

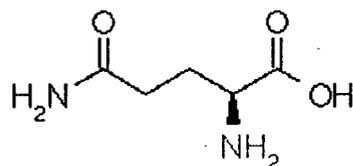
**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-667

MEDICAL REVIEW

NDA 21-667

Glutamine



NDA: 21-667

Chemical Name: Glutamine

Class: Nonessential Amino Acid

Date Received: August 12, 2003

Indication: Treatment of Short Bowel Syndrome

Dose: 30 grams/day Oral

Applicant: Nutritional Restart Pharmaceutical, L.P.

Documents Reviewed: NDA and Data Sets
NDA 21-597
Proposed Package Insert
GI Advisory Committee Meeting, June 25, 2003

Division Director: Robert Justice M.D. M.S.

Deputy Director: Joyce Korvick M.D. M.P.H.

Medical Officer: Gary Della'Zanna D.O. M.Sc.

Biopharmaceutical: Sue Chih Lee Ph.D.

Pharmacology: Ke Zhang Ph.D.

Statistician: Dionne Price Ph.D.

Chemistry: Maria Ysern Ph.D.

Project Manager: Tanya Clayton B.S

CLINICAL REVIEW

Table of Contents

Table of Contents	2
Executive Summary	5
I. Recommendations	5
A. Recommendation on Approvability	5
B. Recommendation on Phase 4 Studies and/or Risk Management Steps	5
II. Summary of Clinical Findings	6
A. Brief Overview of Clinical Program	6
B. Definitions	6
C. Efficacy	6
D. Safety	7
E. Dosing	8
F. Special Populations	8
Clinical Review	9
I. Introduction and Background	9
A. Drug: Glutamine	9
B. State of Armamentarium for Indication	9
C. Important Milestones in Product Development	10
D. Other Relevant Information	12
E. Important Issues with Pharmacologically Related Agents	12
II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews	12

CLINICAL REVIEW

III.	Human Pharmacokinetics and Pharmacodynamics.....	13
A.	Pharmacokinetics	13
B.	Pharmacodynamics	14
IV.	Description of Clinical Data and Sources	14
A.	Overall Data	14
B.	Tables Listing the Clinical Trials.....	14
C.	Post-marketing Experience	15
D.	Literature Review.....	15
V.	Clinical Review Methods.....	15
A.	How the Review was Conducted	15
B.	Overview of Materials Consulted in Review.....	16
C.	Overview of Methods Used to Evaluate Data Quality and Integrity	16
D.	Were Trials Conducted in Accordance with Accepted Ethical Standards.	16
E.	Evaluation of Financial Disclosure.....	16
VI.	Integrated Review of Efficacy.....	16
A.	Brief Statement of Conclusions	16
B.	General Approach to Review of the Efficacy of the Drug.....	17
C.	Detailed Review of Trial by Indication	17
D.	Disposition of Subjects:	24
E.	Protocol Deviations:.....	24
F.	Data Sets Analyzed.....	25
G.	Subjects Baseline Characteristics:	25
H.	Results of Efficacy Evaluations:.....	26
I.	Effects of Covariates on Primary and Secondary Endpoints	29
J.	Persistence of Treatment Effect:.....	30

CLINICAL REVIEW

K.	Efficacy Conclusions	31
VII.	Integrated Review of Safety	31
A.	Brief Statement of Conclusions	31
B.	Description of Patient Exposure	32
C.	Methods and Specific Findings of Safety Review	33
D.	Adequacy of Safety Testing	33
E.	Safety Conclusions.....	33
VIII.	Dosing, Regimen, and Administration Issues.....	34
IX.	Use in Special Populations.....	34
X.	Conclusions and Recommendations.....	35
	Recommendations.....	35

Clinical Review for NDA 21-667

Executive Summary

I. Recommendations

A. Recommendation on Approvability

The Applicant is seeking approval of oral glutamine as a *co-therapy* for the treatment of Short Bowel Syndrome (SBS) in patients receiving growth hormone (rh-GH) and specialized nutritional support. Based on review of the efficacy and safety data in this submission, this reviewer's recommendation is that the NDA be *approved*.

This application is supported by the same study and medical literature that resulted in the approval of Serostim (NDA 21-597) for the treatment of Short Bowel Syndrome (SBS) in patients receiving specialized nutritional support. The results of these studies were discussed during the June 25, 2003, Advisory Committee Meeting and were found to be clinically significant.

The Applicant submitted the results of protocol GH-003 and extensive medical literature to support the approval of oral glutamine for the treatment of SBS. Study GH-003 was successful in demonstrating that a treatment regimen including a specialized oral diet (SOD) with the addition of growth hormone for four weeks and oral glutamine (GLN) for 16 weeks resulted in a statistically and clinically significant reduction in total Intravenous Parental Nutrition (IPN) volume requirement per week in patients with short bowel syndrome. The data demonstrate that the co-therapy of growth hormone with glutamine is more effective than the presently approved treatment of growth hormone with a specialized oral diet.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

No Phase IV commitments are being requested.

CLINICAL REVIEW

Executive Summary Section

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

The clinical program consisted primarily of a 3-arm, 41 patient, double-blind, randomized clinical trial. The study evaluated the effect of glutamine in co-therapy with growth hormone (rh-GH) and a specialized oral diet, in the improvement of residual gut absorptive function in patients with short bowel syndrome. The trial was designed as a multicenter study, however, patients were enrolled in only 2 sites. One site randomized only 3 patients (1 per treatment arm), while the other randomized the majority of the patients (38) in a 2:2:1 ratio. Consequently, Study GH-003 was essentially a single-center study.

B. Definitions

Total volume: the sum of the volumes of IPN, supplemental lipid emulsion (SLE), and intravenous hydration fluid administered each week.

Total calories: the sum of kilocalories for carbohydrate, protein, and fat in the IPN, SLE and kilocalories in the intravenous hydration fluid.

Frequency: 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.

C. Efficacy

The study was comprised of three treatment arms: Groups A, B, and C. For the duration of the study, all patients received a specialized oral diet tailored to their specific nutritional needs. In addition to the specialized diet, Group A received Growth Hormone (rh-GH) for four weeks plus *glutamine placebo for 16 weeks*, Group B received rh-GH for four weeks plus *glutamine for 16 week*, and Group C, received *rh-GH placebo* for four weeks plus *oral glutamine for 16 week*.

The protocol defined the primary efficacy endpoint as the mean change (decrease) in total IPN volume, measured in liters per week after 4 weeks of treatment, from Week 2 to Week 6.

