CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-604/S027

Trade Name: Serostim

Generic Name: [somatropin (rDNA origin) for injection]

Sponsor: Serono, Inc.

Approval Date: August 29, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-604/S027

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-604/S027

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-604/S-027

Serono, Inc.
Attention: Pamela Williamson Joyce
Vice President, Regulatory Affairs
One Technology Place
Rockland, MA 02370

Dear Ms. Joyce:

Please refer to your supplemental new drug application dated October 31, 2002, received November 1, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Serostim [somatropin (rDNA origin) for injection].

We acknowledge receipt of your submissions dated January 29, February 7, June 10, August 12, 19, 28 and 29, 2003.

This supplemental new drug application provides for the use of Serostim [somatropin (rDNA origin) for injection] for HIV patients with wasting or cachexia to increase lean body mass and body weight, and improve physical endurance.

We completed our review of this application, as amended, and it is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed submitted August 29, 2003.

Please submit the FPL electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format-NDAs". Alternatively, you may submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-604/S-027." Approval of this submission by FDA is not required before the labeling is used.

We approved this NDA under the regulations at 21 CFR 314 Subpart H for accelerated approval of new drugs for serious or life-threatening illnesses. Approval of this supplement fulfills your commitments made under 21 CFR 314.510.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must submit, as correspondence to this application with the designation of "Patent Information-FDA Form 3452", patent information on FDA Form 3542, Patent Information Submitted Upon and After Approval of a NDA or Supplement, within 30 days of the date of this letter as required by 21 CFR 314.53(c)(2)(ii) and 314.53(d)(2). The form may be obtained at www.fda.gov/opacom/morechoices/fdaforms/cder/html. To expedite review of this patent declaration form, we request you submit an additional copy of the form to the Center for Drug Evaluation and Research "Orange Book" staff at

Food and Drug Administration
Office of Generic Drug, HFD-610
Orange Book Staff
7500 Standish Place
Metro Park North II
Rockville, MD 20575-2773

We also remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Monika Johnson, Regulatory Project Manager, at (301) 827-9087.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center of Drug Evaluation and Research

Enclosure: Draft Labeling

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

/s/

David Orloff
8/29/03 12:12:57 PM

DEPARTMENT O .EALTH & HUMAN SERVICES

Public Health Service

NDA 20-604

Food and Drug Administration
Rockville MD 20857

Serono Laboratories Inc.
Attention: Mr. Thomas A. Lang
Vice President, Regulatory Affairs
100 Longwater Circle
Norwell, MA 02061

AUG 23 1996

Dear Mr. Lang:

Please refer to your September 11, 1995, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Serostim [somatropin (rDNA origin) for injection], 5 mg/vial and 6 mg/vial.

We acknowledge receipt of your amendments dated October 3, 12, 26, and 31, November 17 (3), 20, 27, and 28 (3), and December 1 (4), 15, 19, and 22, 1995, and January 6, 18, 23, 24 (2), and 31, February 5, 8 (3), 9, 13, 15, 20 (2), March 14, 15, and 26, April 4 (2) and 25, May 1, 10, 17, and 29, June 7, 17, and 27 (3), July 3, 10, 22, 23, 29, and 31, and August 2, 6, 8, 9, 15, 16, 19 (3), 20 (2), and 21, 1996.

This new drug application provides for the indication of the treatment of AIDS wasting and cachexia.

We have completed the review of this application as amended, according to the regulations for accelerated approval published in Title 21 of the Code of Federal Regulations (CFR), part 314, subpart H, and have concluded that adequate information has been presented to demonstrate that the the drug product is safe and effective for use as recommended in the draft labeling. Accordingly, the application is approved under 21 CFR 314.510. Approval is effective on the date of this letter. Marketing of this drug product and related activities are to be in accordance with the substance and procedures of the referenced accelerated approval regulations. In particular, we remind you that all promotional materials must be submitted at least 30 days prior to the intended time of initial dissemination of the labeling or the initial publication of the advertisement.

In addition, please submit three copies of promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, MD 20857

Products approved under the accelerated approval regulations (Subpart 314.510) require further adequate and well controlled studies to verify and describe clinical benefit. We remind you of your Phase 4 commitments specified in your submission dated August 19, 1996. These commitments, along with any completion dates agreed upon, are listed below:

1. A detailed draft Clinical Study Protocol for a confirmatory Phase 4 study based on the Clinical Study Concept Sheet submitted on July 29, 1996, will be submitted within four weeks of the date of this letter. Physical function will be measured by treadmill in the Phase 4 clinical study. 9/23/96

2. Patient enrollment in this Phase 4 clinical study will begin no later than three months from the date of approval of the Phase 4 protocol.

In addition, other Phase 4 commitments, not part of the subpart H approval, agreed upon in your August 20, 1996 submission include:

1. [redacted] b(4)

2. [redacted] shall be provided, when available. b(4)

Interim and final reports should be submitted to this NDA. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

The final printed labeling (FPL) for the professional insert must be identical to the draft labeling submitted on August 19, 1996. Carton and vial labels must be identical to the drafts submitted on August 16 and 20, 1996. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug. Please submit sixteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-604. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Michael F. Johnston, R.Ph.
Consumer Safety Officer
(301) 443-3490

Sincerely yours,

Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine
Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 20-604
HFD-510/Div. files
HFD-510/CSO/mj
HFD-510/SMalozowski/GFleming/DWu/SMoore/DHertig/RSteigerwalt/KBarnette/HAhn/BStadel/EGalliers
HFD-2/M.Lumpkin
HFD-102/L.Ripper
HFD-820/Yuan Yuan Chiu
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-80 (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613 (with labeling)
HFD-735/(with labeling) - for all NDAs and supplements for adverse reaction changes.
HFD-021/J.Treacy (with labeling)
HFD-12/R. Klein

FOI: Phase 4 chemistry commitments may include trade secret information.

drafted: MjohnstonAugust 21, 1996/N20604al

APPROVAL [with Phase 4 Commitments]

Name	Title	Signature	Date
D. Hertig	Pharmacology Rev.	D. Hertig	21 Aug 96
R. Steigerwalt, Ph.D.	Pharm. Tm. Leader	Ronald W. Steigerwalt	8/21/96
G. Barnette, Ph.D.	Biopharm. Rev.		8/21/96
H. Ahn, Ph.D.	Biopharm. Tm. Ldr.		8/21/96
B. Taneja, Ph.D.	Biometric Reviewer		8/21/96
~~D. Marticello~~ E. Nevius Ph.D.	Biometric ~~Tm Ldr~~ Dir pir	Edward Nevius	8/21/96
S. Malozowski M.D.	Clinical Reviewer		9/22/96
G. Fleming M.D.	Clinical Tm. Ldr.		9/22/96
E.Galliers	Sup. CSO		8-21-96
S. Sobel	Dir. DMEDP		8/21/96
D. Wu	Chemist		8/21/96
S. Moore	Chemistry Team Leader	Stephen K. Moore	8/21/96

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-604/S027

LABELING

Serostim®
[somatropin (rDNA origin) for injection]

Rx Only **BX Rated**

DESCRIPTION

Serostim® [somatropin (rDNA origin) for injection] is a human growth hormone (hGH) produced by recombinant DNA technology. Serostim® has 191 amino acid residues and a molecular weight of 22,125 daltons. Its amino acid sequence and structure are identical to the dominant form of human pituitary GH. Serostim® is produced by a mammalian cell line (mouse C127) that has been modified by the addition of the hGH gene. Serostim® is secreted directly through the cell membrane into the cell-culture medium for collection and purification.
Serostim® is a highly purified preparation. Biological potency is determined by measuring the increase in the body weight induced in hypophysectomized rats.
Serostim® is available in 4 mg, 5 mg and 6 mg vials for single dose administration. Serostim® is also available in 8.8 mg vials for multi-dose administration. Each 4 mg vial contains 4.0 mg (approximately 12 IU) somatropin, 27.3 mg sucrose, 0.9 mg phosphoric acid. Each 5 mg vial contains 5.0 mg (approximately 15 IU) somatropin, 34.2 mg sucrose and 1.2 mg phosphoric acid. Each 6 mg vial contains 6.0 mg (approximately 18 IU) somatropin, 41.0 mg sucrose and 1.4 mg phosphoric acid. Each 8.8 mg vial contains 8.8 mg (approximately 26.4 IU) somatropin, 60.19 mg sucrose and 2.05 mg phosphoric acid. The pH is adjusted with sodium hydroxide or phosphoric acid to give a pH of 7.4 to 8.5 after reconstitution.

CLINICAL PHARMACOLOGY
Serostim® [somatropin (rDNA origin) for injection] is an anabolic and anticatabolic agent which exerts its influence by interacting with specific receptors on a variety of cell types including myocytes, hepatocytes, adipocytes, lymphocytes, and hematopoietic cells. Some, but not all of its effects, are mediated by insulin-like growth factor-I (IGF-I).
HIV-associated wasting or cachexia, which commonly involves involuntary loss of lean body mass or body weight, is a metabolic disorder characterized by abnormalities of intermediary metabolism resulting in weight loss, inappropriate depletion of lean body mass (LBM), and paradoxical preservation of body fat. LBM includes primarily skeletal muscle, organ tissue, blood and blood constituents, and both intracellular and extracellular water. Depletion of LBM results in muscle weakness, organ failure, and death. Unlike nutritional intervention for HIV-associated wasting, in which supplemental calories are converted predominantly to body fat, Serostim® treatment resulted in a significant increase in LBM and a decrease in fat mass with a significant increase in body weight due to the dominant effect of LBM gain.
Effects on Protein, Lipid, and Carbohydrate Metabolism:
A one-week study in 6 patients with HIV-associated wasting has shown that treatment with Serostim® 0.1 mg/kg/day improved nitrogen balance, increased protein-sparing lipid oxidation, and had little effect on overall carbohydrate metabolism.

Effects on Nitrogen and Mineral Retention:
In the one-week study in 6 patients with HIV-associated wasting, treatment with Serostim® resulted in the retention of phosphorous, potassium, nitrogen, and sodium. The ratio of retained potassium and nitrogen during Serostim® therapy was consistent with retention of these elements in lean tissue.

PHARMACOKINETICS

Subcutaneous Absorption: The absolute bioavailability of Serostim® [somatropin (rDNA origin) for injection] after subcutaneous administration of a formulation not equivalent to the marketed formulation was determined to be 70-90%. The t½ (Mean ± SD) after subcutaneous administration is significantly longer than that seen after intravenous administration in normal male volunteers down-regulated with somatostatin (3.94 ± 3.44 hrs. vs. 0.58 ± 0.08 hrs.), indicating that the subcutaneous absorption of the clinically tested formulation of the compound is slow and rate-limiting.

Distribution: The steady-state volume of distribution (Mean ± SD) following IV administration of Serostim® in healthy volunteers is 12.0 ± 1.08 L.

Metabolism: Although the liver plays a role in the metabolism of GH, GH is primarily cleaved in the kidney. GH undergoes glomerular filtration and, after cleavage within the renal cells, the peptides and amino acids are returned to the systemic circulation.

Elimination: The t½ (Mean ± SD) in nine patients with HIV-associated wasting with an average weight of 56.7 ± 6.8 kg, given a fixed dose of 6.0 mg recombinant hGH (r-hGH) subcutaneously was 4.28 ± 2.15 hrs. The renal clearance of r-hGH after subcutaneous administration in nine patients with HIV-associated wasting was 0.0015 ± 0.0037 L/h. No significant accumulation of r-hGH appears to occur after 6 weeks of dosing as indicated.

Special Populations:

Pediatric: Available evidence suggests that r-hGH clearances are similar in adults and children, but no pharmacokinetic studies have been conducted in children with HIV.

Gender: Biomedical literature indicates that a gender- related difference in the mean clearance of r-hGH could exist (clearance of r-hGH in males > clearance of r-hGH in females). However, no gender-based analysis is available in normal volunteers or patients infected with HIV.

Race: No data are available.

Renal Insufficiency: It has been reported that individuals with chronic renal failure tend to have decreased r-hGH clearance compared to normals, but there are no data on Serostim® use in the presence of renal insufficiency.

Hepatic Insufficiency: A reduction in r-hGH clearance has been noted in patients with severe liver dysfunction. However, the clinical significance of this in HIV+ patients is unknown.

CLINICAL STUDIES

The clinical efficacy of Serostim® [somatropin (rDNA origin) for injection] was assessed in two placebo-controlled trials. All study subjects received concomitant antiretroviral therapy.

Clinical Trial 1: A 12-week, randomized, double-blind, placebo-controlled study followed by an open-label extension phase enrolled 178 patients with severe AIDS wasting taking nucleoside analogue therapy (pre-HAART era). The primary endpoint was body weight. Body composition was assessed using dual energy X-ray absorptiometry (DXA) and physical function was assessed by treadmill exercise testing. Patients meeting the inclusion/exclusion criteria were treated with either placebo or Serostim® 0.1 mg/kg daily. Ninety-six percent (96%) were male. The average baseline CD4 count/μL

was 85. The results from one hundred forty (140) evaluable patients were analyzed (those completing the 12-week course of treatment and who were at least 80% compliant with study drug). After 12 weeks of therapy, the mean difference in weight increase between the Serostim®-treated group and the placebo-treated group was 1.6 kg (3.5 lb). Mean difference in lean body mass (LBM) change between the Serostim®-treated group and the placebo-treated group was 3.1 kg (6.8 lbs) as measured by DXA. Mean increase in weight and LBM, and mean decrease in body fat, were significantly greater in the Serostim®-treated group than in the placebo group ($p=0.011$, $p<0.001$, $p<0.001$, respectively) after 12 weeks of treatment (Figure 1). There were no significant changes with continued treatment beyond 12 weeks suggesting that the original gains of weight and LBM were maintained (Figure 1).

Treatment with Serostim® resulted in a significant increase in physical function as assessed by treadmill exercise testing. The median treadmill work output increased by 13% ($p=0.039$) at 12 weeks in the group receiving Serostim® (Figure 2). There was no improvement in the placebo-treated group at 12 weeks. Changes in treadmill performance were significantly correlated with changes in LBM .

Figure 1: Mean Changes in Body Composition

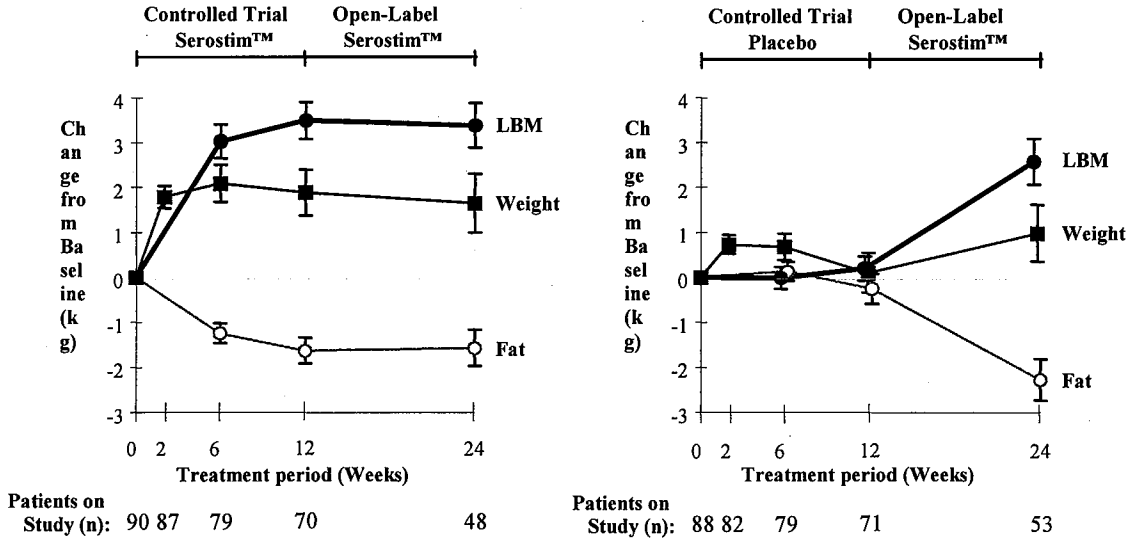
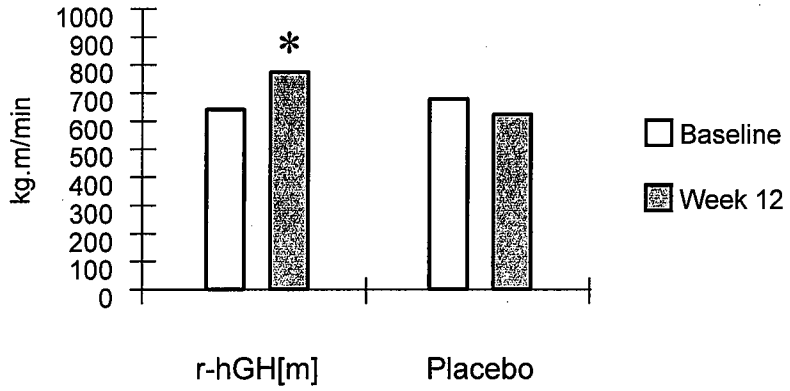


Figure 2: Median Treadmill Work Output



*p = 0.039

Clinical Trial 2: A 12-week, randomized, double-blind, placebo-controlled study enrolled 757 patients with HIV-associated wasting, or cachexia. The primary efficacy endpoint was physical function as measured by cycle ergometry work output. Body composition was assessed using bioelectrical impedance spectroscopy (BIS) and also by dual energy X-ray absorptiometry (DXA) at a subset of centers. Patients meeting the inclusion/exclusion criteria were treated with either placebo, approximately 0.1 mg/kg every other day (qod) of Serostim®, or approximately 0.1 mg/kg daily (qhs) of Serostim®. All results were analyzed in intent-to-treat populations (for cycle ergometry work output, n=670). Ninety-one percent (91%) were male and 88% were on HAART anti-retroviral therapy. The average baseline CD4 count/μL was 446. Six hundred forty-six patients (646) completed the 12-week study and continued in the Serostim® treatment extension phase of the trial.

