc. (Investigator), [Director, Nutritional Restart Centers Hopkinton, MA; ii. K. Iyer MBBS, FRCS (Investigator), Children's Memorial Hospital Chicago, IL; iii. J. Mullen MD [Hospital University of Pennsylvania], and iv. E. Steiger MD [Cleveland Clinic Foundation]

b) Initial teleconference held August 8, 2003[43]

2) Treatment guidelines[44] and product monograph, including supporting text (with explanation of diet) and references

3) Patient education booklet[45]

[43] i. Call participants included Drs. Iyer and Steiger. Dr. Byrne commented via email prior to call
ii. Output was draft guidelines presented in subsequent section of this document (tab entitled "Treatment Guidelines")

[44] drafts or outline included

[45] Ibid.

Educate

First Wave

1) Outreach to likely universe of treaters (SBS) via direct mail, FAX or email, inviting them to visit education website or otherwise respond (e.g., BRC) to receive educational materials
2) Sales force calls with subset of likely universe of treaters. Educational materials left behind.
3) Educational materials distributed to all Serostim® prescribers
4) Accredited educational symposia (likely venues include Nutrition Week, February 9-11, 2004). Note that Serono is among very few pharmaceutical companies that provides unrestricted grant support for a completely independent, accredited provider of continuing medical education: Serono Symposia International, Inc. This organization has a 20+ year history of providing credible education to medical specialists and patients. Current accreditation includes ACCME, ACPE, and ANCC.

Second Wave

1) Educational teleconferences for healthcare providers with experienced users who have completed Serono speaker training
2) Additional educational symposia (potential venues or vehicles include Digestive Diseases Week and enduring CME that could be posted on an appropriate website or mailed)

Validate

Four to six weeks post prescribing, survey (telemarketing, email, or mail) each Serostim® prescriber to assess value of educational materials as they relate to actual experience and solicit suggestions for improvement.

Education Plan for Patients

Development of Educational Materials

The Oley Foundation is a national, independent, non-profit organization that provides up-to-date information, outreach services, conference activities, and emotional support for patients receiving in-home parenteral nutrition, their families, caregivers and professionals. Serono will solicit input from the Oley Foundation in the development of patient-specific materials. Patient materials will be distributed by physicians who've identified a given patient as a candidate for Serostim. This will be supplemented by inclusion of materials in their Serostim prescriptions.

Call Center

In addition, Serono will further support patients and prescribers through a Call Center. Serono currently maintains a fully staffed complimentary Call Center employing a dedicated team of more than 70 fully trained nurses and professionals, seven days per week and twenty-four hours per day to answer incoming calls. These specialists provide answers to questions regarding therapy as well as information and on-going support to patients and their healthcare providers. Services provided via the call center also include, but are not limited to reimbursement support and injection training. In addition to the support currently provided within the therapeutic area of neurology for patients living with multiple sclerosis, Serono is in the process of expanding the scope of its call center to provide support to patients across its other major therapeutic areas including reproductive health and metabolic endocrinology.

c. Educational Program Evaluation Form for Healthcare Providers

The sponsor's DRAFT form [Appendix 1] is designed to ascertain the effectiveness of the educational materials about the use of Serostim® and specialized diet for patients on Parenteral Nutrition for SBS. The listed questions are adequate. These questions are to be answered by the Prescriber. An overall question is asked about how satisfied he/she is with the materials. Additional questions address the appropriateness of the patient/candidate, and the adequacy of the description of the specialized diet, the proposed management of GH therapy and the suggested PN weaning criteria. Two additional questions ask whether the information in these materials and the patient education materials has contributed as much as possible to successful patient outcomes. The prescriber is then asked how he/she would improve these materials.

All in all, these materials appear to be adequate to evaluate the effectiveness of the proposed Educational Plan. However, the sponsor needs to define what constitutes success and what failure. Equally important, potential remedies in the event the Plan is failing should also be prospectively stipulated.

d. Serostomin®/SBS Treatment Guidelines (Appendix 2)

From the details provided in the sponsor's document, the reviewer believes that the proposed DRAFT treatment guidelines document is complete, adequate and useful. An algorithm is provided that illustrates the steps involved in treating SBS with specialized oral diet and Serostim®, a recombinant human growth hormone.

Guidelines are divided into 5 main sections: entitled: patient selection, dietary modifications, growth hormone administration, parenteral nutrition (PN) reduction criteria, and management after Serostim® administration/PN reduction. Procedural details from the algorithm and adequate explanations of each one of these 5 sections are given at the end of the algorithm (Appendix 2).

e. Serostomin®/SBS Patient Handbook Outline (Appendix 3)

On August 27, 2003, the sponsor submitted a DRAFT outline for a proposed Patient Handbook for the purpose of aiding patients with SBS understand their syndrome, nutritional and dietary management and treatment with rh-GH for injection[46].

On October 6, 2003, Jeanine Best [Patient Product Information Specialist, Division of Surveillance, Research, and Communication Support, HFD-410] provided the below summarized comments in response to a consult on the appropriateness and adequacy of the DRAFT Patient Handbook Outline document.

- According to Ms. Best, although the patient handbook is an excellent idea, it should be used as an adjunct education/risk communication material, not the only patient education/risk communication material provided to patients for this product. Patient Information [PPI] should be the primary risk communication tool provided to patients with each prescription and refill. The Serostim® PPI should:

[46] Serono plans to tradename and label the short bowel syndrome indication separately.