CLINICAL REVIEW

Executive Summary Section

Table 1
Study GH-003
Primary Efficacy Evaluation
Mean Change in Total IPN Volume [L/wk] Week 2 to Week 6

Treatment Groups			Incremental gain [L/wk] (p-value)		
A rh-GH	B rh-GH + GLN	C GLN	B vs C	B vs A	A vs C
ITT STUDY POPULATION					
[n = 16]	[n = 16]	[n = 9]	-3.9	-1.8	-2.1
-5.9	-7.7	-3.8	(<0.001)	(0.0226)	(0.043)
<p>* All patients received a Specialized Oral Diet for the duration of the study</p> <p>p-values were determined from pairwise comparisons of treatment Groups B and A vs. Group C by Dunnett-Hsu t-test following ANCOVA with Week 2 as covariate including baseline by treatment interaction.</p> <p>To extend comparisons to include all pairwise comparisons, the FDA statistician, Dr. D. Price applied a Tukey-Kramer test for this comparison.</p>					

In analyses of the Intent-to-Treat (ITT) population and Efficacy Evaluable (EE) population, patients treated with glutamine and a SOD (Group C) had in a 3.8 liter/week reduction in the total IPN volume requirements. Patients treated with rh-GH and a SOD (Group A) had a greater reduction in total IPN volume (-5.9 L). The greatest reduction in total IPN volume requirements however, occurred in Group B, (rh-GH + GLN +SOD), with a 7.7 L/week reduction.

As demonstrated by comparing Group B to Group A, the addition of glutamine significantly improved the efficacy of growth hormone in the treatment of SBS. These results were also supported in the analyses of the EE Population. These data were discussed at the GI Advisory Committee meeting and there was agreement that considerably better results were obtained when growth hormone was administered in co-therapy with glutamine and a specialized oral diet.

D. Safety

All in all, there were no overt safety concerns identified during the study with the use of glutamine in co-therapy with rh-GH and a specialized diet in patients with SBS treated for the duration of the study. The safety profile of the co-therapy (rh-GH +GLN) plus a SOD appears to be similar to the safety profile of the approved rhGH + SOD therapy. The majority of AEs reported in this study were related to the underlying condition (SBS patients on IPN).

CLINICAL REVIEW

Executive Summary Section

E. Dosing

Dose regimen: 30 g Daily (5 g taken 6 times each day orally).

Indication: The Applicant proposes the following :

Oral glutamine is indicated in short bowel syndrome (SBS) _____

Medical Officer Comment:

Clinical trial GH-003 enrolled SBS patients between the ages of 20 and 75 years. There are no data to extrapolate these findings to a pediatric population with SBS. Therefore, the treatment would only be indicated for adults.

Study GH-003 evaluated the safety and efficacy of glutamine for 16 weeks. The submitted data are not adequate to label the product for use beyond 16 weeks. The study did not evaluate the long-term effects of glutamine. The label will need to reflect the duration of the study.

F. Special Populations

In spite of being one of the largest studies in SBS patients, the total number of patients enrolled is too small to generate a meaningful analysis for use in Special Populations.

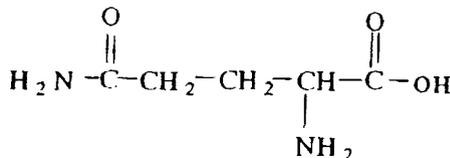
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Clinical Review Section

Clinical Review

I. Introduction and Background

A. Drug: Glutamine



Class: basic amino-acid

Proposed Indication: Oral glutamine is indicated in short bowel syndrome (SBS)

Dose regimen: 30 g Daily (5 g taken 6 times each day orally)

Medical Officer Comment: Clinical trial GH-003 enrolled SBS patients between the ages of 20 and 75 years. There are no data to extrapolate these findings to a pediatric population with SBS. Therefore, the treatment would only be approved for adults.

Study GH-003 evaluated the safety and efficacy of glutamine for 16 weeks. The submitted data and medical literature are not adequate to label the product for use beyond 16 weeks. The study did not evaluate the long-term effects of glutamine. The label will need to reflect the duration of the study.

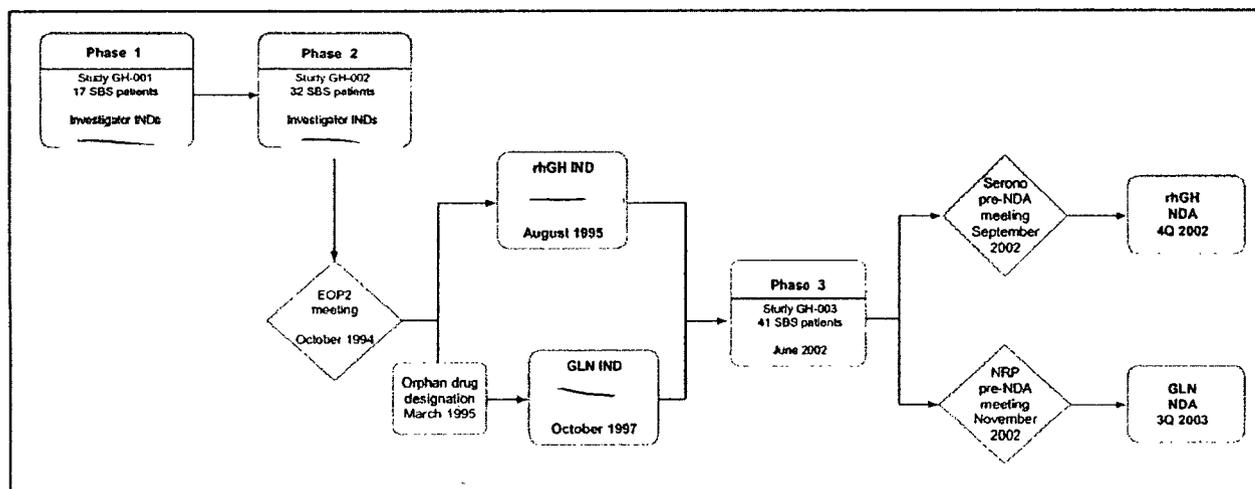
B. State of Armamentarium for Indication

Serostim[®] was the first, and is the only, drug approved for treatment of SBS. It was approved on November 28, 2003 after an Advisory Committee discussion and the Applicant submitting additional medical literature to address the issues of replicability and generalizability. The approval of Serostim was based on the same study and data submitted with this application. Glutamine is presently available over the counter as a dietary supplement.

Clinical Review Section

C. Important Milestones in Product Development

Table 2 Study GH-003 Product Development



EOP2=End of Phase 2; GLN=glutamine; IND=Investigator New Drug application; IPN=intravenous parenteral nutrition; NDA=New Drug Application; NRP=Nutritional Restart Pharmaceutical, L.P.; Q=quarter; rhGH=recombinant human growth hormone; SBS=short bowel syndrome; Serono=Serono, Inc.

(ref Clinical-overview.pdf page 9)

The development program of glutamine to treat patients with SBS is summarized from meetings between the Agency and the Applicant.