Clinical Trial 2 results are summarized in Tables 1 and 2:

TABLE 1: MEAN (MEDIAN) OF CYCLE WORK OUTPUT (KJ) RESPONSE AFTER 12 WEEKS OF TREATMENT
ITT POPULATION

	Placebo	Half-Dose Serostim[b]	Full-Dose Serostim[a]
Cycle work output (kJ)	**n=222**	**n=230**	**n=218**
Baseline	**25.92 (25.05)**	**27.79 (26.65)**	**27.57 (26.30)**
Change from baseline	**-0.05 (-0.25)**	**2.48 (2.30)**	**2.52 (2.40)**
Percent change from baseline	**0.2%**	**8.9%**	**9.1%**
Difference from Placebo			
Mean (2-sided 95% C.I.)	-	**2.53 (0.81, 4.25)**	**2.57[c](0.83, 4.31)**
Median		**2.55**	**2.65**

[a] approximately 0.1 mg/kg daily
[b] approximately 0.1 mg/kg every other day
[c] $p<0.01$

TABLE 2: MEAN (MEDIAN) CHANGE FROM BASELINE FOR LEAN BODY MASS, FAT MASS AND BODY WEIGHT

	Placebo		Half-Dose Serostim[b]		Full-Dose Serostim[a]	
	n	Mean (Median)	n	Mean (Median)	n	Mean (Median)
Lean body mass (kg) (by BIS)	222	0.97 (0.67)	223	3.89 (3.65)	205	5.84 (5.47)
Fat mass (kg) (by DXA)	94	0.03 (0.01)	100	-1.25 (-1.23)	85	-1.72 (-1.51)
Body weight (kg)	247	0.69 (0.68)	257	2.18 (2.15)	253	2.79 (2.65)

[a] approximately 0.1 mg/kg daily
[b] approximately 0.1 mg/kg every other day

The mean maximum cycle work output until exhaustion increased after 12 weeks by 2.57 kilojoules (kJ) in the Serostim® 0.1 mg/kg daily group ($p<0.01$) and by 2.53 kJ in the Serostim 0.1 mg/kg every other day group ($p<0.01$) compared with placebo (Table 1). Cycle work output improved approximately 9% in both active treatment arms and decreased <1% in the placebo group (Figure 3). Lean body mass (LBM) and body weight (BW) increased, and fat mass decreased, in a dose-related fashion after treatment with Serostim and placebo (Table 2 and Figure 4). The LBM results obtained by BIS were confirmed with DXA.

Patients' perceptions of the impact of 12 weeks of treatment on their wasting symptoms as assessed by the Bristol-Meyers Anorexia/Cachexia Recovery Instrument improved with both doses of Serostim® in Clinical Trial 2.

Extension Phase: All patients (n=646) completing the 12-week placebo-controlled phase of Clinical Trial 2 continued Serostim® treatment into an extension phase. Five hundred and forty eight of these patients completed an additional 12 weeks of active treatment. In these patients, changes in cycle

ergometry work output, LBM, BW, and fat mass either improved further or were maintained with continued Serostim® treatment.

INDICATIONS AND USAGE

Serostim® [somatropin (rDNA origin) for injection] is indicated for the treatment of HIV patients with wasting or cachexia to increase lean body mass and body weight, and improve physical endurance. Concomitant antiretroviral therapy is necessary (see PRECAUTIONS).

CONTRAINDICATIONS

Growth hormone therapy should not be initiated in patients with acute critical illness due to complications following open heart or abdominal surgery, multiple accidental trauma or acute respiratory failure. Two placebo-controlled clinical trials in non-growth hormone deficient adult patients (n=522) with these conditions revealed a significant increase in mortality (41.9% vs. 19.3%) among somatropin-treated patients (doses 5.3-8 mg/day) compared to those receiving placebo (see WARNINGS).

Serostim® is contraindicated in patients with active neoplasia (either newly diagnosed or recurrent). Any anti-tumor therapy should be completed prior to starting therapy with Serostim®.

Serostim® [somatropin (rDNA origin) for injection] reconstituted with Bacteriostatic Water for Injection, USP (0.9% Benzyl Alcohol) should not be administered to patients with a known sensitivity to Benzyl Alcohol. (See « WARNINGS »).

Serostim® is contraindicated in patients with a known hypersensitivity to growth hormone.

WARNINGS

Benzyl Alcohol as a preservative in Bacteriostatic Water for Injection, USP has been associated with toxicity in newborns. If sensitivity to the diluent occurs, Serostim® [somatropin (rDNA origin) for injection] may be reconstituted with Sterile Water for Injection, USP. When Serostim® is reconstituted in this manner, the reconstituted solution should be used immediately and any unused portion should be discarded .

See CONTRAINDICATIONS for information regarding increased mortality in growth hormone-treated patients with acute critical illnesses in intensive care units due to complications following open heart or abdominal surgery, multiple accidental trauma or acute respiratory failure. The safety of continuing growth hormone treatment in patients receiving replacement doses for approved indications who concurrently develop these illnesses has not been established. Therefore, the potential benefit of treatment continuation with growth hormone in patients developing acute critical illnesses should be weighed against the potential risk.

PRECAUTIONS

General: Serostim® [somatropin (rDNA origin) for injection] therapy should be carried out under the regular guidance of a physician who is experienced in the diagnosis and management of HIV infection. Inadequate nutritional intake, malabsorption and hypogonadism, which are common in individuals with HIV infection and which may contribute to catabolism and weight loss, should be diagnosed and treated.

HIV and Growth Hormone Considerations: In some experimental systems, recombinant human growth hormone (r-hGH) has been shown to potentiate HIV replication in vitro at concentrations ranging from 50-250 ng/ml. There was no increase in virus production when the antiretroviral agents, zidovudine,

didanosine or lamivudine were added to the culture medium. Additional in vitro studies have shown that r-hGH does not interfere with the antiviral activity of zalcitabine or stavudine. In the controlled clinical trials, no significant growth hormone-associated increase in viral burden was observed. However, the protocol required all participants to be on concomitant antiretroviral therapy for the duration of the study. In view of the potential for acceleration of virus replication, it is recommended that HIV patients be maintained on antiretroviral therapy for the duration of Serostim® treatment.

Increased tissue turgor (swelling, particularly in the hands and feet) and musculoskeletal discomfort (pain, swelling and/or stiffness) may occur during treatment with Serostim®, but may resolve spontaneously, with analgesic therapy, or after reducing the frequency of dosing (see DOSAGE AND ADMINISTRATION).

Carpal tunnel syndrome may occur during treatment with Serostim®. If the symptoms of carpal tunnel syndrome do not resolve by decreasing the weekly number of doses of Serostim®, it is recommended that treatment be discontinued.

Patients should be informed that allergic reactions are possible and that prompt medical attention should be sought if an allergic reaction occurs. None of the 651 study participants with HIV-associated wasting treated with Serostim® for the first time developed detectable antibodies to growth hormone (> 4 pg binding). Patients were not rechallenged.

Recombinant human growth hormone (r-hGH) has been associated with acute pancreatitis.

Hyperglycemia may occur in HIV infected individuals due to a variety of reasons. Treatment with Serostim® 0.1 mg/kg daily and 0.1 mg/kg every other day for 12 weeks were associated with approximately 10mg/dL and 6mg/dL increases of mean blood glucose concentration, respectively. The increases occurred early in treatment. Patients with other risk factors for glucose intolerance should be monitored closely during Serostim® therapy.

During post-marketing surveillance, cases of new onset impaired glucose intolerance, new onset type 2 diabetes mellitus and exacerbation of preexisting 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®.

No cases of intracranial hypertension (IH) have been observed among patients with AIDS wasting treated with Serostim®. The syndrome of IH, with papilledema, visual changes, headache, and nausea and/or vomiting has been reported in a small number of children with growth failure treated with growth hormone products. Nevertheless, funduscopic evaluation of patients is recommended at the initiation and periodically during the course of Serostim® therapy.

Kaposi's sarcoma, lymphoma, and other malignancies are common in HIV+ individuals. There was no increase in the incidence of Kaposi's sarcoma, lymphoma, or in the progression of cutaneous Kaposi's sarcoma in clinical studies of Serostim®. Patients with internal KS lesions were excluded from the studies. Potential effects on other malignancies are unknown.

Information For Patients: Patients being treated with Serostim® should be informed of the potential benefits and risks associated with treatment. Patients should be instructed to contact their physician should they experience any side effects or discomfort during treatment with Serostim®.

It is recommended that Serostim® be administered using sterile, disposable syringes and needles. Patients should be thoroughly instructed in the importance of proper disposal and cautioned against any reuse of needles and syringes. An appropriate container for the disposal of used syringes and needles should be employed.

Patients should be instructed to rotate injection sites to avoid localized tissue atrophy.

Drug Interactions: Formal in vitro drug interaction studies have not been conducted. No data are available on drug interactions between Serostim® and HIV protease inhibitors or the non-nucleoside reverse transcriptase inhibitors.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term animal studies for carcinogenicity have not been performed with Serostim®. There is no evidence from animal studies to date of Serostim®-induced mutagenicity or impairment of fertility.

Pregnancy: Pregnancy Category B. Reproduction studies have been performed in rats and rabbits. Doses up to 5 to 10 times the human dose, based on body surface area, have revealed no evidence of impaired fertility or harm to the fetus due to Serostim®. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Women: It is not known whether Serostim® is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Serostim® is administered to a nursing woman.

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. The 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.

Geriatric Use : Clinical studies with Serostim® did not include sufficient numbers 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 low end of the dosing range.

ADVERSE REACTIONS

In the 12-week, placebo-controlled Clinical Trial 2, 510 patients were treated with Serostim® [somatropin (rDNA origin) for injection]. The most common adverse reactions judged to be associated with Serostim® were musculoskeletal discomfort and increased tissue turgor (swelling, particularly of the hands or feet), and were more frequently observed when Serostim 0.1 mg/kg was administered on a daily basis (Table 3 and PRECAUTIONS). These symptoms were generally rated by investigators as mild to moderate in severity and often subsided with continued treatment or dose reduction. Approximately 23% of patients receiving Serostim 0.1 mg/kg daily and 11% of patients receiving 0.1 mg/kg every other day required dose reductions. Discontinuations as a result of adverse events occurred in 10.3% of patients receiving Serostim 0.1 mg/kg daily and 6.6% of patients receiving 0.1 mg/kg every other day. The most common reasons for dose reduction and/or drug discontinuation were arthralgia, myalgia, edema, carpal tunnel syndrome, elevated glucose levels, and elevated triglyceride levels.

Clinical adverse events which occurred during the first 12 weeks of study in at least 5% of the patients in any one of the three treatment groups are listed below by treatment group, without regard to causality assessment.

Table 3: Controlled Clinical Trial 2 Adverse Events :

Body System Preferred Term	Placebo Patients (n=247) %	0.1 mg/kg qod Serostim® Patients (n=257) %	0.1 mg/kg daily Serostim® Patients (n=253) %
MUSCULOSKELETAL SYSTEM DISORDERS			
ARTHRALGIA	11.3	24.5	36.4
MYALGIA	11.7	17.9	30.4
ARTHROSIS	3.6	7.8	10.7
GASTRO-INTESTINAL SYSTEM DISORDERS			
DIARRHEA	10.1	10.1	5.5
NAUSEA	4.9	5.4	9.1
PSYCHIATRIC DISORDERS			
INSOMNIA	6.1	3.9	5.9
BODY AS A WHOLE - GENERAL DISORDERS			
EDEMA PERIPHERAL	2.8	11.3	26.1
HEADACHE	9.3	10.1	12.6
FATIGUE	4.5	3.5	5.1
RESPIRATORY SYSTEM DISORDERS			
RHINITIS	6.5	5.1	4.0
UPPER RESP TRACT INFECTION	5.7	4.3	3.6
BRONCHITIS	5.3	2.3	4.7
ENDOCRINE DISORDERS			
GYNECOMASTIA	0.4	3.5	5.5
CENTR & PERIPH NERVOUS SYSTEM DISORDERS			
PARESTHESIA	4.5	7.4	7.9
HYPOESTHESIA	2.4	1.6	5.1
METABOLIC AND NUTRITIONAL DISORDERS			
EDEMA GENERALIZED	1.2	1.2	5.9

Adverse events that occurred in 1% to less than 5% of study participants receiving Serostim® during the 12-week, placebo-controlled Clinical Trial 2 are listed below by body system. The list of adverse events has been compiled regardless of causal relationship to Serostim®.

Body as a Whole: rigors, fever, carpal tunnel syndrome (see PRECAUTIONS), night sweats, edema/face edema (see PRECAUTIONS), pain, flu-like symptoms, leg pain, chest pain, asthenia.

Gastrointestinal System: vomiting, abdominal pain, dyspepsia, gastroenteritis, and constipation.

Musculoskeletal System: back pain, musculoskeletal pain (see PRECAUTIONS), and arthropathy.

Central and Peripheral Nervous System: peripheral neuropathy, dizziness, and hypertonia.

Respiratory System: coughing, sinusitis, pharyngitis, and pneumonia.

White Blood Cell and Reticuloendothelial System Disorders: lymphadenopathy

Skin and Appendages: folliculitis, rash, verruca, and maculopapular rash.

Psychiatric: anorexia, depression, anxiety, and somnolence.

Metabolic and Nutritional: hypertriglyceridemia, hyperglycemia (see PRECAUTIONS), and periorbital edema (see PRECAUTIONS).

Immune System Dysfunction: moniliasis, viral infection, and herpes simplex.

Urinary System: urinary tract infection, renal calculus

Vision: conjunctivitis

Cardiovascular, General: dependent edema (see PRECAUTIONS), hypertension, tachycardia

Secondary Terms: accident not otherwise specified

Neoplasms: male breast neoplasm

During the 12-week, placebo-controlled portion of Clinical Trial 2, the incidence of hyperglycemia reported as an adverse event was 3.6% for the placebo group, 1.9% for the 0.1 mg/kg qod group and

3.2% for the 0.1 mg/kg daily group. One case of diabetes mellitus was noted in the 0.1 mg/kg daily group during the first 12-weeks of therapy. In addition, during the extension phase of Clinical Trial 2, two patients converted from placebo to full dose Serostim, and 1 patient converted from placebo to half-dose Serostim, were discontinued because of the development of diabetes mellitus.