- contain comprehensive information based on the prescribing information [PI].
- be written in a **Medication Guide question and answer type format** [see 21 CFR 208]. This format has research and experience to support its communication effectiveness.
- be written at a 6th to 8th grade reading comprehension level[47]
- be non-promotional.
- Have instructions for used appended at the end of the PPI and be clearly written[48].

Ms. Best concluded that the Patient Handbook appeared to provide comprehensive information on the disease, management, and treatment with Serostim®. The Patient Handbook should:

- be written at a 6th to 8th grade reading comprehension level. She recommends to keep sentences short, words simplified, explain any medical or technical term, and bullet information when possible.

- have a font size of at least 10 point to aid in ease of readability

- have adequate background contrast and white space to aid in ease of readability, not be overwhelmed by background pictures or art work.

- be non-promotional in tone.

Ms. Best ends up her consult by stating that ideally the patient handbook would be tested for comprehension among a cross section (varying educational levels, including those with low literacy) of Serostim® treated SBS patients.

IV. Further Amendments to NDA 21-597

1. New Proposed Trade Names

This issue is being addressed separately.

2. Revised Package Insert

Serono's proposed modifications/additions to the Serostim®'s Package Insert are being considered at several meetings of the Serostim® review team, with close participation of the Division's Director. Once Division revisions to the labeling have been agreed upon internally, negotiations with the sponsor will start to achieve a mutually agreeable final version of the Package Insert.

V. Reviewer's Summary/Conclusions

Serostim® [somatropin (rDNA origin)] is a form of human growth hormone produced by recombinant DNA technology. The drug is already marketed for the treatment of AIDS wasting or cachexia. The sponsor of NDA

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[47] This is an optimal comprehension level for all patient materials.

[48] Refer to *Guidance on Medical Device patient Labeling; Final Guidance for Industry and FDA Reviewers* for more information on writing instructions for patients.

21-597 is seeking approval of the product for a new indication: **treatment of Short Bowel Syndrome in patients receiving specialized nutritional support.**

In support of their application, the sponsor submitted results from one pivotal trial **(Study IMP20317).** The Clinical Study Report included information on ethics, investigators and study administrative structure, study objectives, details of results of investigational plan (Clinical Report), efficacy evaluation, safety evaluation, with discussion and overall conclusions, a list of references and appendices. The Protocol was well-designed and apparently well-executed. In summary, the trial was conducted in accordance with accepted ethical standards. The randomization process was properly executed. The protocol-stipulated primary endpoint of efficacy was a reduction, **after 4 weeks of treatment,** in the Total Intravenous Parenteral Nutrition [IPN] volume requirement, measured in liters per week. The definition of Total IPN volume (L/week) was:

- As prospectively stipulated, total IPN volume is the sum of:
  a) IPN volume *plus*
  b) supplemental lipid emulsion (SLE) *plus*
  c) intravenous hydration fluid administered each week.
- IPN and SLE requirements were captured on a daily basis before drug [Baseline] and during Week 2 through 6 [after 4 weeks of treatment].

The experimental treatment consisted of **recombinant human growth hormone (Serostim®); subcutaneous injection at a dose of 0.10 mg/kg/d.**[49] Also made use of was rh-GH placebo; subcutaneous injection; 0.10 mg/kg/d.[50] The 3 groups in the randomized, double-blind trial were:

GROUP A: rh-GH + SOD for 4 weeks [**rh-GH alone**]
GROUP B: rh-GH + SOD [GLN] for 4 weeks [**rh-GH + glutamine**]
GROUP C: rh-GH placebo + SOD[GLN] for 4 weeks [**the control group**]

It is noted that the "active treatment", either growth hormone in co-therapy with active glutamine (**Group B**) or growth hormone alone (**Group A**) is only given for 4 weeks. **This approach does not test long-term effects of the recombinant human growth hormone.** For analysis of results of efficacy evaluations, an acceptable statistical approach was used. The procedures to gather, process, analyze and report trial emerging adverse events, whether clinical or laboratory abnormalities, were all adequate.

Pairwise comparisons of results of the **primary** [change in Total IPN volume[51] from week 2 to 6] and **secondary** [change in Total IPN calories (kcal/wk) and change in IPN or lipid frequency (days/wk)] **endpoints of efficacy** between the rh-GH-containing arms and the control group yielded **statistically significant differences**. These data from primary and secondary efficacy evaluations support the reviewer's view that although the hormone seemed active in this indication, **the preferred mode of administration might be in co-therapy with active glutamine rather than rh-GH alone.** There was, however, uncertainty as to whether these

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[49] Lot numbers TC0409, MMK641A2, and MON668B.

[50] Lot Numbers TC0396 and PLM99-34.

[51] The analyses revealed that the Total Weekly IPN volume results were influenced significantly by patients'

- **weight [p<0.001].** Subjects with higher Bwt experienced greater reductions in total weekly IPN volume than those with lower Bwt .
- **length of residual bowel [p = 0.028].** Subjects with longer residual bowel had larger decreases in Total IPN volume than those with shorter residual bowel.
- **IPN volume history [p = 0.044].** Subjects with a history of higher IPN volume requirements experienced greater decreases in IPN volume during the Treatment Period than those with a history of lower IPN volume requirements.
- **race [p = 0.021].** It was found that Caucasians responded to treatment better than non-Caucasians. The sponsor brings attention to the fact that only 9 out of 41 subjects randomized in Study IMP20317 were non-Caucasians.

