

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

Treatment of Short Bowel Syndrome

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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: C₉₉₀H₁₅₂₈N₂₆₂O₃₀₀S₇
Molecular weight: 22,124
Formulation: lyophilized
Route of Administration: subcutaneous
Strengths: 4mg, 5mg, 6mg, 8.8mg

Related NDA: 20-604

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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 should not be approved at this time. Several issues need to be addressed, clarified, and eventually resolved before the application is approved. Included among these issues are: 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*. On the one hand, 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. On the other, in placebo-controlled, crossover 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 increased.

B. Additional Recommendations

1. A randomized clinical trial to determine the proportion of Short Bowel Syndrome patients in whom administration of recombinant human GH in co-

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therapy with glutamine, in patients who are receiving a specialized oral diet (rh-GH + SOD[GLN]) at the recommended dosage results .

in the patients being weaned completely from IPN and remain off for at least one year following admission into an in-home program.

2. A study, similar in design and execution to that in Ref. 9 (Table 2 of the current review) to assess the efficacy and safety of low-dose rh-GH (0.05 mg/kg/d) when administered in co-therapy with glutamine and SOD in adult home parenteral nutrition-dependent Short Bowel Syndrome Patients.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

The Clinical Program consists primarily of a clinical and statistical Study Report from Protocol IMP20317, a 3-arm, 41 patient total, double-blind, randomized Clinical trial. 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 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 as A, B, and C, in the trial. Group A consisted of active rh-GH plus glutamine placebo in patients who are receiving SOD.

The most important comparison is that of Group B, consisting of rh-GH in co-therapy with (active) glutamine and a specialized oral diet, to Group C, a control arm, consisting of (active) glutamine plus the specialized oral diet plus rh-GH placebo. 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 this trial, 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. 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

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admission into an in-home program. Results using this parameter (Table 8 of the current review) should be considered hypothesis-generating only. Results of evaluations using the protocol pre-stipulated study endpoints seem too incomplete to determine if they are predictive of clinical benefit.

NOTE: Issues regarding the one study approach are discussed 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 rhGH in co-therapy with glutamine and a specialized diet in patients with SBS treated for up to 16 weeks. The safety profile of the triple co-therapy 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 are 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.

A low-dose rh-GH should be considered.

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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), evaluation of the use of the drug in Special Populations is not very helpful. 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. 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 and 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."

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, and 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 use⁴ and Geriatric use⁵.

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 these 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 generally demonstrate few symptoms after resection of up to 50% of the small

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.

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 B₁₂, 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 approaches¹⁰ 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.

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 B₁₂ 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).

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 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	<p>?? Sponsor was Cato Research</p> <p>?? Pre-IND meeting to discuss research plans for the use of the proposed drug combination [Glutamine (GLN) + Growth Hormone (GH)]</p> <p>?? Pre-clinical data seemed to indicate 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.</p> <p>?? 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). An initial group of 7 patients served as their own control; the experience was later expanded to 24 patients. The indication was the reduction/elimination of TPN in patients with absorptive deficiencies, such as 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 to 33%.</p> <p>?? 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.</p> <p>?? 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.</p>
August 3, 1995	<p>?? FDA (DMEDP) letter to sponsor providing comments on design of a clinical trial that would confirm findings and answer questions required for approval.</p> <p>A 3-arm randomized double blind study with 5 patients receiving GH only, 5 receiving GLN only and 5 patients receiving the combination was recommended.</p>
June 15, 1997	<p>?? FDA (DMEDP) letter to sponsor stating that the revised protocol "would suffice as <u>a</u> pivotal study for an NDA". The study revisions did not include the 3-arm design recommended by the Agency.</p>
March 28, 2000	<p>?? The Sponsor (Serono Laboratories and Nutritional Restart Pharmaceutical) submitted a protocol amendment that changed the study design to single center.</p>
June 7, 2000	<p>?? 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.</p>
August 22, 2000	<p>?? 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.</p>

<p>September 6, 2002</p>	<p>?? 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.</p> <p>?? 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:</p> <p>??</p> <ul style="list-style-type: none"> - Group 1: specialized diet including glutamine (SD/GLN, n= 9) - Group 2: 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. <p>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.</p> <p>NOTE: It is worth noting that the sponsor has eventually submitted the information requested at this pre-NDA meeting.</p>
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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. E. 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 VI.D. 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 reviewer is concerned rh-GH may have long-term toxicity. 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 simply unknown.