The types and incidences of adverse events reported during the Clinical Trial 2 extension phase were not different from, or greater in frequency than those observed during the 12-week, placebo-controlled portion of Clinical Trial 2.

During post-marketing surveillance, cases of new onset impaired glucose intolerance, new onset type 2 diabetes mellitus and exacerbation of preexisting 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®.

OVERDOSAGE

Glucose intolerance can occur with overdosage. Long-term overdosage with growth hormone could result in signs and symptoms of acromegaly.

DOSAGE AND ADMINISTRATION

The usual starting dose of Serostim® [somatropin (rDNA origin) for injection] is 0.1 mg/kg subcutaneously (SC) daily (up to 6 mg). It should be administered SC daily at bedtime according to the following dosage recommendations:

Weight Range	Dose
>55kg (>121 lb)	6 mg* SC daily
45-55 kg (99-121 lb)	5 mg* SC daily
35-45 kg (75-99 lb)	4 mg* SC daily
<35 kg (<75 lb)	0.1 mg/kg SC daily

*Based on an approximate daily dosage of 0.1 mg/kg.

Serostim® 8.8 mg with Bacteriostatic Water for Injection, USP (0.9% Benzyl Alcohol), a multi-use vial, should be administered as per the above weight-based dosing table. Serostim 4, 5 or 6 mg with Sterile Water for Injection, USP, single use vials, should be administered to patients requiring 4, 5 or 6 mg daily, respectively, as per the above weight-based dosing table.

Treatment with Serostim® 0.1 mg/kg every other day was associated with fewer side effects, and resulted in a similar improvement in work output, as compared with Serostim® 0.1 mg/kg daily. Therefore, a starting dose of Serostim® 0.1 mg/kg every other day should be considered in patients at increased risk for adverse effects related to recombinant human growth hormone therapy (i.e., glucose intolerance). In general, dose reductions (i.e., reducing the total daily dose or the number of doses per week) should be considered for side effects potentially related to recombinant human growth hormone therapy, which are unresponsive to symptom-directed treatment.

Most of the effect of Serostim® on work output and lean body mass was apparent after 12 weeks of treatment. The effect was maintained during an additional 12 weeks of therapy. There are no safety or efficacy data available from controlled studies in which patients were treated with Serostim® continuously for more than 48 weeks. There are no safety or efficacy data available from trials in which patients were treated intermittently with Serostim.®

Injection sites should be rotated.

Safety and effectiveness in pediatric patients with HIV have not been established.

Each vial of Serostim® 4 mg, 5 mg or 6 mg is reconstituted with 0.5 to 1 mL Sterile Water for Injection, USP. Each vial of Serostim® 8.8 mg is reconstituted in 1 to 2 mL of Bacteriostatic Water for Injection, USP (0.9% Benzyl Alcohol preserved). Approximately 10% mechanical loss can be associated with reconstitution and administration from multi-dose vials. For patients sensitive to this diluent, see « WARNINGS » .
To reconstitute Serostim®, inject the diluent into the vial of Serostim® aiming the liquid against the glass vial wall. Swirl the vial with a gentle rotary motion until contents are dissolved completely. The Serostim® solution should be clear immediately after reconstitution. **DO NOT INJECT** Serostim® if the reconstituted product is cloudy immediately after reconstitution or after refrigeration (2-8°C/36-46°F) for up to 14 days. Occasionally, after refrigeration, small colorless particles may be present in the Serostim® solution. This is not unusual for proteins like Serostim®.

STABILITY AND STORAGE
Before reconstitution: Vials of Serostim® and diluent should be stored at room temperature, (15°-30°C/59°-86°F). Expiration dates are stated on product labels.
After Reconstitution with Sterile Water for Injection, USP: The reconstituted solution should be used immediately and any unused portion should be discarded .
After Reconstitution with Bacteriostatic Water for Injection, USP (0.9% Benzyl Alcohol): The reconstituted solution should be stored under refrigeration (2-8°C/36-46°F) for up to 14 days. Avoid freezing reconstituted vials of Serostim®.

HOW SUPPLIED
Serostim® [somatropin (rDNA origin) for injection] is available in the following forms:
Serostim® vials containing 4 mg (approximately 12 IU) somatropin (mammalian-cell) with Sterile Water for Injection, USP. Package of 7 vials. NDC 44087-0004-7
Serostim® vials containing 5 mg (approximately 15 IU) somatropin (mammalian-cell) with Sterile Water for Injection, USP. Package of 7 vials. NDC 44087-0005-7
Serostim® vials containing 6 mg (approximately 18 IU) somatropin (mammalian-cell) with Sterile Water for Injection, USP. Package of 7 vials. NDC 44087-0006-7
Serostim® vial containing 8.8 mg (approximately 26.4 IU) somatropin (mammalian-cell) with Bacteriostatic Water for Injection, USP (0.9% Benzyl Alcohol). Package of 1 vial.
NDC 44087-0088-1

Manufactured for: Serono, Inc., Rockland, MA 02370

July 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-604/S027

SUMMARY REVIEW

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center For Drug Evaluation and Research

DATE: August 26, 2003

FROM: David G. Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products

TO: NDA 20-604/S-027

SUBJECT: sNDA review issues and recommended action

Background

AIDS associated wasting is a significant clinical consequence of HIV infection of likely multifactorial pathogenesis. Although the advent of highly active antiretroviral therapeutic regimens has reduced the incidence of the wasting syndrome, it nevertheless affects a large number of patients. It is characterized by loss of lean body mass and functional decline and is associated with increased mortality in HIV infection.

Serostim was approved on August 23, 1996 for the treatment of HIV-associated wasting and cachexia based on the results of a randomized, double-blind, placebo-controlled study in 178 patients with HIV, wasting, and receiving nucleoside analogue therapy (pre-HAART). Patients received either placebo or Serostim 6 mg/day for 12 weeks. GH treatment was associated with increases in body weight, lean body mass, and treadmill work output compared to placebo. The effects appeared durable during a 12-week open label extension period. The original application was supported also by a second blinded, placebo-controlled, 12-week trial in 177 patients randomized 2:1 showing a non-significant mean increase in body weight associated with drug relative to placebo. Finally, in a third open-label trial, 20 evaluable patients showed a mean increase in lean body mass of 2.3 kg relative to baseline.

The original label cited the reliance on "surrogate" endpoints in studies of up to 12 weeks' duration, thought did not explicitly limit the recommended treatment period to 12 weeks. The label did recommend reevaluation after 2 weeks of treatment if patients continued to lose weight on Serostim.

Serostim was approved under the accelerated approval regulations ("subpart H"), and a phase 4 study was required as part of the approval "to verify and describe clinical benefit" in the target population. A clinical study "concept sheet" was submitted July 29, 1996 that was to form the basis for a study protocol. According to the action letter, physical function was to be measured by treadmill in the verification study. This was later changed to bicycle ergometry in the protocol.

The current sNDA contains the report of the confirmatory phase 4 study and was received on November 1, 2002. The safety and efficacy data are discussed in detail in Dr. Perlstein's review of this supplement. The following will briefly review the salient points supporting changes to the labeling. The study does, indeed, confirm the results of the study supporting initial approval. The study was not designed to validate the surrogates or intermediate endpoints studied in the trial supporting initial approval as indicators of improved long-term morbid and mortal outcomes. Rather, this study is merely larger than the first study, places work output as the primary endpoint, and investigated the safety and efficacy of two doses of Serostim. It clearly substantiates, or confirms, the findings of the original study. The regulatory requirements under subpart H of 21 CFR 314 are therefore met. Labeling has been negotiated.

Clinical
Study GF-9037
This was a randomized, double-blind trial of 12 weeks' duration in which patients with HIV-associated wasting and cachexia were treated with placebo, Serostim 0.1 mg/kg/day (full dose), or Serostim 0.1 mg/kg every other day (half dose). 757 patients were randomized. Most were males. The primary endpoint of the study was the change from baseline in work output as assessed by bicycle ergometry. Secondary endpoints included change from baseline in LBM, BW, total fat mass. Patients completing the 12-week placebo-controlled phase of the study (85% of the randomized cohort, N=646) were enrolled in an extension study. Of these, 548 patients completed an additional 12 weeks of therapy. Approximately 180 patients completed 48 weeks of therapy (12-week pbo-controlled plus 36-week extension).

Mean work output until exhaustion by bicycle ergometry increased similarly in both active treatment groups relative to placebo. Specifically, the mean change was approximately +9% with Serostim regardless of dose and -1% with placebo. In communications with Dr. Perlstein, the sponsor stated that a person experiencing an increase in exercise capacity of the mean absolute magnitude observed in the study "could be expected to feel less fatigued in the performance of some tasks of daily living." The results by bicycle ergometry comfirm the findings of the original study as measured by treadmill exercise. Figure 1 of Dr. Perlstein's review shows the distribution of effects on work output by treatment group. Approximately 65% of drug treated patients (regardless of dose) increased their work output from baseline to 12 weeks, in contrast to only 46% of placebo patients. This is an approximate 50% increase in the number of responders, defined as those increasing work output over the course of the study. While the effects on exercise capacity are perhaps not necessarily life-altering (and certainly not in all cases), these results certainly support an expectation of a meaningful effect of GH in a substantial percentage (~20%) of patients treated.

Lean body mass increased in a dose-related fashion relative to placebo. The full-dose Serostim group increased LBM by a mean of almost 5 kg relative to placebo.

There were too few women in the trial to permit statistical conclusions about efficacy in females. However, among the approximately 20 women per treatment group, the mean effect on work output was 16% and the absolute frequency of responders (increase in work output relative to baseline) was higher than among the males. Women showed a non-significant, dose-related

increase in LBM relative to baseline compared to placebo of a magnitude similar to that observed in the men.

From figure 5 of Dr. Perlstein's review, it is apparent that most of the effect of Serostim on work output (relative to placebo) is manifest after 12 weeks of treatment. With continued treatment to week 24, the effect was maintained. The same holds true for the change in LBM. Therefore, treatment duration should be 12 to 24 weeks.

Safety

As per Dr. Perlstein's review, 10.3%, 6.6%, and 1.2% of patients in the full-dose Serostim, half-dose Serostim, and placebo groups, respectively, discontinued due to adverse events during the 12-week controlled phase of the study. Most of the Serostim discontinuations appeared related to drug (glucose intolerance, musculoskeletal sxs, edema, carpal tunnel syndrome). Most of the adverse events leading to discontinuation occurred during the initial phase of therapy. As expected, glucose intolerance occurred in Serostim-treated patients much more frequently that in placebo-treated patients, with an approximate doubling relative to baseline of the incidence of fasting glucose levels between 110 and 126 mg/dL (absolute incidence 12-15% over 12 weeks). In addition, at week 4, the incidence of fasting glucose levels between 126 and 250 mg/dL was 9.2% while the incidence in the half-dose group was no different than placebo. Three patients on full-dose Serostim had FBG > 250 mg/dL at week 4. Eight patients were discontinued because of hyperglycemia. Four patients developed new onset diabetes mellitus.

As expected the incidence of musculoskeletal sxs, edema, and carpal tunnel syndrome was greater among Serostim-treated patients and more common at the higher dose of Serostim.

Finally, a dose response was evident regarding the incidence of gynecomastia in males treated with Serostim. No breast malignancies were reported.

The sponsor intends to [redacted] b(4)
Serostim. The labeling already reflects the post-marketing observation of glucose intolerance/diabetes in Serostim-treated patients. The sponsor will also collect [redacted] b(4)
[redacted] The labeling will reflect the similar effects of high dose and low dose Serostim on work output and the dose-related increased incidence of GH-related AEs and will recommend initiation of therapy at the lower dose in patients deemed to be at increased risk for side effects (e.g., glucose intolerance).

Labeling

See comments immediately above. Labeling will also reflect the fact that most of the effect of Serostim is apparent in the first 12 weeks with maintenance of effect with an additional 12 weeks. Because of the side effects of this relatively high dose of GH, the duration of therapy [redacted]

Biopharmaceutics b(4)

No issues.

Pharmacology/Toxicology

No issues.

Chemistry/ Microbiology

No issues

DSI/Data Integrity
As per Dr. Perstein's review, the data were deemed acceptable for review by DSI.

Financial disclosure
As per Dr. Perlstein's review, the financial disclosure information is acceptable and there is no reason to question the integrity or reliability of the data based on conflicts of interest.

ODS/nomenclature
No issues.

Recommendation
This application may be approved.

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

/s/

David Orloff
8/29/03 12:10:53 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-604/S027

MEDICAL REVIEW(S)

MEDICAL OFFICER REVIEW

Division of Metabolic and Endocrine Drug Products (HFD-510)

APPLICATION #:	NDA 20-604, S-027, SE-7	APPLICATION TYPE:	Commercial NDA
SPONSOR:	Serono, Inc.	PROP. BRAND NAME:	Serostim
		GENERIC NAME:	Somatropin (recombinant DNA [rDNA]) origin
		CHEMICAL NAME:	Recombinant human growth hormone (rhGH)
CATEGORY OF DRUG:	Recombinant human growth hormone (rhGH)	USAN / Established Name:	
		ROUTE:	Subcutaneous Injection (SC)
MEDICAL REVIEWER:	Robert S. Perlstein MD, FACP, FACE	REVIEW DATE:	25Aug03

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
31Oct02	1Nov02	Confirmatory Study/SE-7 Supplement Submitted to Fulfill Subpart H/Phase IV Commitment Imposed in 1996	

RELATED APPLICATIONS: All NDAs/INDs pertaining to somatropin therapy for adults with GH deficiency

EXECUTIVE SUMMARY

EFFICACY SUMMARY/CONCLUSIONS: The Sponsor conducted a 12 week, prospective, randomized, parallel group, double blind, placebo controlled, dose ranging study (followed by a 12-36 week extension phase) in patients with human immunodeficiency virus (HIV)-/acquired immunodeficiency syndrome (AIDS)-associated catabolism/wasting to 1) evaluate the clinical efficacy of Serostim compared with placebo in stimulating an increase in the primary efficacy outcome parameter, bicycle ergometry work output (BWO) (as well as changes in multiple other secondary efficacy variables including, most importantly, an increase in lean body mass (LBM) and body weight (BW), and a decrease in total fat mass; 2) establish an optimal dose of Serostim; 3) assess the safety and tolerability of Serostim; and 4) ***confirm the results of Study 5341 conducted by the Sponsor in 1992-1993 which resulted in the accelerated approval of Serostim for the treatment of AIDS-associated wasting in 1996 (in this regard, Study GF-9037 was considered to be an obligatory Subpart H/Phase IV confirmatory study).*** Patients were randomized to full dose Serostim 0.1 mg/kg (up to 6 mg) daily, half-dose Serostim 0.1 mg/kg (up to 6 mg) every other day (alternating with placebo) and placebo during the 12 week, placebo controlled portion of the study. The primary objectives of the 12–36 week extension phase were to establish the durability of the clinical efficacy of Serostim, and to further assess the long-term safety and tolerability of Serostim. The primary efficacy comparison was the change in BWO from baseline to Week 12 between the full dose Serostim group and the placebo group. ***Although not designated by the Sponsor in the original protocol as part of the primary efficacy objective, the difference in the change in BWO from baseline to Week 12 between the Serostim half-dose group and the placebo group was also considered to be of significant importance by the Division. If possible, BWO determinations were to be performed if patients prematurely discontinued from the study.*** The most important secondary efficacy comparison was the change in LBM from baseline to Week 12 between the full dose Serostim group and the placebo group, as well as between the half-dose Serostim group and the placebo group. Both the BWO and LBM analyses were performed in the intent-to-treat (ITT) population ***including*** patients with so-called "inconsistent" measurements (n=670 for BWO and n=650 for LBM). A total of 757 patients were randomized and treated (full dose Serostim [n=253], half-dose Serostim [n=257] and placebo [n=247]). ~85% of treated patients completed the 12 week, placebo controlled portion of the study – ***an acceptable completion rate.*** Five hundred and forty eight patients (~72% of the cohort originally randomized and treated)