<p>October 1994</p>	<ul style="list-style-type: none"> • Sponsor was Cato Research • Pre-IND meeting to discuss research plans for the use of the proposed drug combination [Glutamine (GLN) + Growth Hormone (GH)] • Pre-clinical data seemed to indicate that GH administration was associated with increase in gut weight and length, mucosal mass, and villus height and crypt depth as well as enhancement of ileal and jejunal absorption of water, sodium and amino acids. • Results from a non-randomized, single center (the same center apparently involved in the pivotal trial), investigator-sponsor IND in patients considered dependent on parenteral nutrition (> 7 years) were discussed. An initial group of 7 patients served as their own control; the experience was later expanded to 24 patients. The indication studied was the reduction/elimination of TPN in patients with absorptive deficiencies, such 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%. • Dose of GH was between 0.07 and 0.14 mg/kg/day. • Dose of I.V. administered GLN was between 0.45 and 0.65 g/kg/day for 4 weeks. • FDA suggested studying a different temporal sequence (i.e. administering GH alone, followed by glutamine therapy). It was also noted that if the oral supplementation in
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Clinical Review Section

	<p>lieu of the I.V. GLN supplementation could be used, it would be simpler from a regulatory standpoint.</p> <ul style="list-style-type: none"> • Lack of randomization did not allow definitive conclusions about GH activity in this indication.
August 1995	<ul style="list-style-type: none"> • FDA (DMEDP) letter to sponsor providing comments on design of a clinical trial that would confirm findings and answer questions required for approval. A 3-arm randomized double blind study with 5 patients receiving GH only, 5 receiving GLN only and 15 patients receiving the combination was recommended.
June 1997	<ul style="list-style-type: none"> • FDA (DMEDP) letter to sponsor stating that the revised protocol "would suffice as a pivotal study for an NDA". • The study revisions did not include the 3-arm design recommended by the Agency.
March 2000	<ul style="list-style-type: none"> • The Sponsor (Serono Laboratories and Nutritional Restart Pharmaceutical) submitted a protocol amendment that changed the study design to single center.
June 2000	<ul style="list-style-type: none"> • Letter from FDA (DMEDP) informing sponsor that the single center study design is inadequate as the sole source of evidence to support a regulatory approval.
August 2000	<ul style="list-style-type: none"> • Meeting between FDA and sponsor. The agency stated that in summary, a single study, single-center for this application can be filed (unless there are other filing issues), but the hurdles are high for approvability and the burden is on the sponsor to prove that a single-center study is adequate. The Agency also added that there is no control group and results for a single-center study may not be representative of outcomes in other centers due to differences in standards of care. The DMEDP offered its assistance for development of additional protocols, proposals for bolstering enrollment, etc.
September 2002	<ul style="list-style-type: none"> • Meeting between FDA and the sponsor to discuss results of Protocol 20317 and the planned submission of a supplemental NDA for the addition of a short bowel syndrome indication to the Serostim® labeling [NOTE: The GI MTL was a consultant to DMEDP at this meeting]. • Study 20317 was a 6-week, multicenter, double-blind, in-patient trial, followed by 12 weeks of outpatient observation in male and female patients aged 18 to 75 years who were wholly or partly dependent on TPN. Following a 2-week run-in phase, patients were randomized to the following 3 treatment groups and studied for 4 weeks: <ul style="list-style-type: none"> - Group 1: specialized diet including (active) glutamine (SD/GLN, n= 9) - Group 2: (active) recombinant human growth hormone (0.1 mg/kg/day) with specialized diet excluding glutamine (SD/rh-GH, n= 18) - Group 3: rh-GH (active), at the same dose as that given to subjects in Group 2 (0.1 mg/kg/d) with specialized diet including glutamine (SD/GLN/rhGH, n= 18) - The specialized diet was common to the 3 treatment arms. - The primary endpoint of efficacy was the change in TPN volume, with change in TPN calories and TPN frequency as secondary endpoints. -The Agency asked for clarification as to why the endpoint of change in TPN volume was selected, since according to experts in this field, change in nutritional status is a more clinically meaningful endpoint. In response, the firm stated that the nutritional status of the patients was collected and planned to present these data as part of the NDA submission. Also of concern to the Agency was the lack of a specialized diet

Clinical Review Section

	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.
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D. Other Relevant Information

Glutamine is a non-essential amino acid that is widely available over the counter as a dietary supplement. Upon approval, glutamine will be designated as a drug and a dietary supplement.

E. Important Issues with Pharmacologically Related Agents

The long-term safety profile of glutamine in SBS patients is unknown.

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

NDA 21-667 is a 505(b)(2) application. As such, Nutritional Restart Pharmaceutical L.P. (NRP) did not conduct any non-clinical studies with oral glutamine. The non-clinical data were derived solely from medical literature. This was agreed upon by the Agency during a pre-NDA meeting on November 12, 2002. Glutamine has been widely available over the counter as a dietary supplement for years.

The Applicant submitted multiple non-clinical articles with the NDA as well as additional literature published through October 2003. The non-clinical studies submitted with this application had methods of analysis that varied by study. An assessment of the impurities and degradants in the drug substance used in these studies, and their compliance with Good Laboratory Practice (GLP) regulations (21 CFR 58) is unknown. (See Chemistry Review)

The toxicology studies were conducted by _____ These were not managed under GLP standards since they were conducted before 1979. The Application referenced a number of pharmacology studies in rodents and non-rodents that utilized either oral and parenteral glutamine. These studies demonstrated glutamine, at the proposed dose,

Clinical Review Section

has minimal detrimental effects on animals and has a low order of toxicity. The most relevant change observed in animals was stomach catarrh.

Genotoxicity literature data was very limited, but do not suggest that glutamine has clastogenic potential. However, glutamine has been shown to cross the placenta into fetal circulation, and embryological aberrations have been shown in high-dose glutamine supplemented embryonic culture. (See Pharmacology Review)

III. Human Pharmacokinetics and Pharmacodynamics

Glutamine is a nonessential, 5-carbon amino acid. It is synthesized by various tissues, including skeletal muscle, liver, and adipose tissue. The Applicant submitted literature that support that glutamine is important in normal gastrointestinal (GI) cell structure, function, and regeneration. Although it is not considered an essential amino acid in normal healthy animals, literature supports that in serious disease states it may not be synthesized in adequate amounts and so it becomes "conditionally essential"

A. Pharmacokinetics

Most endogenous glutamine is synthesized and stored in skeletal muscle where the free glutamine is released to other tissues. The Applicant submitted articles to provide information on the absorption, distribution, metabolism, and excretion of exogenously administered glutamine. Increasing exogenous glutamine supply increases blood glutamine concentrations, and may decrease endogenous glutamine de novo synthesis.