Some important issues with pharmacologically-related agents (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- β , 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 gastric, that are trophic.¹⁴

?? At physiological doses in man, peptide YY¹⁵ 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. It 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- β 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- β is in the superficial (non-proliferative) zones. It may therefore be that its major role is to maintain cell migration and differentiation as opposed to proliferation.¹⁶

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)]

¹⁶ TGF- β "knock-out" mice have an increased susceptibility to injurious agents to the colon [Egger, B. et al. Mice lacking transforming growth factor β 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

?? The rapid-response peptides are the trefoil peptide family (e.g. spasmodic 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-workers¹⁸ 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. Ysem, somatropin (rDNA origin) for injection is an approved drug, under NDA 20-604 for treatment of AIDS wasting and 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 application, for a new indication (short bowel syndrome, NDA 21-597) will not increase the use of the active moiety, somatropin.

small intestinal injury [Macdonald, C.E. et al Transforming growth factor β 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-22 as therapy for the short bowel syndrome. Gastroenterology 120:1041-1048 (2001)

?? 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 r-hGH. 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, rhGH [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)

?? 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

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 parentally 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)

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)

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 rGH 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 rGH. Nevertheless, rGH 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 rGH clearance is similar between adults and children. However, only a limited number of pediatric patients were included in the clinical trials.
- ?? 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.
- ?? **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

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)

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

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)
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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 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

> 55	6
45-55	5
35-45	4

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

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

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, 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**

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).

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. Gastroenterology 124: 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 patient's 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	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 +/- 0.3kg 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 ?-aminoisobutyric acid and glucose by BBMVs as measured by a rapid mixing/filtration technique.	?? Treatment with low-dose GH resulted in a statistically <i>insignificant</i> increase in amino-acid transport rates in jejunal and ileal BBMVs. ?? High-dose GH resulted in a generalized 20% -to &0%-stimulation of a-a 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.	<p>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 <i>ad libitum</i> oral diet, but without parenteral support they were unable to adequately maintain hydration and/or nutritional status.</p>	<p>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.</p>	<p>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.</p> <p>Throughout the study all stool was collected and analyzed to determine absorption across the remaining bowel.</p> <p>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.</p>	<p>?? 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.</p> <p>?? 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.</p>
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)				

<p>4.</p>	<p>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.</p>	<p>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.</p>	<p>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.</p>	<p>?? Tx with diet alone did not influence nutrient absorption or stool output.</p> <p>?? 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).</p> <p>?? Fat absorption did not change (61.0 to 60.3%)</p> <p>?? There was also a significant increase of water and sodium absorption.</p> <p>?? 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)</p>
<p>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)</p>				
<p>5.</p>	<p>10 patients (3F, 7M) with SBS for more than 1 year because of Crohn's disease. Some pts. had some blood chemistry 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 2.0 kg (range</p>	<p>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, subcutaneously during 8</p>	<p>Absorptive capacity and biochemical parameters were investigated in a metabolic ward before Tx and during first and last week of Tx. Body composition was determined by DEXA-Scan (Lunar DPX, Scanexport Medical, Helsingborg, Sweden), impedance analysis, and whole body potassium counting.</p>	<p>?? 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.</p> <p>?? Low-dose rhGH doubled serum concentrations of IGF-1 and increased body weight, lean body mass, and total body potassium by 5%.</p> <p>?? Fat-free mass and total body water increased by 6% (p = 0.008).</p> <p>?? Increased in IGF-1 levels correlated with increase in fat-free mass (r = 0.77, p< 0.02).</p> <p>?? No significant changes in absorptive capacity of water, energy, or protein were detected.</p>