completed a total of 24 weeks on-study. No statistically significant differences were observed across treatment groups with respect to multiple continuous and categorical demographic parameters. Most patients were homosexual, Caucasian males, and ~85% of patients in all treatment groups were receiving highly active antiretroviral therapy (HAART). The mean maximum BWO until exhaustion increased signficantly after 12 weeks by 2.57 kJ in the Serostim 0.1 mg/kg daily group and by 2.53 kJ in the Serostim 0.1 mg/kg every other day group compared with placebo. Work until exhaustion was verified by analyzing the scores derived from the Borg RPE scale indicating that a satisfactory and uniform level of exhaustion had been obtained across all 3 treatment groups at both of these time points. Distribution analysis revealed that ~66% and ~64% of full dose Serostim-treated patients and half-dose Serostim-treated patients, respectively, were responders. ***These results confirm the findings observed in the Sponsor's original, label-enabling Study 5341 which demonstrated a significant increase in treadmill work output after 12 weeks of treatment with Serostim 0.1 mg/kg/day (up to 6 mg), and also indicate that full dose and half-dose Serostim have almost identical effects with respect to stimulating an increase in BWO. The associated significant, dose proportional increase in LBM observed during this study enhances the validity of the BWO findings*** (even though this study did not confirm the statistically significant correlation between work output and LBM responses observed during Study 5341). LBM increased significantly after 12 weeks by 4.88 kg in the Serostim 0.1 mg/kg daily group and by 2.92 in the Serostim 0.1 mg/kg every other day group compared with placebo – ***a very clearcut dose-dependent response.*** Distribution analysis revealed that ~91% and ~85% of full dose Serostim-treated patients and half-dose Serostim-treated patients, respectively, were responders. ***These results confirm the findings observed in the Sponsor's original, label-enabling Study 5341 which demonstrated a smaller (3.1 kg in Study 5341 vs. 4.88 kg in GF-9037), but still significant increase from baseline in LBM (compared to placebo) after 12 weeks of treatment with Serostim 0.1 mg/kg/day (up to 6 mg). It is somewhat reassuring that the between-group treatment differences on change from baseline in LBM by bioelectrical impedance spectroscopy (BIS) and dual energy X-ray absorptiometry (DEXA) were similar.*** The mean differences from placebo in change from baseline in BWO and LBM for both active treatment groups was significant in men, but not in women. However, given the very small number of women in the study population, and the absence of a significant treatment-by-gender interaction in the ANOVA performed on the entire ITT study population, ***the lack of a response in women must be interpreted with caution.*** The treatment-by-race interaction in the analysis of variance (ANOVA) performed on the entire ITT study population comparing changes from baseline in BWO between each of the active treatment arms and the placebo group in Caucasians vs. non-Caucasians (constituting ~25% of each treatment arm) was statistically significant. ***The interaction was qualitative in nature. However, in that 1) there is no biologic plausibility for this observation; 2) this is a post hoc exploratory analysis; and 3) this interaction is not seen for LBM, this observation must be interpreted with caution. For the same reasons, this Medical Officer does not feel that an additional study comparing Caucasians and non-Caucasians is necessary nor is it essential to accrue BWO data (in addition to LBM data) in the*** b(4)

The treatment-by-HAART interaction in the ANOVA performed on the entire ITT study population comparing changes from baseline in BWO between each of the active treatment arms and the placebo group in HAART users vs. HAART non-users was weakly statistically significant. The interaction was qualitative in nature. ***Such an interaction is theoretically biologically plausible, i.e. HAART therapy by itself could result in improved BWO/LBM. Nonetheless, given that 1) there were very few patients (~10-13%) not receiving HAART; 2) this is a post hoc exploratory analysis; and 3) this interaction is not seen for LBM, this observation must be interpreted with caution.*** A lower baseline body weight (BW) and lower baseline body mass index (BMI) were significant predictors of a positive BWO response after treatment with full dose (but not half-dose) Serostim. However, regression analyses did not demonstrate significant inverse linear relationships. No other significant predictor of response was discovered amongst BWO and LBM responders. Total fat mass (by DEXA) decreased significantly after 12 weeks by 1.75 kg in the Serostim 0.1 mg/kg daily group and by 1.28 kg in the Serostim 0.1 mg/kg every other day group compared with placebo – ***a clearcut dose-dependent response.*** The decreases in total fat mass were paralleled by dose-dependent decreases in truncal fat mass, limb fat

mass, and the truncal fat mass/limb fat mass ratio. ***The decreases in total fat mass observed in this study confirm similar results from Study 5341, and are readily explained by the powerful, well known lipolytic effect of rhGH.*** BW increased significantly after 12 weeks by 2.1 kg in the Serostim 0.1 mg/kg daily group and by 1.49 kg in the Serostim 0.1 mg/kg every other day group compared with placebo – ***a clearcut dose-dependent response.*** The treatment effect with respect to BW was ~50% of that observed in LBM. ***The increases in BW observed in this study confirm similar results from Study 5341*** (treatment difference was 1.6 kg for full dose Serostim vs. placebo). Consultation was obtained from the Agency's Study Endpoints and Label Development (SEALD) team regarding quality of life (QOL) measurements submitted by the Sponsor. ***The SEALD team reviewer found significant faults with the QOL instruments utilized by the Sponsor and recommended omitting the terms [redacted] from the Package Insert proposed by the Sponsor. This was accomplished (see ahead to Efficacy Recommendations).*** The increase in BWO in 200 patients who had "consistent" BWO measurements at baseline, Week 12 and Week 24 was similar at Week 12 for patients who received either full dose or half-dose Serostim (consistent with the formal statistical analysis presented earlier). However, the additional increase in BWO between Week 12 and Week 24 was somewhat greater in the continuous half-dose patients than in the continuous full dose patients. Dose-dependent increases in LBM at Week 12 were observed in 214 patients who had "consistent" LBM measurements at baseline, Week 12 and Week 24. However, the additional increase in LBM between Week 12 and Week 24 was very modest in patients treated continuously with both full dose and half-dose Serostim. The dose response effect was still apparent at Week 24. A dose-dependent increase in BW was also maintained after 24 weeks of treatment. ***The 24 week results for BWO, LBM and BW described above indicate that the effect of both doses of Serostim was maintained through 24 weeks, i.e., that the response achieved at Week 12 was durable.***

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SAFETY SUMMARY/CONCLUSIONS:

None of the 6 deaths which occurred during the study were felt to be related to the administration of Serostim by the Sponsor or this Medical Officer. Except for 2 patients with significant hyperglycemia and 1 patient with severe gynecomastia, none of the 88 serious adverse events (SAEs) reported by 66 patients during the entire study were felt to be related to the administration of Serostim by the Sponsor or this Medical Officer. A total of 46 patients were discontinued due to adverse events during the placebo controlled phase of the study. ***A dose response relationship was apparent across the 3 treatment groups with respect to the frequency of adverse events leading to study drug discontinuation, in particular adverse events most likely related to Serostim.*** More of these adverse events most likely related to Serostim therapy leading to discontinuation during either phase of the study occurred when either dose of Serostim was first initiated (e.g., study onset or when placebo patients were switched to full dose or half-dose at the beginning of the extension phase) or after an increase in dose (e.g., when half-dose patients were switched to full dose at the beginning of the extension phase under the amended protocol) than during more extended treatment with either half-dose or full dose Serostim. ***A dose response relationship was apparent across the 3 treatment groups with respect to the frequency of treatment emergent adverse events (TEAEs) (as well as adverse events requiring protocol-directed dose reductions), in particular adverse events most likely related to Serostim. Adverse events including arthralgia/myalgia, peripheral edema, and carpal tunnel syndrome/paraesthesia were more frequent during Serostim treatment than during placebo treatment, and more frequent in the full dose group than the half-dose group. These kinds of events are well known during rhGH treatment, and thought to be related to the effects of rhGH on fluid homeostasis and interstitial matrix.*** None of the more severe but unusual adverse events associated with rhGH therapy in children and potentially applicable to adults (e.g., benign intracranial hypertension, proliferative retinopathy, hypercalcemia, or pancreatitis) was reported during this study. ***Glucose intolerance was common during this study, and, in some patients, resulted in substantial hyperglycemia.*** Mean changes in fasting blood glucose levels during the placebo controlled phase were dose-dependent, and ranged from 2 to 10 mg/dL. Shift table analysis during the 12 week, placebo controlled phase of the study ***indicated that the number of patients with elevated fasting blood glucose levels increased soon after Serostim therapy initiation*** (in the full dose

Serostim group much more often than the half-dose Serostim group), ***and then seemed to plateau.*** In patients treated with full dose Serostim for 24 weeks, ***mean fasting blood glucose did not increase further during the second 12 weeks of full dose Serostim therapy.*** In the groups continued on either full dose or half-dose Serostim for an additional 12 weeks during the extension phase, ***there was no progressive increase in the number of patients with abnormal sugars. Twenty five patients manifested a fasting blood glucose level >160 mg/dL at some time during the trial resulting in an intervention.*** 21 patients required dose reduction (fasting blood glucose levels usually normalized). ***8 patients were discontinued from the study because of hyperglycemia (2 during the placebo controlled phase and 6 during the extension phase). Of note, 7 of these 8 patients were receiving full dose Serostim when they were terminated including the 2 patients discontinued during the placebo controlled phase of the study.*** Four of these 8 patients manifested de novo diabetes mellitus on-study - 1 while receiving full dose Serostim during the placebo controlled phase of the study, 2 while receiving full dose Serostim during the extension phase, and 1 while receiving half-dose Serostim during the extension phase. Three other patients were previously known to be diabetic or hyperglycemic by history. ***A significant number of patients manifested gynecomastia during the study. A dose response effect was evident.*** rhGH-induced gynecomastia has previously been reported in adults and children, and the mechanism is not clear. ***Gynecomastia was reported in 14 male patients in the full dose group, 9 male patients in the half-dose group, and only 1 male patient in the placebo group during the placebo controlled portion of the study;*** during the extension phase, 37 male patients receiving full dose Serostim manifested gynecomastia compared with only 4 patients receiving half-dose Serostim. ***Additionally, there were 13 patients (13 events) in the full dose Serostim group and 5 patients (7 events) in the half-dose Serostim group with events coded as breast neoplasm, male.*** The absence of signs/symptoms of malignancy, the presence of a dose response relationship, the occurrence of 75% of these events within 3 months of therapy, and the fact that none of these events continued to worsen during the study (in fact, 100% of these events fully resolved during the study, usually within 4 months) ***suggest that these events most likely are a reflection of rhGH-induced gynecomastia, and not breast malignancy. ~40% of patients receiving full dose Serostim attained mean serum IGF-I SDS >+3 (in contrast to ~15% of patients receiving half-dose Serostim). It is clear that the IGF-I response is dose-dependent.*** If sustained, IGF-I SDS >+2 or, indeed, >+3, could be associated with clinical acromegaloid phenomena (which did not occur during this study) and, theoretically, oncogenic sequelae. [redacted] b(4)

[redacted] In the opinion of this Medical Officer, of the 5 malgnancies which occurred during the study, ***only the 2 cases of lymphoma*** (both patients were receiving full dose Serostim at the time of diagnosis) ***could possibly have been AIDS-related malignancies.*** The median differences in change from baseline for both viral load (HIV RNA) and CD4 T-cell counts were not significant for either of the Serostim groups compared to placebo. ***Nonetheless, as clearly stated in the existing Package Insert, practitioners prescribing Serostim for HIV-/AIDS-associated wasting always need to concurrently administer HAART or some other antiretroviral therapy because of the theoretical risk of rhGH-induced HIV propagation.*** Seven SAEs reported by 7 patients during the placebo controlled phase of the study possibly resulted from AIDS-defining/related opportunistic infections. ***These infections did not occur predominantly in the Serostim-treated groups.***

EFFICACY/SAFETY/DOSING RECOMMENDATIONS (including Labeling Recommendations, Risk/Management Actions, and Phase IV Commitments):

EFFICACY:

1) This Medical Officer strongly endorses the Sponsor's intention [redacted] patients with AIDS-associated wasting treated with Serostim. [redacted] b(4)

[redacted] / Recommendations. The CLINICAL STUDIES section of the most recently proposed Package Insert was modified by this Medical Officer to reflect that 12 weeks of treatment with half-dose Serostim results in an identical BWO result as full dose Serostim, and a significant LBM result (~half as much as full dose Serostim). 3) The CLINICAL STUDIES section of the most recently proposed Package Insert was severely edited by this Medical Officer (after consultation with the Agency's SEALD team) to more accurately and appropriately reflect the results of the QOL assessments performed by the Sponsor. b(4)

SAFETY:

1) This Medical Officer strongly endorses the Sponsor's intention [redacted] patients with AIDS-associated wasting treated with Serostim. Substantial instances of glucose intolerance reported during post-marketing surveillance since the 1996 launch of Serostim in patients with AIDS-associated wasting led to an important modification of the PRECAUTIONS section of the Serostim Package Insert in CY 2000. [redacted] b(4)

[redacted] 2) The Division strongly endorses the Sponsor's intention to [redacted] b(4)) In that 12 weeks of treatment with half-dose Serostim results in an identical BWO result as full dose Serostim, and a significant LBM result (~half as much as full dose Serostim), and substantially less adverse effects compared with full dose Serostim, half-dose Serostim should be used more as initial therapy, especially in patients already diagnosed with diabetes mellitus/impaired glucose intolerance, edema forming diseases such as congestive heart failure, cirrhosis and nephrosis, and musculoskeletal disease, or at significant risk for these diseases. In this regard, a) the ADVERSE REACTIONS section of the most recently proposed Package Insert was modified by this Medical Officer to more clearly reflect the substantially greater amount of rhGH-related adverse effects after treatment with full dose Serostim compared with half-dose Serostim, and b) the DOSAGE AND ADMINISTRATION section of the most recently proposed Package Insert was modified by this Medical Officer to make prescribing physicians more aware that half-dose Serostim may well be a reasonable alternative to full dose Serostim in certain patients.

OVERALL RISK/BENEFIT ASSESSMENT

Study GF-9037, peformed between 1997 and 2002 during the era of HAART therapy at the direction of the Agency to fulfill a Subpart H Phase IV commitment, has successfully confirmed the findings of the original, label-enabling, pivotal clinical trial (Study 5341), performed in 1992-1993 during the pre-HAART era. Treatment of patients with AIDS-associated wasting with 2 large doses of Serostim (0.1 mg/kg daily and 0.1 mg/kg every other day) for 12 weeks results in identical and statistically significant increases in functional exercise capacity (as assessed by BWO until exhaustion), in association with a clearcut dose-dependent increase in LBM (as well as body cell mass). The clinical significance of this change in exercise capacity, however, remains unclear. Therapy with Serostim does not appear to increase HIV replication, lower CD4 T-cell counts or lead to a disproportionate amount of AIDS-related serious opportunistic infections. In addition, most of the adverse effects associated with rhGH therapy are well known and tolerable. However, the administration of Serostim in these large amounts is associated with more consequential risks as well, most importantly significant glucose intolerance in a subset of patients. In addition, there is the unknown risk of whether relatively short-term administration of large amounts of Serostim will increase the likelihood of malignancy in the long-term in a population of patients already prone to oncogenesis (possibly related to IGF-I SDS >+3 in a substantial number of patients during Serostim therapy). In this regard, this Medical Officer strongly endorses the Sponsor's plan to [redacted] patients with AIDS-associated wasting [redacted] b(4)

APPROVABILITY FROM A CLINICAL PERSPECTIVE:

Given that 1) the Sponsor has confirmed the efficacy results of the original label-enabling study; 2) the current mutually agreed upon Package Insert accurately alerts prescribing physicians to the well established risks of high dose therapy with Serostim (in particular, glucose intolerance); 3) the Sponsor plans [redacted] and 4) the Sponsor plans [redacted] this Medical Officer recommends the b(4)

continued approval of Serostim for the treatment of patients with AIDS-associated wasting.

Recommended Regulatory Action: X Approvable _____ Not Approvable

Signed: Medical Reviewer: Robert Perlstein MD Date: 8/25/03
Medical Team Leader/Division Director: David Orloff MD Date: _____

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IV. Description of Clinical Data and Sources

IV.A Materials Reviewed

- All clinical data in the original submission received on 1Nov02.
- Email attachments sent by secure email in response to questions posed by this Medical Officer. See Section V.B.
- Reviews for related NDAs for other approved somatropin products.