Several non-clinical studies of exogenous glutamine showed that it was absorbed rapidly from the lumen of the small intestine, and was then distributed in the plasma to many tissues such as brain, kidney, liver, pancreas, lung, spleen, heart, and muscle. The majority of its metabolic products were incorporated into proteins, nucleotides, or sugars, stored in tissues, or metabolized into urea and excreted in the urine. The Applicant reports different disease states affect glutamine plasma concentrations, turnover, and metabolism. The metabolic clearance rate of glutamine is higher in critically ill patients compared with healthy controls. Baseline glutamine plasma concentrations in healthy subjects typically ranged from 521 $\mu\text{mol/L}$ to 630 $\mu\text{mol/L}$. A single oral glutamine dose of 0.1 g/kg resulted in a peak plasma concentration of $1028 \pm 97 \mu\text{mol/L}$ approximately 30 minutes after dosing. (See Biopharmaceutical Review)

Clinical Review Section

B. Pharmacodynamics

Enterocytes preferentially use glutamine as an energy source. Therefore, glutamine is important in maintaining the integrity of the intestinal mucosa. The Applicant submitted literature on animal studies that demonstrate that supplementation with glutamine after a small-bowel resection positively influenced mucosal adaptation when compared with animals that did not receive glutamine. Animals treated with glutamine had a significant increase in mucosal wet weight, mucosal protein, and mucosal DNA when compared with resected animals that did not receive glutamine. Crypt depths, and villous size ratios (villous height divided by villous width) were significantly higher ($p < 0.05$) in the intestine of resected animals that received glutamine when compared with animals not treated with glutamine. Additionally, studies demonstrated that bacterial translocation was significantly lower in resected animals that received glutamine. (See Pharmacology Review)

IV. Description of Clinical Data and Sources

The Applicant submitted the results from one pivotal trial (Study GH-003) and additional medical literature to support the approval of glutamine for the treatment of SBS. This information was supplemented with the transcript from the GI Advisory Committee meeting, June 25, 2003.

A. Overall Data

Clinical and Pre-Clinical Sections of the NDA
Meeting Minutes
Proposed Package Insert
Submitted Supportive Medical Literature
Additional On-line Literature Search

B. Tables Listing the Clinical Trials

The NDA submission consisted of one clinical and statistical study report from protocol GH-003. The trial enrolled 47 patients. Six of these patients were discontinued (5 for intercurrent illness, 1 withdrew consent). A total of 41 patients were randomized into 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.



Clinical Review Section

C. Post-marketing Experience

Glutamine presently has no approved treatment indications. It is, however, widely available over the counter as a dietary supplement. It is well tolerated, but can cause GI upset at high doses.

D. Literature Review

The Applicant submitted extensive medical literature published through October 31, 2003 to support this application. An additional literature search was performed utilizing the Agency's on-line databases and resources. Publications used during the review included papers on the effect of growth hormone, and glutamine in animal models of short bowel syndrome as well as studies in humans. There are some inconsistencies in the medical literature regarding the efficacy of growth hormone and glutamine in the treatment of SBS. A treatment regimen including growth hormone and glutamine was discussed during the June 2003 GI Advisory Committee meeting. The transcript from this meeting was also considered during this review.

V. Clinical Review Methods

A. How the Review was Conducted

The evidence presented by the Applicant was reviewed and analyzed. A multi-specialty review of the pivotal study and supportive medical literature was performed utilizing the applicant-submitted data. The review included physicians, statisticians, biopharmaceutical specialists, toxicologists, chemists and a project manager.

The materials reviewed included all volumes that constitute the submission, with emphasis on the Clinical Study Report and supportive medical literature. Also considered in the clinical review, were the reviews from pertinent disciplines (chemistry, pharmacology/toxicology, biopharmaceutics, and statistics) and the reviews of NDA 21-597, as well as the transcript from the GI Advisory Committee Meeting, June 25, 2003, since it discussed the results of this study.

Clinical Review Section

B. Overview of Materials Consulted in Review

Clinical and Pre-Clinical Sections of the NDA (including supportive medical literature)
Safety Update Report
Electronic Submitted Data Sets
Proposed Package Insert
MEDLINE
NDA 21-597 Review
GI Advisory Committee Meeting transcript, June 25, 2003

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

A comprehensive review of the clinical study submitted with NDA 21-667 was performed with periodic sampling of the data from the case report forms (CRF). SAS transport files were reviewed utilizing the JMP program. The quality and results of the data were discussed in consultation with the Agency's Biostatistical division.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The Applicant formally stated the study was conducted in conformance with applicable country or local requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research.

E. Evaluation of Financial Disclosure

The Applicant submitted adequate financial documentation and a signed certification stating that they did not enter into any financial agreement with the clinical investigators whereby the value of compensation could be affected by outcome of studies.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

The Applicant submitted results from one pivotal trial, Study GH-003, and extensive medical literature to support the approval of oral glutamine as part of a co-therapy with growth hormone (rhGH) and a specialized oral diet (SOD) to treat patients with short bowel syndrome. Study GH-003 demonstrated that in patients receiving a specialized oral diet, a treatment regimen comprised of 16 weeks of glutamine and 4 weeks of rh-GH

Clinical Review Section

resulted in a larger decrease in total IPN volume requirements than 4 weeks of rh-GH alone.

In patients treated with rh-GH and a specialized oral diet, the average decrease in the total IPN volume requirement was 5.9 liters per week. When glutamine was added to this therapy, the average decrease in the total IPN volume was 7.7 liters per week. These efficacy results were discussed during the GI Advisory Committee meeting and were determined to be clinically meaningful.

Table 3 Study GH-003

Therapeutic Gain by Treatment Group

Treatment Groups Therapeutic gain [L/wk]		
A rh-GH+SOD	B rh-GH+SOD[GLN]	C SOD[GLN]
IFI STUDY POPULATION		
[n = 16]	[n = 16]	[n = 9]
-5.9	-7.7	-3.8
EFFICACY-EVALUABLE STUDY POPULATION		
[n = 15]	[n = 16]	[n = 9]
-5.8	-7.7	-3.8
rh-GH= Serostim (growth hormone) SOD= Specialized Oral Diet GLN= glutamine		

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

The efficacy database included the results from Study GH-003. This study evaluated the efficacy and safety of glutamine, singly and as co-therapy with rh-GH, in the improvement of residual gut absorptive function in patients with short bowel syndrome. Data from CRFs were reviewed and the statistical analyses were discussed in consultation with the biometrics review team.

C. Detailed Review of Trial by Indication

The Applicant submitted results of a single trial entitled: "Randomized, Double-Blind, Controlled, Parallel-Group Evaluation of the Relative Efficacy 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".