	0.9 to 5.8 kg). All required oral or parenteral fluid substitution in combination with electrolytes, vitamins, and minerals.	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 4d on 3 separate occasions, 21 days apart. Active Tx was 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 Tx's were compared by paired <i>t</i> test.	?? rhGH 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 bowel length was 30 to 150 cm and 4 patients had a part of colon in function	Double-blind, placebo-controlled, randomized, crossover. Active Tx consisted of subcutaneous rhGH [0.14 mg/kg/d; Norditropin, Novo-Nordisk AS, Bagsvaerd, Denmark] divided into 2 daily injections, oral l-glutamine (30 g/d; Ajinomoto, Kawasaki City, Japan) divided into 6 doses dissolved in a beverage of the	?? 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). ?? 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	?? 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. ?? Only 1 of 8 patients, who did not receive parenteral lipids, had a Holman index above 0.2, indicative of EFA deficiency.

	(28%, 43%, 86%, and 86%).	patients' choice, and parenteral GLN as GLN-enriched infusions (17% of Nas 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.	were analyzed by GLC.	?? 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.	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. Oral GLN [Cambridge Nutraceuticals, Boston, Mass, USA] was provided at a dose 30 g /d (5 g/ 6x per day)	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.. ?? 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)				

<p>9.</p>	<p>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.</p>	<p>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.</p>	<p>Immediately before the first Tx period (baseline)and at the conclusion of each Tx period day21), a nutrition status (body weight, body mass index, skinfold thickness, bioelectric impedance analysis) assessment was performed.</p> <p>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).</p> <p>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).</p> <p>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.</p>	<p>?? Treatment with GH increased intestinal absorption of energy (15% ± 5%, p < 0.002), nitrogen (14% ± 6%, p < .04), CHOs (10% ±4%, p < 0.04), and fat (12% ± 8%, NS).</p> <p>?? According to the authors' calculations, the increased food absorption represented 37% + 16% of total parenteral energy delivery.</p> <p>?? 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) increased, whereas uptake of GH binding protein decreased (p < 0.01) , without any apparent major adverse effect.</p>
<p>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)</p>				

D. Were Trials Conducted in Accordance with Accepted Ethical Standards
Yes.

E. Evaluation of Financial Disclosure

Adequate Financial documentation was submitted for the following Investigators/Sub-investigators participating in pivotal Protocol No. IMP20317, "Randomized, Double-blind, Controlled, Parallel-Group Evaluation of the Relative Efficacy and Safety of Recombinant Human growth Hormone and Glutamine, Singly and as Co-therapy, in the Improvement of Residual Gut Absorptive Function in Patients with Short Bowel Syndrome":

David B. Lautz, MD [Brigham and Women's Hospital, Boston, MA], David Clark Jacobsen, MD [Harvard Vanguard Medical Associates, Medford, MA], Theresa Byrne, D.Sc., R.D., Nutrition Restart Center, Hopkinton, MA], Malcolm K. Robinson, MD [Brigham and Women's Hospital, Boston, MA], Kishore R. Iyer, MBBS, FRCS, University of Nebraska Medical Center, Omaha, NE] and John K. DiBaise, MD, University of Nebraska medical Center, Omaha, NE].

In this reviewer's opinion, none of these financial disclosures could cast doubt on the findings presented by the sponsor of this NDA.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

As noted in Section I.A. of the current review, the sponsor is seeking the indication "*treatment of SBS in patients receiving specialized nutritional support. Serostim[®] therapy should be used in conjunction with optimal management of SBS*". In support of this request, the sponsor evaluated the effects of the drug in SBS patients who were dependent on intravenous parenteral nutrition for nutritional support. This assessment showed a decrease in the Total IPN volume requirement (therapeutic gain = 3.9 liters per week) in SBS patients who were receiving a specialized diet and were given rh-GH, at the subcutaneously administered daily dose of 0.1mg/kg plus glutamine, in comparison to a control. The latter consisted of SBS patients who, in addition to the specialized diet (as the experimental group) were given glutamine and rh-GH placebo. However, as noted in several sections of the current review, issues such as the clinical validity of the protocol-stipulated primary efficacy parameter, the effect of low-dose of the hormone, replicability/generalizability, the potential toxicity of GH when administered long-term and the role of glutamine and the "specialized diet" need to be carefully considered before definitive conclusions can be formulated.