IV.B Literature Search

Literature regarding HIV-/AIDS-associated wasting and its treatment with rhGH were reviewed for the last 10 years. Appropriate references are cited in the text of this review, and a list of these references appears at the end of this review in Section VI.

V. Miscellaneous

V.A Dates of Meetings and Agreements Between the Division and the Sponsor Pertaining to Study GF-9037

- 23Aug96: Serostim NDA approved with Subpart H/Phase IV confirmatory study requirement.
- 23Sept96: First draft of Study GF-9037 submitted to the Division.
- 20Nov96: Meeting between the Division and the Sponsor to discuss draft protocol.

- 8Apr97: Teleconference between the Division and the Sponsor during which it was agreed that the protocol could be initiated.
- 2June97: Final protocol submitted to the Division.
- 10Jun97: Teleconference between the Division and the Sponsor during which the Division requested changes to protocol.
- 16Dec99: Meeting between the Division and the Sponsor during which agreements were reached on broader inclusion criteria, and a shorter duration for the open label, extension phase (12 weeks instead of as long as 36 weeks).
- 16March00: Submission of revised protocol to the Division incorporating the changes discussed at 16Dec99 meeting.
- **17-19Apr02: Datalock for efficacy and safety results for Study GF-9037.**
- 12July02: PreNDA teleconference between the Division and the Sponsor during which agreement was reached on the content, format and analyses to be included in the GF-9037 study report.
- 1Nov02: Supplemental NDA submission received by the Division.

V.B Teleconferences and Emails During this Review Cycle

Dates of teleconferences with the Sponsor where requests for information were made by this Medical Officer and/or previously submitted responses by the Sponsor were discussed with this Medical Officer:

- 4/4/03, 5/9/03, 5/29/03, 6/2/03, 6/3/03, 6/12/03, 6/16/03, 6/17/03, 6/18/03, 7/2/03, 7/3/03, 7/9/03, 7/10/03, 7/11/03, 7/14/03, 7/18/03, 7/21/03, 7/22/03, 7/23/03, 7/24/03, 7/25/03, 7/28/03, 7/29/03, 7/30/03, 7/31/03, 8/1/03

Dates of additional submissions or emails from the Sponsor responding to requests for information:

- 6/13/03, 7/11/03, 7/14/03, 7/21/03, 7/29/03 - revised Package Inserts by email
- 6/13/03, 6/17/03, 6/20/03, 6/24/03, 6/26/03, 7/4/03, 7/9/03, 7/10/03, 7/11/03, 7/14/03, 7/15/03, 7/28/03, 7/29/03, 7/30/03, 8/4/03, 8/11/03 - responses to information requests by email

V.C Audits/Reports by the Agency's Division of Scientific Investigations (DSI)

On-site inspections were accomplished at 3 centers in the USA in the 5/03-6/03 timeframe (Dr. Anthony LaMarca in Fort Lauderdale, FL [redacted] patients enrolled]; Dr. Patrick Cadigan in Fort Lauderdale, FL [redacted] patients enrolled]; and Dr. W.C. Mathews in San Diego, CA [redacted] patients enrolled]). b(4)

The individual written reports by the Agency's DSI inspectors were carefully reviewed by this Medical Officer.

With regard to Dr. LaMarca: The inspection confirmed that all subjects signed and dated informed consent forms prior to enrolling in the study. The records of 17 subjects were audited for data integrity, with an emphasis on cycle ergometry measurements at baseline and Week 12. Data in source documents and case report forms (CRFs) were compared to data in Sponsor-provided data listings. No significant discrepancies were noted.

FDA Form 483 was not issued.

Data from this site were considered to be acceptable.

With regard to Dr. Cadigan: The inspection confirmed that all subjects signed and dated informed consent forms prior to enrolling in the study. The records of 17 subjects were reviewed in-depth for data integrity, with special emphasis on cycle ergometry measurements. The records were noted to be complete, well organized and legible. Endpoint efficacy data in source documents were compared to data in CRFs, and Sponsor-provided data listings. No major deviations were noted.

An 8 item FDA Form 483 was issued. Of note, 2 subjects did not have adverse events reported to the Sponsor.

Overall, data from this site were considered to be acceptable.

With regard to Dr. Mathews: The inspection confirmed that all subjects signed consent forms prior to enrollment in the study. The records of 15 subjects were reviewed for data integrity. Source documents were noted to be organized, complete and legible. Data in the source documents were concordant with information on the CRFs.

A 6 item FDA Form 483 was issued. Of note, the site did not have documentation indicating that subjects enrolled under Amendment 1A were to be contacted on an annual basis to determine survival status

Overall, data from this site were considered to be acceptable.

OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS by DSI:

- **Both Drs. Cadigan and Mathews submitted adequate responses addressing the deviations noted on FDA Form 483.**
- **The data from all 3 of these clinical sites can be used for the evaluation of Study GF-9037 by DMEDP.**

V.D Internal Consultations

This Medical Officer collaborated frequently with DMEDP's Statistical Reviewer, in particular with regard to the efficacy results observed during the 12 week, placebo controlled portion of the study. In addition, consultations were obtained from 1) the Division of Antiviral Drug Products/HFD-530 (Dr. T. Wu), in particular with regard to the effects of Serostim therapy on markers of disease activity in patients with AIDS, and from the Study Endpoints and Label Development (SEALD) team (L. Burke) with regard to the health outcomes instruments utilized by the Sponsor (see Section VI.A.5.5.6). The content of these consultations have been incorporated into this Medical Officer's review.

V.E Review of Financial Disclosure Information

Review of Form 3454, signed/submitted by the Sponsor's Vice President for Regulatory Affairs, and Section 19.1, indicates that **all primary investigators** and the vast majority of coinvestigators at sites (randomizing and treating patients) **submitted Forms 3455** to the Sponsor disavowing any special financial arrangement with the Sponsor, any significant payment of any kind from the Sponsor, any proprietary interest in the product tested, and any significant equity interest in the Sponsor. By completing Form 3454, the Sponsor certified 1) that "each listed clinical investigator required to disclose to the Sponsor whether the investigator had a proprietary interest in this product or a significant equity in the Sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests"; 2) that "no listed investigator was the recipient of significant payments (or any special financial arrangement) of any other sort as defined in 21 CFR 54.2(f)"; and 3) that the Sponsor has all invidividual investigator financial disclosure forms on file subject to audit. In addition, in Section 19.2, the Sponsor has adequately documented why **Forms 3455 could not be obtained from 1 principal investigator and 4 coinvestigators at site** and **several coinvestigators at 6 other sites where Forms 3455 were obtained from the primary investigator - despite due diligence** on the Sponsor's behalf to obtain such forms. Almost all of these individuals were no longer employed at their original locations and, in spite of multiple attempts by mail and phone, could not be located by the Sponsor.

b(4)

b(4)

Financial disclosure information is therefore is considered to be sufficient.

VI. Reviews of Efficacy and Safety for Clinical Studies

VI. A Review of Efficacy and Safety for the 12 Week, Placebo Controlled Portion and 12-36 Week Extension Phase of Study GF-9037

VI.A.1 Objectives

The primary objectives of the 12 week, prospective, randomized, parallel group, double blind, placebo controlled, dose ranging portion of Study GF-9037 conducted in patients with human immunodeficiency virus (HIV)-/acquired immunodeficiency syndrome (AIDS)-associated catabolism/wasting were:

- To evaluate the clinical efficacy of Serostim compared with placebo in stimulating an increase in the primary efficacy outcome parameter, bicycle ergometry work output (BWO; a measure of exercise function change) - as well as the clinical efficacy of Serostim compared with placebo in stimulating changes in multiple other secondary efficacy variables including, most importantly, an increase in lean body mass (LBM) and body weight (BW), and a decrease in total fat mass.
- To establish an optimal dose of Serostim.
- To assess the safety and tolerability of Serostim.
- ***To confirm the results of Study 5341 conducted by the Sponsor in 1992-1993 which resulted in the approval of Serostim for the treatment of AIDS-associated wasting in 1996. In this regard, Study GF-9037 was considered to be an obligatory Subpart H/Phase IV confirmatory study.***

The primary objectives of the 12-36 week extension phase of Study GF-9037 were to establish the durability of the clinical efficacy of Serostim, and to further assess the long-term safety and tolerability of Serostim. The treatment group of the patients remained blinded during the extension phase of the study.

VI.A.2 Background Information Regarding HIV-/AIDS-Associated Wasting and Brief Summary of Prior Clinical Trials Utilizing Recombinant Human Growth Hormone (rhGH) as a Treatment for HIV-/AIDS-Associated Wasting

Epidemiology: Involuntary weight loss, predominantly loss of LBM and its most critical component, body cell mass (BCM), is often termed "wasting". Wasting was originally designated as an AIDS-defining condition by the Centers for Disease Control (CDC) in 1987 (1), defined as "the involuntary loss of 10% or more of the premorbid BW with chronic fever, weakness, or diarrhea in the absence of other related illnesses contributing to the weight loss". Of the over 60,000 cases of AIDS reported to the CDC through 1990, wasting syndrome was reported in ~17% (2), and as many as 50% of people enrolled in AIDS studies in the late 1980s/early 1990s had involuntary weight loss in excess of 10% of premorbid BW (3). **The introduction of highly active antiretroviral therapy (HAART) in 1996 has diminished the prevalence of HIV-/AIDS-associated wasting, *but ~1/3 of patients receiving HAART who have viral load reductions still lose LBM/BCM* (4). In a prospective observational study of more than 7300 European patients between 1994 and 1998, 6% of the patients still had wasting as the AIDS-defining illness in 1998**

(5). Overall reviews of AIDS-associated wasting can be found in references 6-8.

Pathophysiology: The pathophysiology of AIDS-associated wasting has not been fully elucidated and is almost certainly multifactorial involving inadequate energy intake (anorexia/malabsorption), and altered metabolism (4, 9). The metabolic defects contributing to AIDS-associated wasting appear to represent a multifaceted failure of the adaptive mechanisms which normally occur in response to starvation - possibly related to the adverse effects of elevated levels of cytokines including tumor necrosis factor, and interleukins 1 and 6. In this regard, metabolic rate (resting energy expenditure) has been shown to be inappropriately increased in many HIV-infected individuals (10). AIDS-associated wasting is further characterized by a failure to effectively increase fatty acid oxidation and convert to a fat-based fuel economy to meet the body's energy needs (11). As a result, excessive gluconeogenesis requiring/consuming amino acids derived from excessive protein ***catabolism*** results in depletion of functional/structural protein stores and loss of LBM/BCM (11).

Clinical Significance: The clinical implications of AIDS-associated wasting are very significant. Loss of 10% (or even 5%) of body weight at the time of AIDS diagnosis (4; 12-13) is associated with decreased survival. Survival correlates even more closely with changes in LBM/BCM than with reduction of total BW (12). A loss in BCM to 54% of normal or of BW to 66% of ideal BW in patients with AIDS is incompatible with survival (12). Furthermore, a BCM of <30% of normal portends a survival rate of only 20% after ~15 months (14), compared with 70% survival at 2 years for AIDS patients who maintain their BCM (an effect which is independent of CD4 T-cell count) (15). Loss of LBM leads to weakness, organ failure, secondary immune dysfunction, general inanition and ultimately death.

Overview of treatment options for AIDS-associated wasting: Clearly then, the need to aggressively treat the loss of LBM/BCM and total BW in patients with AIDS-associated wasting is self evident. Available treatment options for HIV-associated wasting have recently been reviewed (4, 16). Nutritional counseling to ensure that the intake of protein, fat, and carbohydrates is adequate, and evaluation/treatment of underlying opportunistic infection(s), cancer and gastrointestinal disease should be accomplished. Unfortunately, nutritional interventions have proven to be singularly unsuccessful in replenishing LBM in patients with AIDS-associated wasting. Strategies/anabolic therapies are therefore needed to selectively increase LBM and muscle mass not only to decrease morbidity and mortality, but also to improve functional capacity. A recent study in men with AIDS-associated wasting demonstrated that cross-sectional muscle area is a significant predictor of regional muscle strength as well as overall functional status (9). With respect to anabolic therapies, testosterone should be provided to patients with documented hypogonadism. Oral anabolic steroids may also modestly improve muscle

strength and body composition (17); however, these steroids often cause significant liver dysfunction. Recombinant human growth hormone (rhGH) has been approved for use for patients with AIDS-associated wasting since 1996.

Previous use of rhGH in the treatment of AIDS-associated wasting: Several lines of evidence support a role for rhGH in the treatment of AIDS-associated wasting. First, the known actions of GH appear to be ideally suited to addressing the metabolic abnormalities known to occur in AIDS-associated wasting. rhGH promotes positive nitrogen balance and therefore increases LBM by increasing the cellular uptake of amino acids (most likely via insulin-like growth factor I [IGF-I]), and by increasing lipolysis (a direct effect of rhGH) and therefore the availability of fatty acids as a source of fuel in the malnourished AIDS patient (diminishing the need for protein catabolism) (18). Second, there is a body of evidence suggesting that AIDS-associated wasting may be characterized by a degree of functional GH deficiency (GHD) and relative GH resistance that results in low levels of IGF-I and insulin-like growth factor binding protein 3 (IGFBP-3) (hence, reduced ability to form the IGFBP-3 ternary complex [19-20]). Thirdly, rhGH has been shown to have potentially beneficial effects on the immune system and hematopoiesis (reviewed in reference 21). In this regard, a pilot study has suggested that rhGH might have immunostimulatory effects in HIV-infected patients (22).

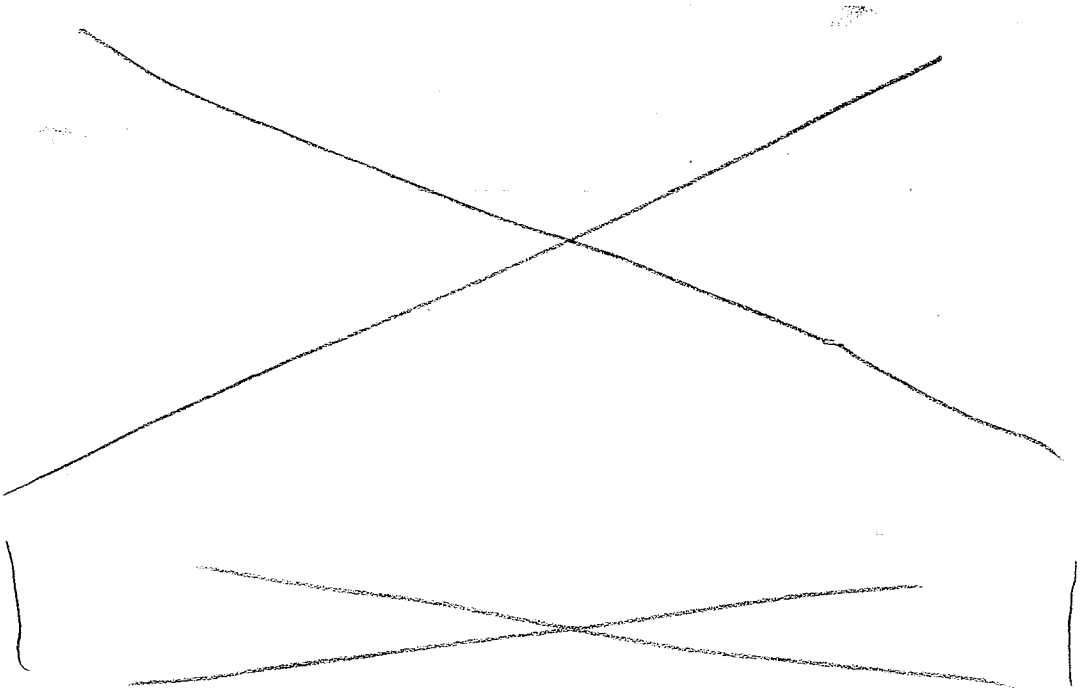
A number of reviews have been published discussing the anabolic effects of rhGH in patients with AIDS-associated wasting (4; 6-7; 16; 23-27), and recently an editorial was published discussing the rational use of rhGH in HIV-infected patients (28).