Clinical Review Section

- The study was initiated on July 23, 1998 and completed on June 27, 2002.
- The study was a randomized, double-blind, placebo controlled, parallel-group, 3-arm, Phase III clinical trial.
- There were two Principal Investigators :
 1. David Lautz, MD [Brigham and Women's Hospital, Boston MA], with three Sub-investigators and Nutritional Restart Center, Wellesley, MA as the study site
 2. 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.
- 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 specialized oral diet supplemented with either glutamine or glutamine placebo; subjects were reevaluated as outpatients 12 weeks later.
- The primary objective of the study was to evaluate the change in total intravenous parenteral nutrition (IPN) requirements measured during Week 2 (last week of baseline period) to Week 6 (last week of Treatment Period) in adult, IPN-dependent, SBS subjects receiving a specialized oral diet (SOD).
- The study population consisted of 41 randomized patients:
(age range : 20 to 75 y; age categories : < 65y, (33); >= 65y, (8);
Caucasian (32), Non-Caucasian (9); females (29) and males (12).

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Clinical Review Section

Table 4 Study GH-003

Characteristics of the Study population

INCLUSION CRITERIA	REASONS FOR EXCLUSION
<ul style="list-style-type: none"> • M or F, between 18 and 75y of age 	<ul style="list-style-type: none"> • Body mass index greater than 28
<ul style="list-style-type: none"> • Diagnosis of SBS with less than or equal to 200 cm small bowel 	<ul style="list-style-type: none"> • Pregnancy or lactation • Ongoing, chronic infectious disease
<ul style="list-style-type: none"> • Eat at least some solid food on a regular basis, but require at least 3000 cal. per week of IPN for nutritional support 	<ul style="list-style-type: none"> • 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)
<ul style="list-style-type: none"> • 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. 	<ul style="list-style-type: none"> • History of mental deficiency or illness that might compromise with the requirements of the study. [History of psychiatric eating disorder or drug or alcohol abuse were reasons for exclusion] • Sustained hypertension (arterial pressure of $\geq 160/100$ 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 dysfunction • Established diagnosis of diabetes mellitus • Hypoxemic pulmonary disease (i.e. resting $pAO_2 \leq 75$ 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
<ul style="list-style-type: none"> - 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 	
<ul style="list-style-type: none"> - For pts. with known hypertension or other cardiovascular disorder, be both compensated and stabilized on a regular therapeutic regimen 	

Medical Officer Comment:

The study population was adequate for this type of study.

Clinical Review Section

- The Applicant states that the dose of glutamine was selected on the basis of past experience in SBS patients and suggestions from the Agency during the pre-IND meeting on October 19, 1994. Each patient received a daily oral supplement of glutamine (30 g/d) or glutamine placebo (27 g/d) divided into 6 single dose packets that were each mixed with water or Crystal Light beverage according to the patient's preference. Patients consumed the beverages with meals or snacks at 2 -to 3-h intervals during the day. The volume of the beverage could be varied according to the patient's tolerance.

The dosage of rh-GH chosen for this study was based upon previous experience in SBS patients. Doses ranging from 0.07 to 0.14 mg/kg/d have been shown to be effective in decreasing IPN-dependence in SBS patients. A dose of 0.10 mg/kg/d was selected because of its "good safety and efficacy profile". 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).

All study participants received an oral diet individualized to meet their nutritional needs. It is important to note that modifications to the diet throughout the treatment period were necessary to maintain adequate nutrition status.

- The randomization scheme and codes were submitted and reviewed. Patients were randomly assigned to one of the 3 treatment arms in a 2:2:1 ratio (Group A, B, C) using a block size of 5. Randomization codes were maintained in sealed envelopes in the medical monitor's locked file. The randomization process was properly executed.

The study qualifies as being double-blinded. The methods of maintaining blinding of participating physicians and patients were adequate.

- The procedures to handle prior and concomitant medications were adequate. Equally adequate were the procedures to determine treatment compliance.
- 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 Applicant states that following a discussion with the DMEDP, IPN volume was selected to achieve an accurate analysis of efficacy since it is less variable than IPN calories. IPN and SLE requirements were captured on a daily basis during Week 2 through 6.

Clinical Review Section

Definition of Total IPN volume (administered per week):

As prospectively stipulated, total IPN volume is the sum of:

- a) IPN volume plus
- b) supplemental lipid emulsion (SLE) plus
- c) intravenous hydration fluid administered each week.

Medical Officer Comment:

The appropriateness of the primary efficacy parameter and whether the results were clinically meaningful was discussed during the June 25th, 2003 GI Advisory Committee meeting. The majority of the committee members voted that the primary efficacy parameter was acceptable and that the results were clinically meaningful. It was discussed that the infusion of one liter of IPN takes 6 to 8 hours, which can significantly impact on the patients quality of life.

- 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 was defined as the sum of kilocalories for carbohydrates, proteins, and fats in the IPN.
 2. Mean change in IPN or SLE frequency (days per week) from Week 2 to 6. Frequency was 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. Again, a decrease of one day in IPN or SLE is considered clinically meaningful.

The Applicant also analyzed/compared weight change from week 2 to Week 18. Growth hormone or growth hormone placebo were discontinued on Week 6 (4 weeks treatment). Patients were continued on glutamine or glutamine placebo through Week 18 (16 weeks treatment). Weight changes for each of the three treatment groups over time are described in the following table.

Clinical Review Section

Table 5 Study GH-003
Summary of Mean Weekly Weights from Week 2 to Week 18 by
Treatment Group in the EE Population

Treatment Group	Week 2 (Mean±SD)	Week 18 [Mean ± SD]	Week 18-Week 2	p-value*
rhGH	63.0±10.1	58.9±10.5	-3.8±2.7	<0.001
rhGH/GLN	63.7±11.7	58.7±9.4	-5.0±5.0	<0.001
GLN	62.3±8.6	60.0±9.1	-2.3±2.8	0.037

EE=efficacy evaluable; GLN=glutamine; rhGH=recombinant human growth hormone; SD=standard deviation.

* P-values from paired t-test within treatment groups.

(ref. Table 8.8 study-report-535111 (GH-003 addendum) page 23)

There was a reduction in weight in all three groups over the 16-week period. The Applicant attributes this to hydration that occurred during 2 weeks of in-hospital stabilization since the patient's mean weight during the screening visit was less than Week 2 (rhGH patients weighed 61.4±10.4 kg; rhGH/GLN patients weighed 62.1±11.4 kg; and GLN patients weighed 61.3±8.5)

- Test Medication:

Glutamine: 30 g Daily (5 g taken 6 times each day orally) or Placebo.
 (Serostim®) subcutaneous injection 0.10 mg/kg/d or Placebo
 Specialized oral diet

- Duration of treatment and treatment group:

All patients received a specialized oral diet (SOD) for the duration of the study.

GROUP A:

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

GROUP B:

rh-GH + GLN + SOD for 4 weeks followed by GLN + SOD for 12 weeks.

GROUP C:

GLN + SOD for 4 weeks followed by GLN + SOD for 12 weeks.