NOTE: In all cases with a significant co-variate, the effect of the ***main test medication arm*** (group B, rh-GH + SOD[GLN]) **remained highly significant** In those instances with a significant co-variate, **the comparison of Group A (rh-GH alone, without active glutamine as co-therapy) to Group C (the control) remained significant only when weight was used as a co-variate.**

finding were **clinically significant.** In addition to the **pivotal question** on the clinical validity/relevance/importance of the protocol-stipulated primary and secondary endpoints of efficacy --all of which had yielded **statistically significant differences** between the rh-GH-containing arms and the control-- questions/uncertainties remained on replicability[52], generalizability[53], durability, appropriate dose and long-term safety.

To address the above-mentioned issues/concerns, members of the GI AC to the FDA met on June 25, 2003 to discuss NDA 21-597. Following presentations by key sponsor representatives and FDA personnel, the Committee members discussed, provided answers and voted on the six specific questions posed by the Agency. Details of Committee deliberations, concerns, their final vote and additional recommendations, are provided within the text of the current review. The first 2 Questions addressed the clinical significance of the primary [**Question 1**] and secondary [**Question 2**] end-points of efficacy. In the final analysis, there was general agreement that a **3.9 L/wk** [obtained with rh-GH in co-therapy with glutamine] as well as a **2.1 L/wk** [obtained with rh-GH alone] reduction of the Total IPN volume burden, shown to be statistically significant, is also **clinically significant.** Likewise, the results of secondary efficacy evaluations [change in Total IPN calories and change in IPN or Lipid frequency, Question 2], were also declared **clinically significant**. The Committee's vote on durability [**Question 3**] was close [4 Yes, 5 No]. It took considerable discussion and clarification of uncertainties for the Committee to realize that the question was on durability, not maintenance of effect. It needs to be reiterated that Study IMP20317 was set to assess the efficacy and safety of a **4-week course of rh-GH**, either alone or in co-therapy with glutamine in SBS patients. **It was not the objective of this study to assess durability.** The Committee's vote on **Question 4** [generalizability] was 2 Yes, 7 No. Considerable discussion, confusion, and requests for Agency clarifications reflect the initial vote on this question [4 Yes, 5 No]. Although some Committee discussants felt that there was a need to have the pivotal clinical trial reproduced with a confirmatory study, the MTL believes that the replicability/generalizability issue has been, to a large extent, satisfactorily addressed. **First,** the 41 patient study is the largest ever carried out and this is remarkable if one considers that one is dealing with an orphan indication. **Second,** from the AC presentations (all parties) and subsequent deliberations, it was clear that the actual design of the Protocol, including Study Population, assessment of endpoints, and prospectively stipulated analyses, left little if any doubt that the study was well-designed and apparently well-executed; consequently, the data from trial IMP20317 are valid. **Third,** the pre-referral treatment was performed by the referring physicians and this was done outside of a residential treatment setting. **Fourth,** the 41 participating patients were geographically dispersed across 26 US states and 2 foreign countries. **Fifth,** SBS was diagnosed by standard and consistent norms by now postulated in the AGA Technical Review document. **Sixth,** several members of the AC recommended to explore the possibility of **Continuing Education,** use of support and training materials and many other appropriate communication tools, for both, patients and physicians. The reviewer believes this is good advice. This constitutes a reasonable approach when any new treatment option is made available. Regarding **Question5**, there was near unanimous agreement that there were no overt safety concerns about the use of rh-GH for the **short-term [4-weeks] sought by the sponsor**

[52] Results of only one trial in 41 patients (IMP20317) were submitted as part of NDA 21-597.

[53] In the final analysis, the bulk of the patients in Study IMP20317 originated from one center only, and, due to known variations in the standard of care, this center may or may not be representative of the general U.S. population.

Long-term use [off-label] is some concern, mainly because of the lack of information. Finally, **Question 6**, dealing with demonstration of safety and effectiveness of rh-GH alone or in co-therapy with glutamine in patients with SBS and additional studies they would recommend was rephrased after Agency clarification on the several possible answers was provided.. The final vote on the modified question was 3 Yes, 6 No. Although some discussants recommended additional studies, the Committee was unclear as to what should be done before approval and what may be requested as Phase IV commitments.

Based on the assessment of the overall available evidence, which included the initial Medical Team Leader's review, considerations, deliberations, discussion of concerns and recommendations around the 6 questions on efficacy and safety addressed at the June 25, 2003 GI Advisory Committee meeting, the Division concluded that NDA 21-597 was **approvable.**

At a July 23, 2003 meeting between Serono and FDA representatives, the sponsor was informed that NDA 21-597 is **approvable.**

Serono was told that the following deficiencies must be addressed before approval of the application is granted [**NOTE**: these deficiencies are listed here in the order they have been reviewed and evaluated in the current review. This sequence is different from the order the deficiencies were listed in the initial MTL's review of the 21-597 application or the order in which they were communicated to the sponsor at the July 23, 2003 meeting. However, the **content is the same**] 1. Additional data in support of replicability/generalizability, which consists of A. Data on additional patients treated by Drs. Li and Zhu in China and B. Statistical Meta-review of published literature on SBS; 2. Initial data in support of durability of effect, which consists of follow-up information on the 41 patients treated in Study IMP20317; and 3. An Educational Plan.