After the publication of a number of encouraging pilot studies in the early 1990s, the Sponsor conducted the first large scale, randomized, double blind, placebo controlled, international, multicenter trial utilizing rhGH as a therapy for patients with AIDS-associated wasting. This study formed the basis for Agency approval of Serostim (Serono's formulation of rhGH) for the treatment of AIDS-associated wasting (Serono Study Report 5341; 29). One hundred seventy eight patients *receiving nucleoside analogue therapy (pre-HAART era)* with a documented unintentional weight loss of at least 10% or weight less than 90% of ideal BW were randomized to either Serostim 6 mg/day or placebo for 12 weeks. Significant improvements in BW, LBM and treadmill work output were observed in Serostim-treated patients compared with placebo-treated patients. There were no significant changes with continued treatment beyond 12 weeks suggesting that the original gains of BW and LBM were maintained.

Treatment of patients with AIDS-associated wasting for 12 weeks appeared to be relatively safe during Study 5341 (29). A similar

number of patients withdrew from the Serostim and placebo groups (22% versus 19%). Adverse events reported more frequently in the rhGH group were those commonly associated with rhGH treatment, i.e. edema and arthralgia/myalgia; these events were usually mild or moderate, and often resolved with continued treatment or dose reduction. Fifteen Serostim-treated and 3 placebo-treated patients required a dose reduction. Small increases in mean fasting blood glucose and glycated hemoglobin were observed in rhGH-treated patients. Similar numbers of new HIV-associated events (i.e., AIDS-defining infections or neoplasms) were reported in the 2 treatment arms, and no significant changes in CD4 or CD8 lymphocyte counts or plasma HIV RNA level occurred in either treatment group during the study. ***Of note, both rhGH and rhIGF-I reportedly increase HIV replication in infected T lymphocytes, but not in the presence of azothiaprine (30). Therefore, the administration of rhGH to patients with AIDS-associated wasting should always be accompanied by treatment with inhibitors of HIV replication. This caveat is clearly stated in the existing Package Insert.***

Since the approval of Serostim in 1996 as a treatment for AIDS-associated wasting, glucose intolerance has been the most significant adverse event observed during post-marketing surveillance. A number of cases of new onset impaired glucose intolerance, new onset diabetes mellitus and exacerbation of preexisting diabetes mellitus have been reported (some patients requiring hospitalization for diabetic ketoacidosis and/or diabetic coma). In some patients, these conditions improved when Serostim was discontinued, while in others the glucose intolerance persisted. *These findings necessitated a post-approval labeling change in the PRECAUTIONS section of the Package Insert.*



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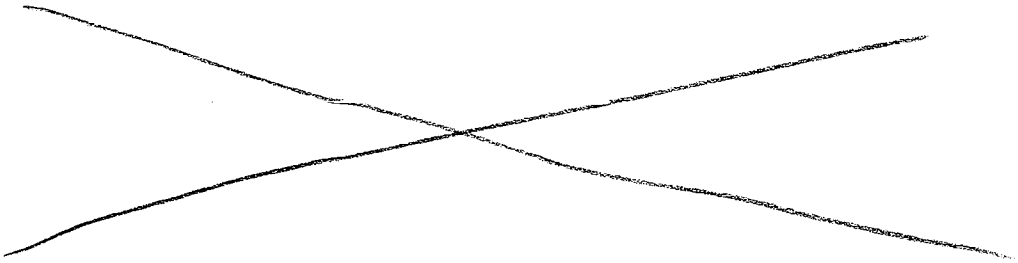

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The intent of the present study (Study GF-9037) was to ***confirm*** the efficacy and safety of Serostim in adult patients with AIDS-associated wasting in a 12 week, randomized, double blind, placebo controlled trial which was followed by an open label, extension phase for as long as 36 additional weeks.

VI.A.3 Study Design

VI.A.3.1 Description of Study GF-9037 - A Randomized, Parallel Group, Double Blind, Placebo Controlled, Dose Ranging, Multicenter Study of Recombinant Human Growth Hormone (Serostim) in the Treatment of HIV-Associated Catabolism/Wasting

Study GF-9037 was a 12 week, international, multicenter (n=57), prospective, randomized, parallel group, double blind, placebo controlled, dose ranging study (which was followed by a 12-36 week extension phase) designed to compare the efficacy and safety of Serostim versus placebo in the treatment of HIV-associated catabolism/wasting. ***Study GF-9037 was considered to be an obligatory Subpart H/Phase IV confirmatory study in the United States intended to confirm the results of the label enabling clinical trial (Study 5341) conducted by the Sponsor in 1992-1993 which resulted in the accelerated approval of Serostim for the treatment of AIDS-associated wasting in 1996,*** and a phase III study in the rest of the world. A total of 732 patients were planned for enrollment to ensure approximately 534 evaluable patients (178 in each of the 3 treatment groups). Patients meeting the eligibility criteria were initially randomly allocated in a 1:1:1 ratio to 1 of the following 3 treatment groups:

- Full Dose Treatment Arm: Serostim 0.1 mg/kg (up to a maximum of 6 mg) daily during the placebo controlled phase.
- Half-Dose Treatment Arm: Serostim 0.1 mg/kg (up to a maximum of 6 mg) alternating with placebo during the placebo controlled phase.
- Placebo Treatment Arm: Placebo only during the placebo controlled phase.

According to the original protocol design, immediately upon completion of the 12 week placebo controlled phase, placebo patients were to be re-randomized 1:1 to either full dose or half-dose Serostim for an additional 36 weeks, while patients receiving full dose or half-dose Serostim were to be continued on the same treatment regimen during the 36 week extension phase. The treatment group of the patients remained blinded during the extension phase of the study for patients enrolled under the auspices of the original protocol. Subsequent protocol amendments (Amendment 1 effective 10Feb99 for non-USA sites, and Amendment 1A effective 29Feb00 for sites in the USA) stated that immediately upon completion of the 12 week placebo controlled phase, all patients (full dose, half-dose, and placebo) were to be switched to open label, full dose daily Serostim for an additional 12 weeks.

Precise dose reduction parameters (see Section VI.A.4.2.5 ahead) were incorporated into the protocol in the event moderate or severe Serostim-related toxicity became apparent.

The study design schematics (before and after Amendment 1) are presented in Figure 1.

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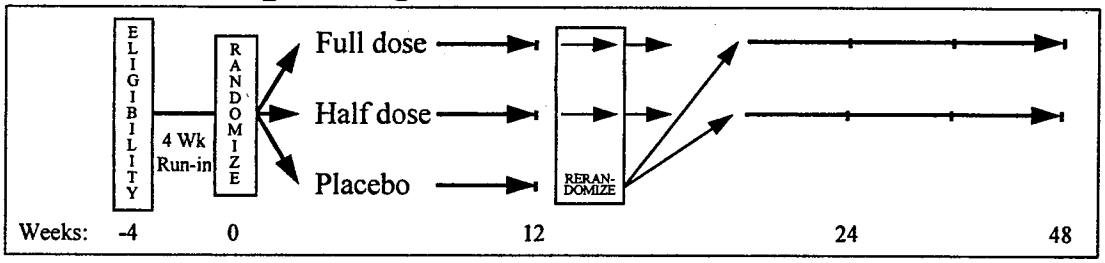
Figure 1 - Study Schematic

Initial Study Design



Amended Study Design (Amendments 1 and 1A)

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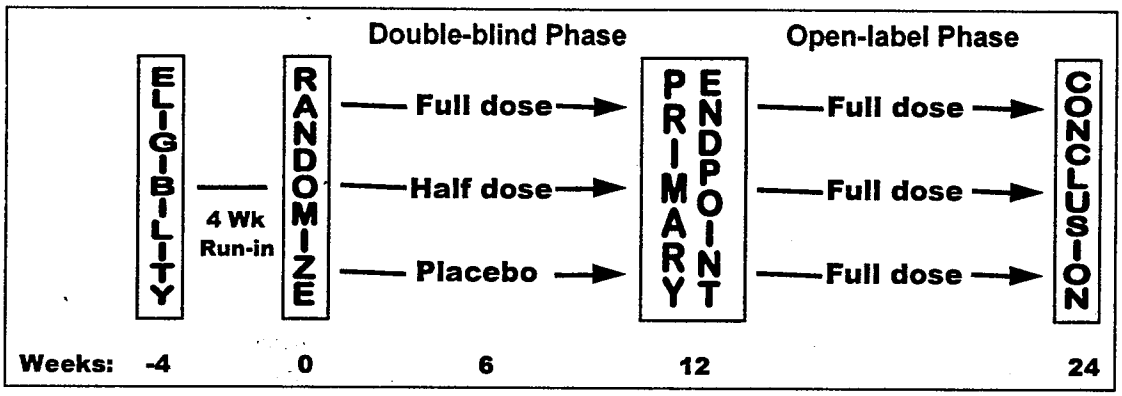


The primary efficacy endpoint was the difference in the change from baseline to Week 12 in BWO between the Serostim full dose group (***and the Serostim half-dose group***) and the placebo group. Secondary comparisons included the difference in the change from baseline to Week 12 in LBM as measured by bioelectrical impedance spectroscopy (BIS) between the 2 Serostim treatment groups and the placebo group. Safety was assessed by monitoring for the well known adverse sequelae associated with the use of rhGH products, i.e. glucose intolerance, edema, arthralgia, myalgia, and carpal tunnel syndrome. In addition, HIV viral load and serum levels of IGF-I were monitored, and oncogenic events were ascertained.

Study visits for efficacy and safety assessments were scheduled at baseline, and then after 2, 4, 8, and 12 weeks of treatment with regard to the placebo controlled portion of the study. Additional study assessments were scheduled after 16, 24 and 48 weeks of treatment with regard to the open label extension phase. BWO, the primary efficacy variable, and LBM, the most important secondary efficacy parameter, were determined at baseline and after 12, 24 and 48 weeks of treatment. Other efficacy and safety variables were measured more frequently. See Table 1 ahead for a tabular depiction of efficacy and safety study assessments.

VI.A.3.2 Protocol Amendments (overview)

The original protocol, dated 21May97 was amended 6 times. Amendments 1 (10Feb99) and 1A (29Feb00) shortened the study to 24 weeks overall (as noted above in Section VI.A.3.1), and provided for the [redacted] Amendment 1A also deleted the exclusion of patients receiving secondary prophylaxis for AIDS-related opportunistic infections. Amendment 3 (8May01) decreased the level of fasting blood glucose required for inclusion and toxicity adjustment (i.e., dose reduction/interruption/discontinuation)(see Section VI.A.4.2.5 ahead). b(4)

VI.A.4 Materials and Methods

VI.A.4.1 Subjects

VI.A.4.1.1 Subject Selection

The protocol called for the enrollment of at least 732 adult patients with AIDS-associated wasting.

VI.A.4.1.2 Inclusion Criteria

- Clearly documented HIV infection, confirmed by one of the following: Western blot, immunofluorescence assay, HIV culture, polymerase chain reaction (PCR) amplification, branched DNA (bDNA) signal amplification or the presence of p24 antigen. These tests may have been performed at any time in the past, but the results must be available for review by the Sponsor prior to entry into the study.
- Evidence of AIDS-associated wasting, with at least 1 of the following:
  - Documented unintentional weight loss of at least 10%, or
  - In the absence of unintentional weight loss of 10%, weight less than 90% of ideal BW, or
  - In the absence of unintentional weight loss of 10%, body mass index <20 kg/m^2
- At least 18 years of age
- Receiving at least 100% of estimated caloric requirement as per current nutritional regimen, according to a formal nutritional analysis (changed in Amendment 1 to 90%)
- Met the following laboratory testing criteria at the Week -4 pre-study screening visit:
  - **Fasting blood glucose <120 mg/dL (Changed in Amendment 3 to <110 mg/dl)**
  - AST, ALT, and amylase <3 times the upper limit of normal
  - Fasting serum triglyceride level <500 mg/dL (or <5.64 mmol/L)
- Taking an antiretroviral medication that is approved or available under a treatment IND
  - The patient must have been receiving antiretroviral therapy for at least 8 weeks prior to study Day 1
  - The patient must agree not to change the antiretroviral regimen during the 12 weeks of study drug administration (unless medically mandated)

VI.A.4.1.3 Exclusion Criteria

- Medical history of any of the following:
  - **Fasting blood glucose >120 mg/dL, or 2 hour postprandial serum glucose >140 mg/dL (changed in Amendment 3 to fasting blood glucose >110 mg/dL) and/or history of diabetes mellitus/hyperglycemia**

- Any disorder associated with moderate to severe edema (e.g., cirrhosis, nephrosis, congestive heart failure, lymphedema)
- Carpal tunnel syndrome (unless resolved by surgical release)
- Unstable or untreated hypertension; angina pectoris/coronary artery disease
- Any active malignancy, except for localized cutaneous Kaposi's sarcoma
  - Prior radiation therapy or systemic chemotherapy
- A CNS mass, or CNS process associated with active neurological findings
- Pancreatitis
- Recent acute critical illness requiring an intensive care unit due to 1) complications following open heart or abdominal surgery, 2) multiple accidental trauma, or 3) acute respiratory failure
- Allergy or hypersensitivity to rhGH

- Chronic diarrhea (defined as 6 or more liquid stools per day)
- Evidence of malabsorption, gastrointestinal bleeding, or obstruction
- Active AIDS-defining opportunistic infection or new systemic therapy for an opportunistic infection within 60 days prior to receiving study drug
- Untreated or suspected serious systemic infection, or persistent fever >101°F during the 30 days prior to study entry
- Used glucocorticoids within the past six months
- New therapy for wasting, including parenteral or oral hyperalimentation, tube feeding, anabolic or progestational agents, and appetite stimulants
- rhGH therapy within the last year
- Active substance abuse or dementia which would prevent informed consent or compliance with study activities
- If female, pregnant or breast feeding

VI.A.4.1.5 Subject Discontinuation

- Missed more than 10 total doses of study drug during the study
- Missed more than 7 doses in a row of study drug administration at any time
- Missed the Week 12 major assessment by more than 7 days
- **Persistent toxicity according to the dose adjustment algorithms in Section VI.A.4.2.5**
- Onset of acute critical illness requiring intensive care unit due to 1) complications following open heart or abdominal surgery, 2) multiple accidental trauma, 3) acute respiratory failure, or 4) unrelated serious intercurrent illness

- Development of any active malignancy, including progression of existing Kaposi's sarcoma lesions (>50% lesion growth) or any new Kaposi's sarcoma lesions
  - Used systemic chemotherapy or radiation therapy (except minimal radiation of an extremity for Kaposi's sarcoma)
- Initiated a new AIDS-associated wasting intervention during the study.
- Changed the antiretroviral regimen during the 12 weeks of study drug administration (unless medically mandated)
- Discontinued antiretroviral therapy (***all patients must remain on an approved antiretroviral therapy for the duration of the study***)
- Pregnancy

VI.A.4.2 Study Treatment

VI.A.4.2.1 Formulation/Drug Delivery

Serostim was provided by Serono as described in the Package Insert as 6 mg single dose vials. Placebo was supplied in matching glass vials containing excipients only.

VI.A.4.2.2 Treatments Administered - Dosage and Administration

Dosing was by daily injections in the evening (preferably at bedtime) to approximate the natural secretory pattern of pituitary GH. The 3 treatment arms during the placebo controlled phase of the study, and dosing during the extension phase of the study (before and after Amendments 1 and 1A) are described in Section VI.A.3.1.

VI.A.4.2.3 Method of Treatment Assignment - Randomization

The treatment assigned to each patient was determined according to a computer-generated randomization list produced by the Serono Corporate Biometrics Department during both phases of Study GF-9037. The treatment group of the patients remained blinded during the extension phase of the study.

VI.A.4.2.4 Selection of Doses

In the present study, the Serostim dosage selected for the full dose treatment arm, 0.1 mg/kg (up to 6 mg) daily was identical to the efficacious dose administered in the previous label-enabling Phase III study (Study 5341). In addition to confirming the treatment effects previously observed with this dose, a second objective of the present study was to assess the effects of a lower dose. The dose chosen for

the half-dose treatment arm was 0.1 mg/kg (up to 6 mg) every other day.