Clinical Review Section

- 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:

The sample size calculation was based on the number of patients (i.e. 17) studied by Byrne [Advances in the management of patients with intestinal failure Transpl Proc 28:2683-2690 (1996)]. 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:

1. That the difference in the decrease of IPN volume between Group B (rh-GH + GLN + SOD) and Group C (GLN + SOD) is 6.6 L per week and
2. That the decrease in IPN volume between Group A (rh-GH + SOD) and Group C (GLN + SOD) is 6.6 L per week and
3. That the pooled root mean squared error is 5.5 L per week.

- Effects of Covariates

Statistical models of the effects of other covariates on the primary and secondary parameters were assessed. Covariates that were assessed include: age, sex, race, weight (this included weight history), time since diagnosis of SBS, time since last resection (< 12 months or \geq 12 months), length of residual jejunum-ileum, presence of an intact colon, and IPN history (this included weekly IPN volume, calories, and frequency).

Clinical Review Section

Results:

D. Disposition of Subjects:

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

**Table 6 Study GH-003
Summary of Patient Accrual
Number of Patients Randomized per Site and Treatment Arm**

Site	Treatment Groups		
	A rh-GH	B rh-GH + [GLN]	C [GLN]
01	15	15	8
02	1	1	1
Subtotal	16	16	9

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

Medical Officer Comment:

From the information summarized above, it is hard to characterize Study GH-003 as multicenter. The vast majority of the patients in this study were randomized at one site (Site 01) while the other (Site 02) randomized only one patient per arm. It is clear that Site 2 did not contribute significantly to the data used to assess efficacy and safety. Thus, GH-003 is primarily a single center study. This single center study was determined to be acceptable to support approval of growth hormone for the treatment of SBS.

E. Protocol Deviations:

The clinical report included a listing of all patient termination data, organized by site and treatment group, including patient identifier, specific reasons for discontinuation, and the date of discontinuation or termination. At the time of discontinuation, the blind was not broken for any subject. In the final analysis, no gross imbalances regarding protocol deviations were identified among the 3 treatment arms.

Clinical Review Section

F. Data Sets Analyzed

There were 3 data sets analyzed: a) Intent to Treat (ITT) (n = 41), defined as all subjects who were randomized into the trial; b) Efficacy Evaluable (EE) (n = 40), defined as subjects who 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 treatments and those who did not have any protocol violations with a clinical impact; and c) Treatment Responders. The Treatment Responder population included all subjects who demonstrated a complete response (i.e., a 100% reduction in total IPN volume) at Week 6.

G. Subjects Baseline Characteristics:

The 3 treatment groups were comparable in terms of demographic profile, disease state and other baseline characteristics. 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, predominately Caucasian. The treatment arms were similar in baseline weight (Group A = 61.4 kg, Group B = 62.1 kg, and Group C = 61.3 kg). 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. When considering these comparisons, the number of subjects per group was not sufficient for statistical analysis. Similarly, at baseline, there was no statistically significant difference among the 3 treatment groups with regards to SBS and IPN history

The following variables: 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 were carefully analyzed because they may influence outcome. No statistically significant difference among the 3 treatment groups was identified. Group A had the longest mean residual small and large bowel.

Clinical Review Section

Table 7 Study GH-003

Summary of Disease Baseline Characteristics

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

H. Results of Efficacy Evaluations:

Table 8 Study GH-003
Primary Efficacy Evaluation
Mean Change in Total IPN Volume [L/wk]
from Week 2 to Week 6

Treatment Groups*			Therapeutic gain [L/wk] (p-value)		
A rh-GH	B rh-GH+GLN	C GLN	B vs C	B vs A	A vs C
ITT STUDY POPULATION					
[n = 16]	[n = 16]	[n = 9]	-3.9	-1.8	-2.1
-5.9	-7.7	-3.8	(<0.001)	(0.0226)	(0.043)

* All patients received a Specialized Oral Diet for the duration of the study

p-values were determined from pairwise comparisons of treatment Groups B and A vs. Group C by Dunnett-Hsu t-test following ANCOVA with Week 2 as covariate including baseline by treatment interaction.

To extend comparisons to include all pairwise comparisons, the FDA statistician, Dr. D. Price applied a Tukey-Kramer test for this comparison.

Clinical Review Section

Groups Being Compared

There were 3 arms in the trial. All patients received a specialized oral diet for the duration of the study. The comparator arms included Group A, which included growth hormone without glutamine, Group B which included growth hormone with glutamine and Group C, which received only glutamine.

Although there was not a placebo control arm to compare the efficacy of glutamine alone, a comparison between Group B vs. A, can provide an assessment of the effect that glutamine adds to the approved treatment. This comparison was not predefined in the protocol. These analyses were performed by Dr. Dionne Price, FDA statistician, and are included in the reviewer's efficacy Tables above.

Primary Efficacy Parameter

For both, the ITT and the EE population, a reduction in the total IPN volume requirement was noted in patients who received glutamine and SOD (Group C). The therapeutic gain for Group C was small (3.8 L/wk). Treatment with growth hormone and SOD (Group A) resulted in a greater mean reduction in total IPN volume (-5.9 L) than glutamine alone (-3.8 L).

The efficacy of glutamine is demonstrated by comparing the results of Group B to Group A. In comparing the reduction caused by growth hormone (Group A) to growth hormone plus glutamine (Group B), there is an additional reduction in total IPN volume requirements of 1.8L. This additional 1.8L reduction is statistically significant and, as mentioned above, clinically meaningful.

These results support that the optimal treatment regimen includes growth hormone and glutamine in conjunction with a specialized oral diet. Treatment with growth hormone + glutamine produced a 7.7 L reduction in total IPN volume for the ITT population. These results are also supported and confirmed in the statistical analyses of the EE population.

Secondary Efficacy Parameters

The Applicant presented results for the two secondary efficacy parameters: a) mean change in total IPN calories, b) mean change in IPN or SLE Frequency from Week 2 to Week 6.

In an statistical approach similar to that for the primary efficacy parameters, additional calculations by Dr. Price were performed. The results for the secondary efficacy endpoints are included in the Table 9.

Clinical Review Section

**Table 9 Study GH-003
Secondary Efficacy Evaluation
ITT Study Population
from Week 2 to Week 6**

Treatment Group			Therapeutic gain [d/wk] (p-value)		
A rh-GH	B rh-GH + GLN	C GLN	B vs C	B vs A	A vs C
Mean Change in Total IPN Calories [kcal/wk]					
[n = 16]	[n = 16]	[n = 9]	-3117.9	-1412.9	-1705.0
-4338.3	-5751.2	-2633.3	(<0.001)	(0.0436)	(0.043)
Mean Change in IPN or SLE Frequency [d/wk]					
[n = 16]	[n = 16]	[n = 9]	-2.2	-1.2	-1.0
-3.0	-4.2	-2.0	(<0.001)	(0.0478)	(0.025)

* All patients received a Specialized Oral Diet for the duration of the study

After 4 weeks of treatment (Week 6), subjects who received growth hormone in conjunction with glutamine (Group B) had the largest decrease in total IPN calorie content and mean change in IPN or SLE frequency. Comparing Group B to Group A, there was a significant reduction in total IPN calorie content (therapeutic gain = -1412.9 kcal/wk) and weekly frequency of IPN administration (therapeutic gain = -1.2 d/wk). These results support the conclusion that the optimal treatment regimen includes growth hormone in co-therapy with glutamine. The results in the EE population were nearly identical to the ITT analysis.