With regard to item **1. A.,** above, the sponsor was asked to update the information from a recent publication presented at the time of the June 25, 2003 GI AC meeting. This research, which uses the Serono rh-GH is being carried out by Dr. Jieshou Li of Nanjing, China. A translation of the entire manuscript-including data from 37 patients --27 in the previous publication, 10 in the update--should be submitted. The information to be submitted should include the demographic data, the small intestinal length of participating patients, with information on the ileo-cecal valve and colon, time since diagnosis of SBS, and the actual treatment per patient [amount and regimen of rh-GH, amount of oral glutamine per kg per day] and other aspects of nutritional support (amount of kcal per day from enteral nutrition, and amount of CHO and fat in the diet). Parameters of evaluation should include nitrogen balance, plasma levels of proteins, intestinal absorptive capacity, and the number of patients who were weaned off parenteral or enteral nutrition completely and were able to live on a well-tolerated high-carbohydrate low-fat diet, so as to get an idea of durability of effect. Under **1. B.**, to further document short-term efficacy and safety of the drug under different clinical settings but with Protocol designs similar to IMP20317, and in an attempt to address other issues such a dose-response, the sponsor was asked to analyze literature publications where the results of the trials demonstrated that rh-GH is efficacious. It was noted that for this information to be useful, the emphasis should be in studies using not only the Serono rh-GH product but also the proposed Serono regimen. In addition, whenever possible, source documents should be obtained. Under

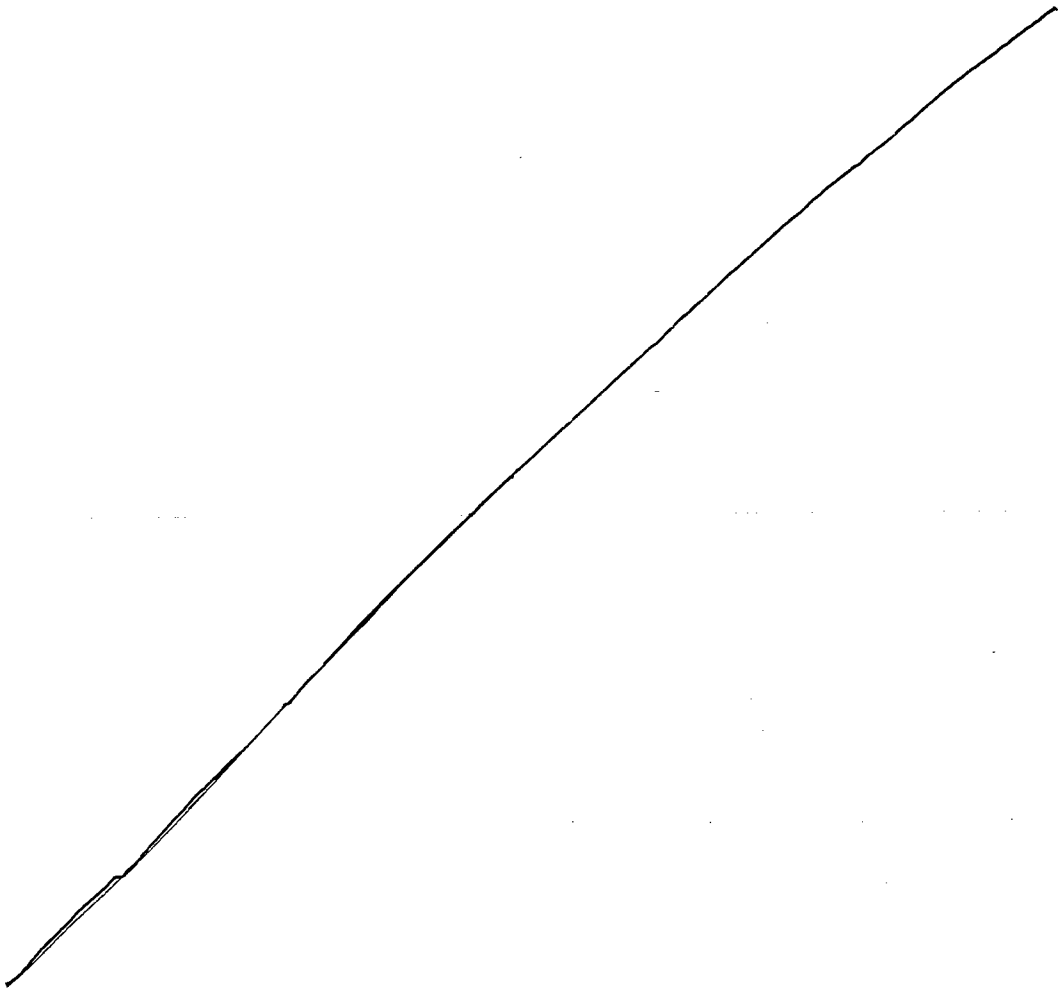
item 2., the sponsor was asked to present follow-up information [as long as possible after treatment discontinuation] on the 41 patients treated in Study IMP20317. These data were expected to provide initial information in support of the durability issue. Finally, **under 3.** Serrono was asked to propose an Educational Plan. The applicant was asked to provide a comprehensive Educational Plan for physicians prescribing the drug, ancillary personnel involved in the care of the SBS patient, notably specialized personnel such as nutritionists and other health care providers. The plan is expected to include continuing education in all aspects of the clinical condition as well as all aspects of the treatment regimen [rh-GH either alone or in co-therapy with glutamine]. The sponsor plan is expected to include training materials, communication, all kinds of support of these patients and a periodical appraisal of the success of the plan. Potential remedies in the event the Plan is failing should also be prospectively stipulated.