B. General Approach to Review of the Efficacy of the Drug

The efficacy database consists primarily of results from pivotal Protocol No. IMP20317, a (one) randomized clinical trial undertaken to evaluate the "relative" 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: <ul style="list-style-type: none"> - 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: <ul style="list-style-type: none"> 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 are 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 rhGH 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). 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-to3 -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. As noted by Dr. D. Price, the FDA Statistician reviewer, 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 information on the diet is 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, rhGH + SOD; Group B, rhGH + SOD[GLN]; and Group C, rhGH 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 the subject of 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

- ?? Total volume is the sum of the volumes of:
- a) IPN volume plus
 - b) supplemental lipid emulsion (SLE) plus
 - c) intravenous hydration fluid administered each week.

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.

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 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

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.

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.

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 Byrne⁴¹.

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 (rhGH + 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 rhGH groups, Group A: rhGH + SOD; Group B : rhGH + SOD [GLN] to the GLN-supplemented diet group (Group C: rhGH placebo + SOD [GLN]) by using the Dunnett-Hsu t-test.

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 who entered the study, 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 (RhGH + SOD)	GROUP B (rhGH + 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. The 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 thereby contributing non-significantly to the data used to assess efficacy and safety of the drug in SBS patients.

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. 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 in 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 this is an 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 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. Similarly, 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, jejunioileal bypass for morbid obesity and other. There were no gross imbalances among the treatment arms in underlying condition resulting in bowel resection and 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 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 rhGH+SOD n = 16	Group B rhGH+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 [mL/wk]	1970.6	1852.2	1877.8	N.S.
Mean IPN calories per week [kcal/wk]	1580.4	1486.3	1460.7	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 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 rh-GH, is a suitable control to test the effect of growth hormone (rh-GH) alone. For this comparison to be valid, there must be no significant changes between these two arms (B and C) in SOD as well as GLN.
- ?? Another comparison of interest might be that of B (3 co-therapies) **to A**, a test arm consisting of 2 co-therapies, rh-GH and SOD, but containing no 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 (alone) is settled by comparing results of Group B to C**. 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. In their summary Tables of efficacy, the sponsor also included a comparison between Groups A and C. Assuming that SOD is common to both arms, this comparison is of little if any interest because it would test the effect of 2 variables: rhGH (in arm A) vs. GLN (in arm C). If carried out (as the sponsor has) this represents 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 assessed in detail in the reviewer's efficacy evaluations and it is only briefly commented upon within the text of this review.

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. An unquestionably meaningful clinical nutrition endpoint would be the proportion of patients that, as the result of the intervention (administration of rh-GH

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%.

+ SOD[GLN]) **go off TPN and better yet, remain off TPN long-term.**

- ?? 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 rhGH alone versus rhGH 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, 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. A decrease of less than 2 liters of Total IPN volume does not seem to be clinically important.
- ?? 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.). The reviewer believes that no firm conclusions may be drawn from such a comparison.

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.

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 rhGH + SOD	B rhGH + 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
<small>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: In the E-E Study Population, the number of patients is 15 because results of Patient No. 106 are not included.</small>					

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 test medication arm) 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 rh-GH). The results with secondary parameters of efficacy, reduction of 3,117.9 kcal/wk, and especially, a reduction by 2 out of 7 days per week in the need for Total IPN do not seem to be clinically impressive. It is important to note that neither the primary nor the secondary parameters of efficacy measures 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 evaluation for the secondary efficacy endpoints are included in Table 7.

Although, according to the sponsor's statistical analyses, the difference between Groups A and C are statistically significant for the secondary parameters of assessment, the clinical impact, a reduction of 1705.0 kcal per week, but specially, one day less (6 instead of 7) in Total IPN or SLE, are of questionable clinical relevance.

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 with small number of patients per cell. 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. But each one of these parameters of evaluation may be subject to different definitions and varied interpretations. These parameters are hard to standardize. 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 initial data, it is worth mentioning that including percentages of patients when the total Study Population is so small is not very helpful. From the comparison of Groups B (the 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 result in more patients that could be weaned off Total IPN**. Confirmation of these findings would be important.