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Clinical Review Section

**Table 10 Study GH-003
Secondary Efficacy Evaluation
ITT Study Population
from Week 2 to Week 6**

Treatment Groups		
A rh-GH	B rh-GH + GLN	C GLN
Complete Wean from IPN, Lipids, and I.V. Hydration		
[n = 16]	[n = 16]	[n = 9]
4	4	1
Complete Wean from IPN and Lipids (I.V. Hydration Allowed)		
[n = 16]	[n = 16]	[n = 9]
5	7	1

* All patients received a Specialized Oral Diet for the duration of the study

The protocol defined weaning parameters as:

1. Ability to hydrate; and
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.

The small number of patients per cell in these categories precludes a definite conclusion. However, the results support the findings that the optimal treatment regimen includes growth hormone and glutamine.

I. Effects of Covariates on Primary and Secondary Endpoints

Covariates that were assessed for the ITT Population included: age; sex; weight; time since diagnosis of SBS; time since last resection (< 12 months or >= 12 months); length of residual jejunum-ileum; presence of an intact colon; and IPN volume history (this included weekly IPN volume, calories, and frequency, the efficacy evaluation parameters assessed in the trial).

The analyses revealed the following:

1. Total Weekly IPN volume results were significantly influenced by patients' weight [p<0.001]
2. Subjects with higher body weight experienced greater reductions in total weekly IPN volume than those with lower body weights
3. Total Weekly IPN volume results were significantly influenced by length of residual bowel [p = 0.028].

Clinical Review Section

4. Subjects with longer residual bowel had larger decreases in Total IPN volume than those with shorter residual bowel.
5. Subjects with a history of higher IPN volume requirements experienced a significantly greater decrease in IPN volume during the Treatment Period than those with a history of lower IPN volume requirements [p = 0.044].
6. Caucasians seem to respond to treatment better than non-Caucasians. However, no definitive conclusion can be drawn since only 9 out of 41 subjects randomized were non-Caucasians [p = 0.021].

In all cases with a significant covariate, Group B, (rh-GH + glutamine) remained highly significant. Total IPN calorie results for the ITT 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 Population. Patients with higher body weight responded better to treatment than those with lower body weights. Covariate analyses for the EE population yielded results similar to those for the ITT Population.

J. Persistence of Treatment Effect:

The Applicant attempted to evaluate the persistence of treatment effect. To accomplish this, the change in weekly IPN volume, calories and frequency was analyzed from Week 2 to Week 18. For Week 18, summary data only were recorded in the CRF on the basis of contact with the patient's local physician.

**Table 11 Study GH-003
Persistence of Treatment Effect**

Summary of Change in IPN Volume, Calories, and Frequency Week 2 to Week 18 ITT Population			
Endpoint	Group A [n = 16]	Group B [n = 16]	Group C [n = 9]
Change in weekly IPN Volume from Week 18 to Week 2 (L/wk)	-5.9	-7.2	-4.7
Change in weekly IPN Calories from Week 18 to Week 2 (kcal/wk)	-3522.2	-5347.3	-2254.0
Change in weekly IPN frequency From Week 18 to Week 2 (days/wk)	-2.9	-3.9	-1.9

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

Clinical Review Section

Medical Officer Comment:

Although the quality of the data collected at Week 18 is not the same as evaluated for the primary endpoint, the analyses support that a treatment regimen with a specialized oral diet, growth hormone for 4 weeks, and glutamine for 16 weeks is more efficacious than growth hormone and a specialized oral diet alone. Furthermore, the analyses support that the treatment effect, for the most part, is maintained for 16 weeks. The label will need to reflect that there is inadequate data to assess safety and efficacy of glutamine beyond 16 weeks of therapy.

Other

Drug concentration data were not collected. Drug-Drug and Drug-Disease Interactions were not analyzed statistically.

K. Efficacy Conclusions

Analyses using the prospectively defined primary endpoint demonstrated that the administration of glutamine in co-therapy with growth hormone and a specialized oral diet was associated with a statistically and clinically meaningful 7.7L reduction in the total weekly IPN volume requirement. The data from the primary and secondary efficacy endpoints support that the optimal treatment regimen includes both glutamine and growth hormone in conjunction with a specialized oral diet.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

The safety profile of glutamine in co-therapy with growth hormone and a specialized oral diet appears to be similar to the safety profile of the *approved* growth hormone treatment. Glutamine is available over the counter as a dietary supplement. The Applicant states they are not aware of any reports of safety concerns resulting from glutamine supplementation from the use of medical foods and dietary supplements.

Increases in renal function laboratory values are common in patients receiving parenteral nutrition. Because of the increased amine load provided by glutamine administration, which may further stress the kidney, regular monitoring of renal function should be performed in patients with renal impairment.

Fluctuations in liver function studies are common in patients treated with parenteral nutrition. Therefore, regular monitoring of liver function studies should be performed in patients receiving treatment with growth hormone and glutamine.

Clinical Review Section

B. Description of Patient Exposure

**Table 12 Study GH-003
Glutamine Exposure
Medical Literature through October 31, 2003**

Duration (Weeks)	Mean Daily Dose (g)						Total (Any Dose)	Percentage of Subjects for Each Duration
	0<Dose ≤5 g	5<Dose ≤10 g	10<Dose ≤20 g	20<Dose ≤30 g	30<Dose ≤50 g	50 g<Dose		
0<Dur ≤1	12*	15	18	31			76	7.7
1<Dur ≤2	6†	67	3	46	1	18	141	14.4
2<Dur ≤4	322‡	22	42	93	7		486	49.5
4<Dur ≤12		64	25	8	21		118	12
12<Dur ≤24			10	26			36	3.7
24<Dur ≤48			2	45			47	4.8
48<Dur ≤96				43			43	4.4
Dur>96				34			34	3.5
Total (any duration)	340	168	100	326	29	18	981	
Percentage of Subjects Receiving Daily	34.7	17.1	10.2	33.2	3	1.8		

Dur=duration.

* Pediatric oncology patients.

† Premature infants.

‡ 314 of these subjects were premature neonates.

(Table 2.7.4.4, Cutoff date October 31, 2003)

The Applicant submitted glutamine exposure data for Study GH-003 and available medical literature through October 31, 2003. In Study GH-003, subjects were administered glutamine 30 g/d for 16 weeks. The Applicant reports 981 subjects received oral glutamine in clinical studies reported in medical literature through October 31, 2003. Sixty-two percent of these subjects received doses of oral glutamine up to 20 g/d. Thirty three percent received 20 to 30 g/d oral glutamine; and 5% of the subjects received greater than 30 g/d. Seventy-two percent of the subjects received oral glutamine for 1 day to 4 weeks. Twenty-eight percent of the subjects received oral glutamine for 4 weeks to 5 years.