On **August 27, 2003**, the sponsor submitted information on each of the above-listed deficiencies that need to be addressed in order for NDA 21-597 to be approved. Without exception, all of the requested information and the formulation of an education plan, has been properly addressed. The sponsor's submission, the main object of this review, was evaluated in detail in Section III of the current review. A concise account of the reviewer's summary/conclusions from these subsections follows.

With regard to III. 1. A. the sponsor presented a comprehensive account and an update of the Study by Drs. Li and Zhu and their co-workers from Nanjing, China The trial is an **uncontrolled review of practice and results in their referral institution.** The study is set to investigate the effect of rehabilitation therapy for SBS on patient nutritional status [as determined by body weight, serum total protein, serum albumin and hemoglobin concentration] and intestinal adaptation [as determined by daily stool frequency, stool nitrogen content (Kjeldahl), and intestinal D-xylose absorption]. Because there is no concurrent control, the data compared results before and after the experimental treatment which included a rehabilitation diet plus the subcutaneous injection of GH manufactured by Serono, at the daily dose of 0.0532 mg/kg/d plus glutamine. From the available results, the sponsor concluded that, after the treatment, nutritional status of the patients improved markedly, and intestinal absorptive capacity improved. The reviewer agrees that the results of this trial appear to lend some support to the concept of generalizability of the treatment. But a number of constraints, arising from the design and execution of the trial, preclude the formulation of definite conclusions on efficacy. Among these constraints are lack of randomization and double-blinding [two powerful tools to minimize bias], lack of a suitable and relevant control, and the fact that --although the treatment duration was 3 weeks-- the product was tested at less than half the daily dose used in pivotal study IMP20317.

Under III. 1. B., and with the intention of reviewing all relevant published literature on the use of GH in SBS, the sponsor tabulated the summarized results of SBS publications. Thirteen studies and reports, comprising a total of 214 subjects, were listed. Of these, 3 are double-blind, controlled studies comprising a total of 28 patients. One additional double-blind, controlled study with a total of 10 patients was summarized separately because --although placebo was used as a comparator-- no between group comparisons were reported. The remaining studies, comprising 176 patients, are not placebo controlled. As shown in Table 4 of the current review, there was no

consensus on the dose or manufacturer's brand of GH to be used. Only one of the listed studies, that of Zhu et al [reviewed in detail under Section III. 1., A. of the current review], used GH manufactured by Serono. Although they may, somehow, add to the concept that the GH treatment is generalizable, in the final analysis, results of these studies were not very helpful. A formal meta-analysis was not considered because of the large variety of endpoints employed in the published studies examined and the lack of validated means of combining these endpoints with the clinical endpoint [reduction in IPM requirements] used in Serono Study IMP20317.



On the other hand, reviewed under Section III. 3. of the current review is the DRAFT Educational Plan proposed by the sponsor. The Plan is to be finalized and represents a Phase IV commitment. Although minor adjustments might be needed, the proposed Plan is comprehensive and nearly complete. Most of the Plan components are presented in the current review in the form of Appendices. The DRAFT Plan consists of 1. an Executive Summary; 2. an Educational Plan for Health Providers [with the following components: Identify Members of the Target

Audience (likely universe prescribers, SBS and Serostim® prescribers (SBS), Fully Developed Educational Materials, Educate (consisting of a First Wave and a Second Wave} and Validate]; 3. an Educational Plan for Patients [which includes Development of Educational Materials and a Call Center); 4. an Educational Program Evaluation Form for Healthcare Providers; 5. a Serostim®/SBS Treatment Guidelines; and 6. A Serostim®/SBS Patient Handbook Outline. Although these DRAFT documents all seem adequate, the following revisions are recommended:

i. DRAFT Educational program Evaluation Form for Healthcare Providers

The DRAFT Educational Program Evaluation Form for Healthcare providers appears to be adequate to evaluate the effectiveness of the proposed Educational Plan. However, the sponsor needs to prospectively define what constitutes success and what failure. Equally important, potential remedies in the event the Plan is failing, should also be prospectively stipulated.

ii. DRAFT Serostomin®/SBS Patient Handbook Outline

The Patient Handbook is an excellent idea but it should be used as an adjunct education/risk communication material, not the only patient education/risk communication material provided to patients for this product. Patient Information should be the primary risk communication tool provided to patients with each prescription and refill. The DRAFT Patient Handbook appears to provide comprehensive information on the disease, management, and treatment with Serostim®. The Patient Handbook should:

- be written at the 6th to 8th grade reading comprehension level. Keep sentences short, words simplified, explain any medical or technical term, and bullet information when possible.
- have a font size of at least 10 point to aid in ease of readability
- have adequate background contrast and white space to aid in ease of readability; not be overwhelmed by background pictures or artwork
- be non-promotional in tone

Ideally, the Patient Handbook would be tested for comprehension among a cross section [varying educational levels, including those with low literacy] of Serostim® treated SBS patients.

VI. Recommendations for Regulatory Action

1. NDA 21-597, Serostim® for the treatment of SBS patients, should be approved.

2. **Phase IV Commitments:**
   Complete the development of and set up an **Educational Plan** once all components of such a Plan have been revised and finalized. The Program should start within four months of drug approval.