Table 8 Study IMP20317 Categorical Change (100% reduction) in Frequency of IPN or SLE Administration from Week 2 to Week 6		
ITT POPULATION		
Groups		
A rhGH + SOD	B rhGh + SOD[GLN]	C SOD[GLN]
[n = 16]	[n = 16]	[n = 9]
5	7	1
[5]*	[8]*	[1]*
<small>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. * A, B, and C, patients who remained weaned off IPN at 16 weeks</small>		

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 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 demonstrate that all groups increased their IPN requirements similarly during the Follow-up Period. These data are interpreted as showing that the persistence of treatment effects during the Follow-up Period was similar for all 3 treatment arms.

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** (including weekly IPN volume, calories, and frequency).

?? 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 subjects with lower body weights.
- **length of residual volume [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 were non-Caucasians.

NOTE : In all cases with a significant covariate, the effect of the test medication arm (group B, rhGh + 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.

⁴⁶ In those instances with a significant covariate, the comparison of Group A to C remained significant only when weight was used as a covariate.

?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.

D. Efficacy Conclusions

The question of efficacy is settled by comparing the active rh-GH-containing arm, Group B (rh-GH + SOD[GLN]) to Group C, the control. 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 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 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 rhGH in co-therapy with GLN (and SOD) in patients with SBS treated for up to 16 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 rhGH was a maximum of 28 days at 0.10 mg/kg/d (32 subjects)⁴⁷.

⁴⁷ Total exposure of subjects to rhGH placebo was a maximum of 28 days at 0.10 mg/kg/d (9subjects).

C. **Methods and Specific Findings of Safety Review**

- ?? During the Baseline Period, 88% of rh-GH +SOD[GLN] subjects and 88% of those receiving rh-Gh + SOD reported at least one Baseline Sign and Symptom (BSS) in comparison to 78% of those in the SOD[GLN] Group.
- ?? There were no deaths in this trial.
- ?? The most frequently reported BSSs included edema, fatigue, and gastrointestinal disorders, **all of which are signs and symptoms of SBS**.
- ?? During the treatment period, all of the subjects receiving rh-GH + SOD[GLN], as well as all of those treated with rh-GH+SOD reported at least one AE as compared with 89% of SOD[GLN] subjects.
- ?? The proportion of subjects experiencing at least one treatment-related AE in the rh-GH + SOD[GLN], rh-GH + SOD⁴⁸, and SOD[GLN] treatment groups was 88%, 94%, and 22%, respectively. Although 94% vs 22% appears quite different, these percentages are calculated from small number of patients. These are 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 occurrence 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 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 in all, 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 is 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. It is worth noting that long-term safety matters with growth hormone require further discussion.

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, Brammert 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-workers⁵¹, 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 this 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 dose

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 Brammert 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).

of 0.1 mg/kg subcutaneously daily to a maximum of 8 mg daily" . Based on 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)** and **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, 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). Therefore, 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 included.

X. OTHER

There are three issues, already noted during 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 demands 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 colonocytes⁵² 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 permeability⁵³. Enteral rather than parenteral GLN has also been shown to induce trophic or regenerative effects on the bowel⁵⁴. But the effects of GLN in the clinic appear inconsistent. Based on evaluations by Dr. D. Price, FDA Statistician, in Study IMP20317, the contribution of glutamine to the effect observed with growth hormone is not substantial.
- ?? 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 and that the evidence supporting a low-fat diet is based on short-term balance studies, where compliance is demanded, rather than on body weight 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

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)

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 issue is further addressed in Dr. Price's statistical review.

XI. Conclusions and Recommendations

A. 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. However, the clinical relevance of this endpoint (reduction in Total IPN volume requirement per week) must be established prior to approval.

B. Recommendations

NDA 21-597 deficiencies must be addressed.

FINAL NOTE: Regulatory discussion on the one study approach can be found in the following FDA document: **Guidance for Industry. Providing Clinical Evidence of Effectiveness for Human 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>]

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