VI.A.4.2.5 Dosage Intervention (Reduction/Interruption/Discontinuation)

Severe toxicity:

Treatment with study drug was to be suspended/interrupted for the following severe toxicities:

- **Severe hyperglycemia (symptomatic, or fasting blood glucose ≥140 mg/dL or 2 hour postprandial blood glucose ≥240 mg/dL). The toxicity grading for severe hyperglycemia was modified in Amendment 3 effective 8May01. The original criteria for severe hyperglycemia was any blood sugar >400mg/dL.**
- Marked hypertension (symptomatic, or >200/110 mm Hg)
- Congestive heart failure
- Severe paraesthesias
- Acute pancreatitis
- Serum triglycerides >1500 mg/dl (or >16.9 mmol/L)

If the toxicity resolved within 7 days or less, daily dosing may have been resumed at 50% of the pre-toxicity dose. If the toxicity did not resolve within 7 days of dose interruption, the individual should have been discontinued from the study.

Study participants experiencing any of the following were to be discontinued immediately and were not to be allowed to resume treatment:

- Pseudotumor cerebri/benign intracranial hypertension
- A new diagnosis of cancer
- Progression of an existing neoplasm, including progression of existing Kaposi's sarcoma lesions (>50% lesion growth) or any new Kaposi's sarcoma lesions
- Severe systemic allergic manifestations (e.g., bronchospasm, laryngospasm, desquamation) thought to be related to Serostim administration

Moderate toxicity:

The daily dose of study drug was to be reduced by 50% for the following moderate toxicities:

- **Fasting blood glucose >126 mg/dL or 2 hour postprandial blood glucose >200 mg/dL. The toxicity grading for severe hyperglycemia was modified in Amendment 3 effective 8May01. The original criteria for moderate hyperglycemia was fasting blood sugar >160 mg/dL.**
- Asymptomatic hypertension (<200/110 mm Hg)

- Intolerable tissue turgor
- Intolerable arthralgias not responsive to anti-inflammatory therapy
- Carpal tunnel syndrome
- Serum triglycerides >700 mg/dL but <1500 mg/dL (>7.90 mmol/L, <16.94 mmol/L)
- Moderate systemic allergic reaction (e.g., pruritus, erythema)

If the toxicity did not resolve within 14 days of dose reduction, treatment was to be withheld/interrupted until the problem improved. If the toxicity was still unresolved within 7 days of dose interruption, the patient should have been discontinued from the study.

VI.A.4.2.6 Concomitant Therapy

Optimal antiretroviral treatment was to be maintained throughout the entire 12 week double blind period. Only medically mandated changes were permitted. Medications which were considered necessary for treatment of an intercurrent disease were given at the discretion of the investigator.

VI.A.4.2.7 Treatment Compliance

Patients were requested to record the time and day of all injections, and to return all used vials of study drug as well as all unused study drug to the study site.

VI.A.4.2.8 Product Accountability

When the investigator or pharmacist received the study drug, he/she checked for accurate delivery, signed and returned the enclosed documentation to the Sponsor to acknowledge receipt. The amount of drug delivered was entered on the drug accountability form, which was used as a drug balance sheet. The dispensing of study drug was carefully recorded on the drug accountability form and information was provided to the Sponsor's monitor at each monitoring visit.

VI.A.4.3 Study Assessments

VI.A.4.3.1 Screening Assessments at Week -4 and the 4 Week Run-In Period

As can be seen in Table 1 ahead, in order to determine if eligibility criteria had been met and to obtain baseline parameters for on-study

efficacy and safety assessments, each potential enrollee had the following performed at Week -4:

- Complete AIDS-/HIV-oriented medical history and physical examination including body weight (BW), screening for carpal tunnel syndrome and funduscopy
- Hematology and chemistry profile including fasting blood glucose, lipid profile, and thyroid function tests
- HIV-related parameters including quantitation of HIV RNA copies and CD4 T-cell counts
- Anti-rhGH antibodies
- Serum IGF-I levels
- Baseline measurements of primary and secondary efficacy parameters, i.e. BWO, LBM (by BIS as well as dual energy X-ray absorptiomety [DEXA] at selected sites), total fat mass by DEXA, 6 minute walk test, and quality of life (QOL) scores using 2 different instruments

In addition, nutritional status was carefully assessed, and all patients were encouraged to maintain ≥100% of eucaloric requirements.

A run-in period was conducted between Week -4 and Week 0/Day 1 to allow equilibration of any changes in weight or body composition associated with study entry. Most of the evaluations performed at Week -4 were repeated at Week 0/Day 1 in order to establish baseline trends in efficacy/safety assessments. During this run-in period, study drug was not administered, and no new medical interventions for AIDS-associated wasting or new antiretroviral regimens were allowed.

VI.A.4.3.2 Assessments During Treatment

VI.A.4.3.2.1 Efficacy Parameters for Study GF-9037 (In Particular the 12-Week, Randomized, Placebo Controlled Portion)

VI.A.4.3.2.1.1 Primary Efficacy Parameter (see Table 1 ahead)

The primary efficacy endpoint for this study was the difference in the change in BWO from baseline to Week 12 between the Serostim full dose group and the placebo group. ***Although not designated by the Sponsor in the original protocol as part of the primary efficacy objective, the difference in the change in BWO from baseline to Week 12 between the Serostim half-dose group and the placebo group was also considered to be of significant importance by the Division. If possible, BWO determinations were to be performed if patients prematurely discontinued from the study.*** BWO was also measured at Weeks 24 and 48 during the extension phase of the study.

BWO measurements (expressed in kilojoules [kJ]) were to be ascertained *after maximal effort.* The initial workload was set at 50 W, and then increased by 25 W every minute of the test until the patient experienced exhaustion or inability to exercise further. In an attempt to better assess the extent of physical exhaustion achieved, patients were to be questioned in accordance with the Borg Perceived Exertion and Pain Scale (Borg RPE) (36). In addition, the total duration of the BWO test was to be recorded.

Note: A standardized 6 minute walk test was to be conducted at selected sites as an alternative measure of physical functional capacity. During this test, the distance patients were able to ambulate (at a normal walking pace) in 6 minutes was determined.

VI.A.4.3.2.1.2 Secondary Efficacy Parameters (see Table 1 ahead)

Between-group (full dose Serostim vs. placebo, *and half-dose Serostim vs. placebo*) treatment differences on the change from baseline in:

- LBM: LBM was to be measured by BIS (using [redacted] equipment). In addition, LBM by DEXA was to be determined at select sites, and BCM was to be measured by BIS as backup maneuvers. Although BCM, the most critical component of LBM reflecting intracellular fat-free solid/muscle + intracellular water), is considered the marker which best characterizes the degree of wasting in patients with HIV infection, the predictive equations for the use of BIS to measure BCM are not standardized, leading to variable results. Therefore, although decreases in LBM in patients with AIDS-associated wasting may be blunted by the relative increase in extracellular water which often accompanies loss of BCM in these patients, the fact that LBM can be measured by validated techniques (including BIS) *has led to the general consensus that LBM is the best marker available today to evaluate changes in body composition in response to rhGH treatment in patients with the AIDS-associated wasting syndrome.* LBM measurements were scheduled at baseline and Week 12, as well as at Weeks 24 and 48 during the extension phase. *Once again, if possible, LBM determinations were to be performed if patients prematurely discontinued from the study.* b(4)
- Total fat mass measurements by DEXA were scheduled at baseline and Week 12, as well as at Weeks 24 and 48 during the extension phase.
- BW: The definition of HIV-/AIDS-associated wasting (involuntary loss of at least 10% of BW with chronic fever, weakness or diarrhea in the absence of other related illnesses) is useful for epidemiological purposes, but BW measurements have limited use in practice because they do not address malnutrition, specifically the loss of BCM/LBM that occurs in most HIV-infected patients with wasting. Patients were to be weighed unclothed, after voiding, in the fasting state, ideally in the morning, on each occasion. BW was to be measured on a certified and calibrated hospital scale with an

accuracy of ±0.2 kg. Three successive weight determinations were to be recorded. BW measurements were scheduled at baseline and Weeks 2, 4, 8 and 12, as well as at Weeks 16, 24 and 48 during the extension phase.

- QOL measurements: QOL was to be assessed using the Bristol-Meyers anorexia/cachexia recovery instrument (BACRI) and the Multidimensional Health Status Assessment (MHSA) at baseline and Weeks 4, 8 and 12, as well as at Weeks 24 and 48 during the extension phase. Subsequent to Amendments 1/1A, QOL assessments were not performed after Week 12.

VI.A.4.3.2.2 Safety Parameters (See Table 1)

- Adverse events (every study visit)
- Medical history/physical examination (baseline and Weeks 4, 8, 12, 16, 24 and 48)
- Standard safety laboratory tests including fasting blood glucose (but not glycated hemoglobin or insulin levels), lipids and thyroid function tests (baseline and Weeks 12, 24 and 48 for all laboratory tests; baseline and Weeks 4, 8, 12, 16, 24 and 48 for fasting blood glucose and lipids)
- HIV-related parameters (HIV RNA copies at baseline and Week 12; CD4 T-cell counts, lymphocyte subset analysis and TRECs at baseline and Weeks 12, 24 and 48)
- Anti-rhGH antibodies (baseline and Week 12)
- Serum IGF-I levels (first introduced in 5/01 [Amendment 3]; baseline and Week 12)

Table 1

Flow Chart of Efficacy and Safety Assessments for the 12 Week Double Blind, Placebo Controlled Portion of the Study as Well as the 12-36 Week Extension Phase of the Study

	STUDY WEEK								
Week	-4[1]	0	2	4	8	12	16	24	48[0]
Type of Visit	Major	Major	Weight	Minor	Minor	Major	Extension Phase		
Eligibility/Exclusion	X								

Adverse events	X	X	X	X	X	X	X	X	X
History/Physical examination	X	X		X	X	X	X	X	X
Major blood tests[3]	X	X				X		X	X
Minor Blood Tests[4]				X	X		X		
HIV RNA	X	X				X			
CD4+	X	X				X		X	X
Lymphocyte subsets including CD4/CD8[6]	X	X				X		X	X
T cell receptor excision circles (TRECs)[6]	X	X				X		X	X
Serum anti-rhGH antibodies		X				X			
IGF-I and IGFBP-3[6]		X				X			
Bicycle ergometry work output (BWO)	X	X				X		X	X
Lean body mass (LBM) by BIS	X	X				X		X	X
LBM/total fat mass by DEXA[2]	X	X				X		X	X
Body weight (BW)	X	X	X	X	X	X	X	X	X
6 minute walk test[2]	X	X				X		X	X
QOL - MHSA[5]	X			X	X	X		X	X
QOL - BACRI[5]				X	X	X		X	X

[0]Amendment 1 in 2/99 shortened the study to 24 weeks for all non-USA sites; Amendment 1A in 2/00 shortened the study to 24 weeks for all USA sites.
[1]Following visit at -4 weeks, patients were observed during a 4 week run-in period
[2]Tested at selected study sites only.
[3]Major blood tests: CBC/diff/platelets; fasting blood glucose, Na+/K+/Ca++, BUN/creatinine; liver tests, amylase; cholesterol/triglycerides.
[4]Minor blood tests: Fasting blood glucose; cholesterol/triglycerides.
[5]QOL instruments were available in English, French, German and Spanish only. QOL was only performed at Weeks 4, 8, 12, 24 and 48 for patients on the original protocol. After Amendment 1 was effected, QOL was only performed at Weeks 4, 8 and 12.
[6]Introduced in Amendment 3 in 5/01.

VI.A.4.4 Statistical Analysis

VI.A.4.4.1 Sample Size Calculation

Using a 2-sided, 2-sample t-test, a sample size of 178 evaluable patients per treatment group was determined to provide 80% power for detecting a 12.9 kJ treatment difference in the change from baseline to the end of the 12 week placebo controlled treatment period in BWO between the full dose Serostim group and the placebo group (assuming a type 1 error rate of 5% and standard deviation of 43.23 kJ). These estimates of treatment effect and variance were based on the observed difference in the change in treadmill work output between the same 2 treatment groups in Serono Study 5341. In addition, with respect to LBM (the most important secondary efficacy parameter), it was calculated that a sample size of 178 evaluable patients would provide ~100% power for detecting a 1.53 kg (standard deviation of 2.49 kg) difference in the change from baseline to Week 12 in LBM between the full dose Serostim group and the placebo group (once again assuming a 5% type 1 error rate). Assuming a 27% withdrawal or unevaluable rate, the number of patients randomized needed to be 732 (244 per treatment group) in order to achieve 534 evaluable patients (178 per treatment group).

VI.A.4.4.2 Baseline Comparisons

The Sponsor planned to employ descriptive statistics to present baseline demographic data (e.g., age, race, sex, BW, HIV RNA level, etc). Comparative analyses of continuous baseline demographic parameters across treatment groups were to be performed using a 2-way main effects analysis of variance (ANOVA) model with effects for treatment and center. The Cochran-Mantel-Haenszel (CMH) general association test was to be utilized to compare categorical baseline demographic parameters across treatment groups.

VI.A.4.4.3 Efficacy Analysis

VI.A.4.4.3.1 Primary Efficacy Variable (as well as Secondary Efficacy Variables)

VI.A.4.4.3.1.1 Statistical Model

The primary efficacy comparison was the change in BWO from baseline to Week 12 between the full dose Serostim group and the placebo group. ***Although not designated by the Sponsor in the original protocol as part of the primary efficacy objective, the difference in the change in BWO from baseline to Week 12 between the Serostim half-dose group and the placebo group was also considered to be of significant importance by the Division. If possible, BWO determinations were to be performed if patients prematurely discontinued from the study.*** The most important secondary efficacy comparison was the change in LBM (by BIS) from baseline to Week 12 between the full dose Serostim group and the placebo group, as well as between the half-dose Serostim group and the placebo group.

The continuous parameters (change from baseline in BWO, LBM, total fat mass, BW, and HIV RNA level) were to be analyzed using a 2-way main effects ANOVA model with effects for treatment and center. The point estimates for the pairwise treatment differences were to be calculated using the Hodges-Lehmann method, and the confidence intervals were to be calculated using the method devised by Moses for distribution-free confidence intervals. For all efficacy parameters (excepting BWO)*, if the ANOVA revealed a significant treatment effect, Hochberg's multiple comparison procedure was to be used to compare each of the 2 Serostim-treated groups (sequentially) to the placebo group with respect to the changes from baseline for BWO, LBM, total fat mass, BW, HIV RNA level etc. The Sponsor did not plan to directly compare the treatment effects (compared to placebo) of the 2 doses of Serostim.

***Although not projected in the Sponsor's protocol and therefore not included in the Sponsor's original submission for Study GF-9037, at the request of this Medical Officer, both the Sponsor and the Division's Statistical Reviewer subsequently performed (an unranked) ANOVA followed by the Hochberg test to**

compare each of the 2 Serostim-treated groups (sequentially) to the placebo group with respect to the change from baseline for BWO.

In addition, the Sponsor planned to perform [redacted] b(4)

VI.A.4.4.3.1.2 Populations/Datasets to be Analyzed

The protocol called for the analysis of both the intent-to-treat (ITT) and Evaluable Populations. All patients who received at least 1 injection of double blind treatment who had an assessment at baseline and at least 1 post-baseline assessment were to be included in the ITT Population. The Evaluable Population [redacted] b(4) was defined as all patients included in the ITT Population who completed the initial, 12 week, placebo controlled period of the study, and were at least 80% compliant with their dose regimen.