.....
Hugo E. Gallo-Torres, MD, PhD, PNS
Medical Team Leader (GI Drugs)
HFD-180

Appendices

Appendix 1

DRAFT Serostim®/SBS Educational Program Evaluation Form

DRAFT Serostim®/SBS Educational Program Evaluation Form

You recently received educational materials from Serono, Inc. about the use of Serostim® and specialized diet for patients on Parenteral Nutrition (PN) for Short Bowel Syndrome. To ascertain the effectiveness of the materials, *especially as they relate to your actual experience*, we would like to ask a few questions. Your answers will help us improve future educational initiatives.

Thank you very much for your time.

	Evaluation	Very Dissatisfied	Dissatisfied	Neutral	Satisfied	Very Satisfied
1)	Overall, how satisfied are you with the materials.	1	2	3	4	5
2)	Please indicate how you feel about the following statements concerning these materials:	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
a)	The materials adequately described	1	2	3	4	5
b)	appropriate candidates for GH and special diet therapy.	1	2	3	4	5
c)	Concurrent specialized diet therapy is	1	2	3	4	5
d)	adequately described The management of GH therapy is adequately described Suggested PN weaning criteria were helpful	1	2	3	4	5
e)	The information in these materials contributed as much as possible to successful patient outcomes	1	2	3	4	5
f)	The patient education materials contributed as much as possible to successful patient outcomes.	1	2	3	4	5

1) How would you improve these materials?

Comments

2) Do you wish to be contacted about your responses? ❑ Yes ❑ No

Contact Information (Optional)

Name: «PrescriberName»
Institution: «Institution»
Address: «Address1»
«Address2»
«Address3»
«City», «State» «Zipcode»

Appendix 2

DRAFT Serostim®/SBS Treatment Guidelines

DRAFT Serostim®/SBS Treatment Guidelines

Patient Selection

- 18 years of age or older
- BMI ≥17 kg/m^2
- Able to ingest some solid food regularly but PN still required
- Stable medication (e.g., antidiarrheal) regimen
- Acceptable liver and renal function
- Small bowel ≤200 cm
- Stable following bowel resection surgery (e.g., at least 1-month post-resection)
- Intact stomach and duodenum plus:
  - — ≥30% functioning colon and ≥15 cm intact jejunum and/or ileum
    and/or
  - — <30% functioning colon but ≥90 cm intact jejunum and/or ileum
    and/or
  - — Stool output ≤3.5 L/day

Dietary Modifications

- ***Check nutrient status***
  - ***— Measure body weight and height***
    - — Obtain baseline biochemical screen—hemoglobin, hematocrit, serum electrolytes, iron, total iron-binding capacity, albumin or transferrin, phosphorous, and trace element levels
- **Begin dietary modifications at least 2 weeks prior to growth hormone therapy**
- Adequate daily calories based on formula*: REE x AF (1.2 to 1.5) x MF (1.2 to1.7)
- Total daily caloric intake according to following ratio:
  - — Carbohydrates 50% to 55%: Proteins 20%: Fats 25% to 30%
  - — Recommended mainly in form of complex carbohydrates, amino acid-rich proteins (e.g., chicken, fish, turkey), fats rich in linolenic and linoleic acid
- Oral rehydration solutions – 1.5 L/day
- Oral nutrient supplementation to include multivitamin, vitamin B12, vitamins A, E, D, K, calcium, zinc (if stool >1 L/day), potassium, magnesium, and phosphorus as needed based on biochemical screen
- Glutamine supplementation based on physician judgment
- If colon is intact, avoid oxalate-rich foods

Administration of Serostim®

- Calculate appropriate dose (see Table 1)
  - — 0.10 mg/kg/day to maximum of 8 mg/day
- Injections administered each evening for 4 weeks
- Avoid changes to concomitant medications
- Patients and physicians to monitor for adverse events:
  - — Treat moderate fluid retention and arthralgias symptomatically or dose reduce by 50%
  - — Discontinue Serostim® for up to 5 days for severe toxicities
  - — Upon resolution of symptoms, resume at 50% of original dose
  - — Permanently discontinue if severe toxicity recurs or does not disappear within 5 days

Reduction in PN

- At each weekly evaluation re-assess for reduced PN needs based on following criteria:
  - — Weight maintenance or gain in absence of fluid accumulation

  Plus two of the following:
  - — Urine output ≥1000cc/day *and/or*
  - — Oral intake>GI output by 500cc/day *and/or*
  - — Stable laboratory values (ie, Hgb, Hct, BUN, creatinine, electrolytes)
- Patients must also consistently consume 80% to 100% of estimated total caloric requirements.
- If criteria are met, PN may be decreased weekly by up to 25% of the pre-treatment regimen or by the volume of urine that exceeds 1000 cc/day.

PN Reduction Management

- After baseline visit, follow-up calls with patient or home care nurse at weeks 1 2, and 3, of Serostim® treatment and visits at weeks 4 and 8, with additional visits at physician's discretion.
- Despite complete or partial discontinuation of PN after 4 weeks of Serostim®, some patients may still require intravenous hydration fluid — administer at physician's discretion

REE=resting energy expenditure; AF=activity factor; MF=malabsorption and diarrhea factor; PN= Parenteral Nutrition

Patient Selection:

To be considered for Serostim® therapy, eligible patients diagnosed with SBS should meet the following criteria:

- Small bowel ≤ 200 cm
- Stable following bowel resection surgery (e.g., at least 1 month post resection)
- Intact stomach and duodenum plus 1 or more of the following:
  - ≥30% of colon functional, and ≥15 cm of jejunum and/or ileum intact
  - <30% of colon functional, but ≥90 cm of jejunum and/or ileum intact
  - Stool output ≤3.5 L/day