Medical Officer Comment: In Study GH-003, patients received 30g/d of oral glutamine for 16 weeks. The submitted supporting medical literature is not adequate to label glutamine as safe and effective beyond 16 weeks.

Clinical Review Section

C. Methods and Specific Findings of Safety Review

Safety data from this study, the medical literature, and supporting studies were reviewed.

During the Baseline Period, 88% of the patients in Group B (rh-GH +SOD[GLN]) and 88% of the patients in Group A (rh-GH + SOD) reported at least one Baseline Sign and Symptom (BSS). In comparison, only 78% of the patients in Group C (SOD[GLN]) reported a BSS. There were no deaths during this trial.

The most frequently reported BSSs included edema, fatigue, and gastrointestinal disorders. Edema was reported more often in patients receiving growth hormone. Edema is a labeled adverse event for growth hormone. The latter two are signs and symptoms of SBS.

During the treatment period, all of the subjects (100%) receiving growth hormone (Groups B and A) reported at least one AE as compared with 89% of the glutamine alone subjects (Group C). The proportion of subjects experiencing at least one AE during the Follow-up Period was similar among the 3 treatment groups.

The proportion of subjects reporting at least one *treatment-related* AE in Group B, A and C was 88%, 94%, and 22%, respectively. These percentages were calculated from a small number of patients, therefore are difficult to interpret.

Variations in laboratory values are expected in this 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 or treatment related pattern was detected.

D. Adequacy of Safety Testing

Given that SBS is an orphan indication and that growth hormone was recently approved for treatment of SBS using these same studies, this reviewer believes that the safety testing in NDA 21-667 was adequate. In the medical literature, submitted with the application, 21% of the subjects received oral glutamine for more than 24 weeks. The literature did not describe any significant safety concerns.

E. Safety Conclusions

All in all, there were no overt safety concerns with the use of glutamine in co-therapy with growth hormone and a specialized diet in patients with SBS treated for up to 16 weeks. The safety profile of the co-therapy (rh-GH+SOD+GLN) appears to be similar to the safety profile of rhGH + SOD.

Clinical Review Section

VIII. Dosing, Regimen, and Administration Issues

Proposed Indication(s):

INDICATIONS AND USAGE Section of the labeling reads:

“Oral glutamine is indicated in short bowel syndrome (SBS) _____

_____”

Dose: 30 g Daily (5 g taken 6 times each day orally).

Regimen: “Each dose of Oral Glutamine should be reconstituted in 8-oz (250-mL) glass of water. It should be consumed with meals or snacks at 2- to 3-hour intervals while awake. Recommended duration of treatment with oral glutamine is for *16 weeks* _____”

Medical Officer Comment: The proposed regimen of 0.1 mg/kg/d subcutaneous rh-GH plus glutamine was shown to be safe and effective when assessed under the experimental conditions in Study GH-003. The proposed treatment duration of 16 weeks to 3 years is not supported by Study GH-003 or the medical literature. Based on these studies, Serostim was approved for 4 weeks of therapy. The following statement is present in the Serostim label for the SBS indication: Administration for more than 4 weeks has not been adequately studied. Based on the existing data, the glutamine label should have a treatment duration of 16 weeks. Additionally, the label should include the following statement: “Administration for more than 16 weeks has not been adequately studied.”

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 enrolled in Study GH-003 is too small to perform meaningful analysis for “special populations”

Clinical Review Section

X. Conclusions and Recommendations

Long-term Total Parenteral Nutrition (TPN) is a supportive rather than curative therapy for patients with severe SBS. In addition to extraordinary costs, there are many complications that may accompany TPN use. These complications include: hepatic and gall bladder dysfunction, progressive renal insufficiency, bone demineralization, catheter sepsis, and numerous nutrient deficiencies.

The results of Study GH-003 were discussed at a GI Advisory Committee Meeting, June 25, 2003. The Advisory Committee members agreed that the reduction in the total IPN volume requirements demonstrated in Study GH-003 was clinically significant. Serostim was approved for the treatment of Short Bowel Syndrome in patients receiving specialized nutritional support. Its approval was based on the same data and supporting medical literature submitted with this NDA. The data demonstrate that patients who were treated with growth hormone, glutamine and a specialized diet (Group B) had a larger reduction in weekly total IPN requirements than patients treated with growth hormone and the specialized diet (Group A). The data support that the optimal treatment regimen includes glutamine.

All of the outstanding issues identified during the review of the Serostim NDA have been addressed through the GI Advisory Committee Meeting, June 25, 2003, and additional medical literature that was submitted to support the concept of generalizability of the treatment.

Recommendations

The data submitted by the Applicant supports approval of glutamine for use with growth hormone and a specialized oral diet for the treatment of for the treatment of SBS patients. The safety and efficacy of this treatment has not been adequately studied beyond 16 weeks. The final printed label will need to reflect this.

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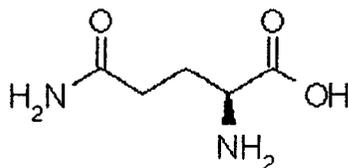
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Gary DellaZanna
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MEDICAL OFFICER

Hugo Gallo Torres
5/25/04 06:02:36 PM
MEDICAL OFFICER

CLINICAL REVIEW

NDA 21-667 Glutamine



NDA: 21-667

Chemical Name: Glutamine

Class: Nonessential Amino Acid

Date Received: August 12, 2003

Indication: Treatment of Short Bowel Syndrome

Dose: 30 grams/day Oral

Applicant: Nutritional Restart Pharmaceutical, L.P.

Documents Reviewed: NDA and Data Sets
Safety Update, December 5, 2003
Proposed Package Insert
NDA 21-597
GI Advisory Committee Meeting, June 25, 2003

Division Director: Robert Justice M.D. M.S.

Deputy Director: Joyce Korvick M.D. M.P.H.

Medical Officer: Gary Della'Zanna D.O. M.Sc.

Biopharmaceutical: Sue Chih Lee Ph.D.

Pharmacology: Ke Zhang Ph.D.

Statistician: Dionne Price Ph.D.

Chemistry: Maria Ysern Ph.D.

Project Manager: Tanya Clayton B.S.



Clinical Review Section

Addendum:

This is to clarify that the review of NDA 21-667 included the information submitted with the December 5, 2003 safety update report. The safety update was reviewed and considered during the writing of the conclusions and recommendations.

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/s/

Gary DellaZanna
5/27/04 08:30:12 AM
MEDICAL OFFICER

Hugo Gallo Torres
5/27/04 01:36:49 PM
MEDICAL OFFICER