Additionally, patients should:

- Be 18 years of age or older
- Maintain body mass index ≥17 kg/m^2
- Eat some solid food on a regular basis but require PN for nutritional support
- Maintain acceptable liver and renal function based on the following laboratory values:
  - Total serum bilirubin < 3 times the upper limit of normal
  - Serum creatinine level ≤ 3 mg/dL

Avoid treatment or proceed with appropriate caution in patients with the following clinical conditions:

- Secretory bowel disease: stool output ≥800 mL/24 hours when there has been no oral intake of food for 24 hours
- Pregnancy or lactation
- History of cancer within 5 years (with the exception of nonmelanoma skin cancer or in situ carcinoma of the cervix)
- Diabetes mellitus
- Uncompensated cardiac failure
- Carpal tunnel syndrome

Dietary Modifications

At least 2 weeks before initiation of Serostim® therapy, nutrient status should be checked and dietary modifications made to prepare patients for the reduction in both volume and frequency of

intravenous nutrition that will accompany administration of Serostim®. Nutrient status is assessed through determination of body weight and height as well as a biochemical screen. The baseline biochemical screen involves measurements of hemoglobin, hematocrit, serum electrolytes, including calcium and magnesium, iron, total iron-binding capacity, albumin or transferrin, phosphorous, and trace elements.

By ensuring adequate nutritional status through oral feeding, the diet promotes nutrient absorption and independence from PN. Specific instructions should be tailored to the patient's individual requirements based on food sensitivities and nutrient deficiencies; however, the following general dietary guidelines are suggested:

Calories

- Calculate daily caloric requirements using the following formula: daily calories=REE x AF (1.2 to 1.5) x MF (1.2 to 1.7)
  - REE=Resting Energy Expenditure
  - AF=Activity Factor based on patient's level of physical activity
  - MF=Malabsorption and diarrhea factor
- Nutrient-dense foods are recommended to limit food volume
- Six to eight meals per day suggested

Carbohydrates

- 50% to 55% of total daily caloric intake should be in the form of carbohydrates. Emphasize complex carbohydrates (e.g., rice, potato, pasta) and limit simple sugars.

Proteins

- 20% of total daily caloric intake should be protein, which is provided at each of 6 to 8 meals per day. Emphasize protein sources rich in amino acids (e.g., chicken, fish, and turkey).

Fats

- 25% to 30% of total daily caloric intake should be fat. Recommended fats are rich in linolenic and linoleic acid (e.g., soybean oil, safflower oil) to avoid essential fatty-acid deficiencies.

Fluids

- Initiate oral rehydration solutions (carbohydrate and sodium-containing beverages) at 1.5 L/day
  - Increase as needed based on stool volumes and/or urine output
- Limit hypo- and hyperosmolar beverages
- Fluid intake should occur regularly throughout the day

Oral Nutrients

To avoid the long-term complications of altered bowel function, prevent nutrient deficiencies, and maintain serum electrolyte concentrations, the following oral nutrient supplementation is suggested:

- Multivitamin/mineral supplements (1 to 2 tablets daily)
- Vitamin B12 (100 µg to 300 µg monthly—if terminal ileum has been removed, administer via intramuscular injection)

- Fat-soluble vitamins (i.e., A, E, D, K)
- Calcium (1500 mg to 3000 mg daily)
- Zinc if stool volumes are greater than 1 L/day (15 mg daily)
- Potassium, magnesium, phosphorus as needed to maintain serum concentrations
- Glutamine (30 g/day administered in single-dose packets (5 g) mixed with water or other suitable beverage)
  - Based on physician judgment, diet may be supplemented with glutamine taken 6 times daily at 2 to 3 hour intervals with meals or snacks. A dose may be delayed for up to 2 hours due to transient intolerance.

Oxalate should be avoided in patients with an intact colon to prevent calcium-oxalate renal stone formation.

Administration of Serostim®

Serostim® is administered subcutaneously according to weight (0.10 mg/kg/day) up to a maximum dose of 8 mg/day. The specific dose can be calculated or determined from the dosing algorithm presented in Table 1. Serostim® injections are administered each evening for 4 weeks.

Volume of administration can be up to 1 ml. The medication is supplied in 8.8-mg vials with bacteriostatic water for dilution. For patients receiving <8 mg/day, the residual reconstituted solution can be stored overnight in a refrigerator and used as part of the next day's injection.

Table 1. Serostim® Dosing Algorithm Based on Body Weight

Weight Range		Dose
Kilograms	Pounds	Dose of rhGH (mg)
≥ 75	≥ 165	8.0
65 - 74.9	143 - 164.9	7.0
55 - 64.9	121 - 142.9	6.0
45 - 54.9	99 - 120.9	5.0
35 - 44.9	77 - 98.9	4.0

During administration of Serostim®, it is recommended that patients remain on their regular concomitant medications. Modifications should be avoided, although a diuretic may be added if required to manage fluid retention resulting from Serostim® therapy.

The following moderate toxicities can generally be managed by reducing the daily dose of Serostim by 50% or to 0.05 mg/kg/d:

- Significant ankle swelling not responsive to diuretic agents*
- Joint or hand pains not responsive to anti-inflammatory drugs*
- Serum triglycerides ≥ 500 mg/dL but < 750 mg/dL measured prior to lipid infusion

- Blood glucose > 160 mg/dL fasting
- Blood pressure ≥ 150/110 mm Hg

* Patients should be taught to recognize the symptoms associated with these adverse events. Patients who complain of these symptoms, or any other new-onset symptom, should be instructed to call their treating physician for advice as to the next step in management (e.g., dose reduction or discontinuation as deemed appropriate).

Stop Serostim® immediately if there are signs or symptoms of an anaphylactic reaction (*e.g.*, laryngospasm or bronchospasm) following subcutaneous injection.

Severe toxicities are rare. They include:

- Congestive heart failure
- Pancreatitis—serum amylase >2 times upper limit of normal
- Severe paresthesias
- Significant allergic reaction
- Benign intracranial hypertension
- Abnormal biochemical test results, particularly:
  - Severe elevation in serum triglycerides (≥750 mg/dL) measured prior to lipid infusion
  - Severe hyperglycemia —any blood sugar ≥ 200 mg/dL

Treatment with Serostim® should be suspended for up to 5 days if any of the above severe toxicities occur. Upon resolution of the adverse event, Serostim® may be resumed at a dose reduced by 50% to 0.05 mg/kg/day. Failure of the event to resolve within 5 days or recurrence of a severe toxicity indicates that Serostim® should be discontinued permanently.

Reduction of PN During Treatment

After a baseline visit, it is recommended that patients are evaluated by phone (weeks 1, 2 and 3 of Serostim® therapy) and visits (week 4 of Serostim® therapy, and then again a month later). More frequent calls or visits may be recommended at the physician's discretion. Reductions can be made to a patient's PN regimens if the patient meets the following criteria:

- Maintenance of or weight gain in the absence of fluid accumulation
- Two of the following:
  - Urine volume: output of at least 1000 cc/day for adults
    - PN should be reduced by the average volume of urine that exceeds 1000 cc/day (e.g., if the patient averages 1500 cc/day for a week, decrease PN by 500cc/day)
  - Positive enteral balance: oral intake greater than GI output by 500 cc/day
  - Stable hemoglobin, hematocrit, BUN, and creatinine values

In addition, patients must consistently consume 80% to 100% of estimated total caloric requirements to be considered for a reduction in PN.

Failure to meet the criteria precludes reduction in PN until the next weekly evaluation. Should PN be reduced and the patient experiences volume-related adverse reactions, the physician should restore the PN volume to that prescribed prior to the last reduction.

PN may be reduced weekly by up to 25% of the pretreatment regimen, although more specific quantities can be determined by urine volume as described above.

Management after Serostim®/PN Reduction

To assess adequacy of nutritional and hydration status, it is suggested that patients return to their physician at week * (one month following 4 weeks of Serostim® therapy). Additional visits may be required at the physician's discretion.

Intravenous hydration fluid may still be required following 4 weeks of Serostim® treatment even though PN has been completely or partially discontinued. Intravenous fluids should be administered based on the physician's judgment.

Appendix 3

DRAFT Serostim®/SBS Patient Handbook Outline

DRAFT Serostim®/SBS Patient Handbook Outline

I. Short Bowel Syndrome (SBS)
   a. Description - What is SBS?
      i. Consequence of surgical removal of large portion of small intestine
      ii. Why does it occur? Inability to absorb fluid and nutrients
      iii. Signs and symptoms of SBS
         1. Include diarrhea, dehydration, weight loss
         2. Other conditions which result from impaired absorption of nutrients and resulting malnutrition
      iv. Course of illness

   b. Treatment
      i. Dietary management – to be described in detail in section II
      ii. Intravenous nutrition – frequently required, at least initially, to maintain nutritional needs
         1. Benefits: provides critical fluid and nutrition
         2. Drawbacks
            a. Potential medical complications (e.g., blood clots, infection)
            b. Modification of lifestyle
            c. Cost
      iii. Enteral formulas – sometimes used to supplement oral or intravenous nutrition
      iv. Serostim®– practical treatment guidelines to be discussed in section III
         1. Clinical study overview – purpose and desired outcome of treatment
         2. Efficacy
         3. Side effects
            a. What to look for
            b. What to do if they occur

II. Dietary Recommendations – specialized oral diet for SBS
   a. Goals of proper dietary management
      i. Avoid symptoms associated with severe malabsorption
      ii. Decrease reliance on intravenous nutrition
   b. Optimal caloric intake – determined by physician based on activity level, resting energy expenditure, and malabsorption/diarrhea
   c. Recommended carbohydrate, protein, and fat intake
      i. Complex carbohydrates
      ii. Amino acid-rich proteins (e.g., chicken, fish, turkey)
      iii. Linolenic and linoleic acid-rich fats (e.g., soybean oil, safflower oil)
   d. Consume food in small quantities
   e. Oral rehydration recommendations
   f. Vitamin and mineral supplementation

g. Glutamine supplementation
h. Avoidance of oxalate-rich foods

III. Serostim® Treatment Guidelines - Overview
a. Are you a candidate for Serostim®?
b. What to expect as you prepare to start therapy (e.g., diet, monitoring by your physician)
c. How Serostim® is administered
    i. Subcutaneous administration
    ii. Frequency and duration
d. What to expect with Serostim®
    i. Adverse events – what to look for, how to treat, and when to call your healthcare provider.
e. What your doctor will look at before reducing your intravenous nutrition administration
    i. Weekly evaluations
    ii. Criteria
f. After the Serostim® is administered – following up with your physician

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/s/

Hugo Gallo Torres
11/13/03 10:31:23 AM
MEDICAL OFFICER