[redacted] b(4) **; ITT Population should be the primary analysis population. The vast majority of the efficacy analyses contained in this Medical Officer's review were performed on datasets from the ITT Population (by the Division's Statistical Reviewer, and also in some instances by the Sponsor).**

Another important issue with regard to the ITT Population analyses requires comment/clarification. [redacted] b(4) Sponsor did perform sensitivity analyses utilizing 2 different ITT Populations with respect to both BWO and LBM (by BIS). With regard to BWO, the Sponsor either excluded 77 patients with "inconsistent"* BWO measurements from their ITT Population (n=570) or included these patients (n=647). **For the record, the BWO analyses presented in this Medical Officer's review were performed by the Division's Statistical Reviewer (and belatedly by the Sponsor) in the "maximized", preferred ITT population containing 670 patients** [redacted] b(4) Similarly, with regard to LBM (by BIS), the Sponsor either excluded 44 patients with "inconsistent"** LBM (by BIS) measurements from their ITT population (n=606) or **included these patients (n=650). The LBM (by BIS) analyses presented in this Medical Officer's review were performed by the Division's Statistical Reviewer in the "maximized", preferred ITT population also containing 650 patients.**

*"Inconsistent" BWO measurement as defined by the Sponsor = A BWO value reported on the CRF which differs by ≥1 kJ from the calculated BWO based on the duration of the ergometer test and the bicycle protocol.

**"Inconsistent" LBM (by BIS) measurement as defined by the Sponsor = A LBM (by BIS) value which is greater than the patient's BW, i.e. LBM = BCM + extracellular matrix, and does NOT include body fat.

VI.A.4.4.3.2 Extension Phase Descriptive Statistics

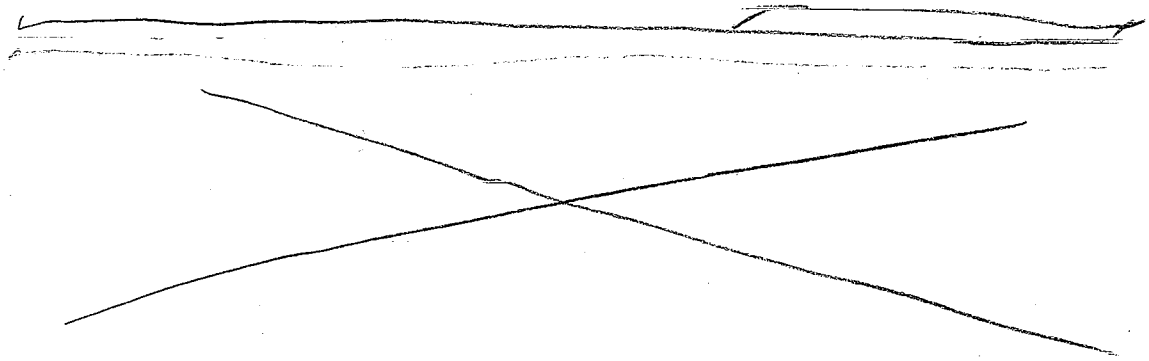
All patients who received at least 1 injection of double blind treatment with an assessment at Week 12, and at least 1 post-Week 12 assessment were to be tabulated via descriptive statistics. Change in BWO, LBM (by BIS), and BW from baseline to Week 24 (patients on both the original and amended protocols), and baseline to Week 48 (patients on the original protocol only) were to be summarized. For purposes of definition, "baseline" for the patients treated with placebo during the double blind phase of the study was the measurement obtained at the Week 12 visit (the last visit during placebo treatment prior to first treatment with Serostim). "Baseline" for the patients treated with Serostim during the placebo controlled portion of the study was the measurement obtained just prior to the initiation of double blind treatment.

VI.A.4.4.4 Safety Analysis

The Safety Population was defined as all patients treated with at least 1 injection of study drug. Laboratory and other safety values (including vital signs) were to be summarized with simple descriptive statistics, frequency tables, shift tables or patient data listings for the Safety Population by dose group.

VI.A.4.4.5

b(4)



b(4)

VI.A.4.5 Data Quality Assurance

Monitoring visits by the Sponsor's Clinical Research Associates (CRAs) took place approximately every 4 to 10 weeks, or as needed. As part of monitoring visits, CRAs were required to compare CRFs with source documents, in addition to checking them for completeness and accuracy. Completed CRF sections were checked for missing pages and screened for data entry. Data were double entered, compared, and checked using computer programs. Ongoing audits of the database were conducted to ensure that the data entered were a true representation of the original CRF entries. In addition, the Sponsor conducted 12 internal audits at various study sites and 3 "investigator meetings" in 1997, 1999 and 2000.

VI.A.5 Results

VI.A.5.1 Patient Disposition and Protocol Violations

VI.A.5.1.1 Patient Disposition

A total of 770 patients were randomized, and 757 patients were subsequently treated. Patient randomization by geographic region is shown in Table 2. The vast majority of the randomized patients were from the USA (~57% of the total number of patients randomized) and Europe ~32%). A total of 61 sites on 4 continents in 10 countries randomized study patients (5 of these sites randomized patients but did not initiate treatment). Ten sites (7 in the USA and 3 in Europe) randomized >20 patients, and 10 sites randomized 10-20 patients (7 in the USA and 3 in Europe) = >50% of the randomized patients. Some sites only randomized a very small number of patients.

Table 2
Patient Randomization by Geographic Region, Treatment Group and Overall

	Placebo n=255	Half-Dose Serostim n=259	Full Dose Serostim n=256	All Patients n=770
Region	n (%)	n (%)	n (%)	n (%)
USA	144 (56.5)	147 (56.8)	146 (57.0)	437 (56.8)
Europe	82 (32.2)	82 (31.7)	82 (32.0)	246 (31.9)
Australia	26 (10.2)	27 (10.4)	26 (10.2)	79 (10.3)
Asia	3 (1.2)	3 (1.2)	2 (0.8)	8 (1.0)

Table 3 depicts patient disposition by treatment group and overall during the entire study - the 12 week, placebo controlled, double blind phase, and also the 12-36 week, extension phase. A total of 757 patients (stratified by center) were randomized and treated (full dose Serostim [n=253], half-dose Serostim [n=257] and placebo [n=247]). **~85% of treated patients completed the 12 week, placebo controlled portion of the study.** Five hundred and forty eight patients (~72% of the cohort originally randomized and treated) completed a total of 24 weeks on-study, including ~69% of the patients receiving full dose Serostim for all 24 weeks. Only ~23% of patients completed 48 weeks on-study.

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On Original

Table 3
Patient Disposition by Treatment Group and Overall

Disposition During First 12 Weeks	Placebo	Half-Dose Serostim	Full Dose Serostim	All Patients

Number of Randomized Patients	255	259	256	770
Number of Treated Patients	247	257	253	757
Number of Treated Patients Who Discontinued Prior to Week 12	21	38	52	111
Number of Treated Patients Who Completed Week 12	226	219	201	646

Disposition During the Extension Phase	Placebo to Half-Dose Serostim	Placebo to Full Dose Serostim	Half-Dose to Half-Dose Serostim	Half-Dose to Full Dose Serostim	Full Dose to Full Dose Serostim	All Patients
Number of Treated Patients Entering Extension Period	44	182	81	138	201	646
Number of Treated Patients Who Discontinued Prior to Week 24						98*
Number of Treated Patients Completing 24 Weeks of Treatment	34	145	73	122	174	548
Number of Treated Patients Who Discontinued After Completing 24 Weeks of Treatment as per Amendments 1/1A Which Shortened the Extension Phase to 12 Weeks						303
Number of Treated Patients Who Discontinued Prior to Week 48						68*
Number of Treated Patients Completing 48 Weeks of Treatment	30	29	62	0	56	177

*166 patients were discontinued from the study after Week 12 (see Table 5 ahead).

As shown above in Table 3, ~15% of treated patients (111/757) were discontinued during the 12 week, placebo controlled portion of the study. The reasons for patient discontinuation are listed in Table 4. Not surprisingly, **patients were discontinued from the study in a dose-related fashion** (~21% from the full dose Serostim group, ~15% from the half-dose Serostim group, and ~9% from the placebo group). With regard to the **111 patients who were discontinued, 46 (41.4%) were terminated because of adverse events (26 [23.4%] in the full dose Serostim group, 17 [15.3%] in the half-dose Serostim group, and 3 [2.7%] in the placebo group.** See Tables 29 and 30 in Section VI.A.5.6.6.2.1 in Safety Results for details and comment (as well as Section VI.A.5.6.5 for comment regarding 2 deaths unrelated to Serostim treatment listed in Table 4). The other most common reasons for discontinuation were "patient decision unrelated to an adverse event" (21/111 [18.9%]), "non-compliance with study drug" (16/111 [14.4%]), and "lost to followup" (12/111 [10.8%]).

Table 4

Reason for Patient Discontinuations by Treatment Group, and Overall, Up to 12 weeks*

	Half-Dose	Full Dose	All

Discontinuation Reason	Placebo n=247 n (%)	Serostim n=257 n (%)	Serostim n=253 n (%)	Patients n=757 n (%)
Patient decision	6 (2.4)	16 (6.2)	19 (7.5)	41 (5.4)*
Persistent toxicity according to the dose adjustment algorithms (see Section VI.A.4.2.5)	0	2 (0.8)	5 (2.0)	7 (0.9)*
Adverse event not listed above	1 (0.4)	7 (2.7)	8 (3.2)	16 (2.1)*
Death	0	1 (0.4)	1 (0.4)	2 (0.3)
Missed more than 10 total doses of study drug during study weeks 0-12	4 (1.6)	5 (1.9)	7 (2.8)	16 (2.1)*
Missed the Week 12 major assessment by more than 7 days	0	0	1 (0.4)	1 (0.1)
Discontinuation of antiretroviral therapy at the discretion of the investigator	1 (0.4)	0	0	1 (0.1)
Protocol violation not listed above	1 (0.4)	3 (1.2)	4 (1.6)	8 (1.1)
Lost to follow up	6 (2.4)	3 (1.2)	3 (1.2)	12 (1.6)
Other	2 (0.8)	1 (0.4)	4 (1.6)	7 (0.9)*
Total	21 (8.5)	38 (14.8)	52 (20.6)	111 (14.7)

*46 patients who were discontinued because of an adverse event include 7 patients listed as "persistent toxicity according to the dose adjustment algorithms", 16 patients listed as "adverse event not listed above", 20/41 patients listed as "patient decision", 2 patients listed as "other", and 1 patient listed as "missed more than 10 total doses of study drug during study weeks 0-12 (see Tables 29 and 30 ahead).

Table 5 lists the reasons for patient discontinuations during the extension phase of the study. With regard to the 166 patients who were discontinued, 65 (39.2%) were terminated because of adverse events. The vast majority of these 65 patients were receiving full dose Serostim as opposed to half-dose Serostim; however, ~80% of the patients entering and completing the first 12 weeks of the extension phase were being treated with full dose Serostim. See Section VI.A.5.6.6.2.2 in Safety Results for details and comment (as well as Sections VI.A.5.6.5 and VI.A.5.6.6.6.2 for comment regarding 3 deaths and 2 de novo malignancies unrelated to Serostim treatment, respectively, listed in Table 5). The other most common reasons for withdrawal were "patient decision unrelated to an adverse event" (?26?/166), "non-compliance with study drug" (21/166), and "lost to followup" (24/166).

Table 5
Reason for Patient Discontinuations by Treatment Group, and Overall, after 12 weeks

	Placebo to Half-Dose Serostim	Placebo to Full Dose Serostim	Half-Dose to Half-Dose Serostim	Half-Dose to Full Dose Serostim	Full Dose to Full Dose Serostim	All Patients
	n=44	n=182	n=81	n=138	n=201	n=646
Discontinuation Reason	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patient decision	8 (18.2)	21 (11.5)	3 (3.7)	6 (4.3)	10 (5.0)	48 (7.4)
Persistent toxicity according to the dose adjustment algorithms (see Section VI.A.4.2.5)	1 (2.3)	6 (3.3)	0	2 (1.4)	2 (1.0)	11 (1.7)
Any active malignancy, including progression of existing Kaposi's sarcoma lesions (> 50% lesion growth) or any new lesion*	0	0	0	0	2 (1.0)	2 (0.3)
Adverse event not listed above	1 (2.3)	12 (6.6)	3 (3.7)	3 (2.2)	11 (5.5)	30 (4.6)
Death	1 (2.3)	1 (0.5)	0	1 (0.7)*	0	3 (0.5)
Missed more than 10 total doses during the extension study	0	1 (0.5)	0	5 (3.6)	1 (0.5)	7 (1.1)
Missed more than 7 doses of study drug in a row at any time	2 (4.5)	4 (2.2)	3 (3.7)	1 (0.7)	4 (2.0)	14 (2.2)
Initiation of a new AIDS wasting intervention during study weeks -4 to 12	1 (2.3)	0	0	0	0	1 (0.2)
Discontinuation of antiretroviral therapy at the discretion of the investigator	0	0	0	1 (0.7)	1 (0.5)	2 (0.3)
Protocol violation not listed above	0	2 (1.1)	1 (1.2)	3 (2.2)	2 (1.0)	8 (1.2)
Lost to follow up	2 (4.5)	4 (2.2)	4 (4.9)	6 (4.3)	8 (4.0)	24 (3.7)
Other	0	2 (1.1)	5 (6.2)	2 (1.4)	7 (3.5)	16 (2.5)
Total	16 (36.4)	53 (29.1)	19 (23.5)	30 (21.7)	48 (23.9)	166 (25.7)

2 other malignancies (Hodgkin's lymphoma and acute myelogenous leukemia) were diagnosed 6 and 7 months, respectively, off therapy, and 1 other malignancy (disseminated cerebral lymphoma) resulted in and is listed as a death in this table (see Section VI.A.6.6.6.2 ahead).

VI.A.5.1.2 Protocol Deviations

All protocol deviations were reviewed by this Medical Officer, in particular those related to violation of inclusion/exclusion criteria. Nine patients did not meet the prespecified criteria for AIDS-associated wasting; however, 4 of these patients had sustained >9% weight loss, and were granted exemptions. One patient with a history of type 2 diabetes mellitus (Patient [redacted] was misenrolled, as were 4 patients with a "history of hyperglycemia". Two of these patients were discontinued from the study while receiving full dose Serostim during the extension phase because of persistent hyperglycemia; the other 3 patients required Serostim dose reductions when their fasting blood glucose levels exceeded the protocol-directed threshold. See Table 40 in Section VI.A.5.6.6.5.2.3 ahead. This Medical Officer does not feel that the other protocol deviations reviewed were consequential.

b(6)

VI.A.5.2 Patient Demographics and Baseline Characteristics

As depicted in Table 6, patients in the Sponsor's ITT population initially randomized to the 3 study arms were well matched with respect to age, sex and race. The mean age for all treatment groups was ~40. Approximately 90% of each treatment group were males. Furthermore, in each treatment group, Caucasians, African-Americans

and Hispanics accounted for approximately 72-80%, 8-12%, and 9-14%, respectively, of the study subjects. No statistically significant differences were observed across treatment groups when these continuous and categorical demographic parameters were analyzed.

Table 6

Demographic Characteristics of the ITT population

Characteristic		Placebo	Half-Dose Serostim	Full Dose Serostim	All Patients	p-values[1]
Age (yrs)	n	222	230	218	670	0.8297[2]
	Mean (SD)	40.6 (8.0)	41.0 (8.4)	40.8 (8.1)	40.8 (8.2)	0.9822[2]
	Median	40.0	40.0	39.5	40.0	
	Range	(21.0, 68.0)	(24.0, 77.0)	(24.0, 73.0)	(21.0, 77.0)	
Sex, n (%)	Male	201 (90.5)	212 (92.2)	198 (90.8)	611 (91.2)	0.6458[3]
	Female	21 (9.5)	18 (7.8)	20 (9.2)	59 (8.8)	0.8075[3]
Race, n (%)	White	177 (79.7)	175 (76.1)	157 (72.0)	509 (76.0)	0.3153[4]
	Black	18 (8.1)	18 (7.8)	26 (11.9)	62 (9.3)	0.1203[4]
	Asian	4 (1.7)	4 (1.7)	5 (2.3)	13 (1.9)	
	Hispanic	20 (9.0)	31 (13.5)	30 (13.8)	81 (12.1)	
	Other	3 (1.4)	2 (0.9)	0	5 (0.7)	

(1) The first p-value for footnote (2) is for the overall treatment effect, and the second p-value is for the comparison between the full dose Serostim group and the Placebo group.
(2) p-value from an ANOVA on ranked data with effects for treatment and pooled center
(3) p-value from CMH general association test

(4) p-value from CMH general association test

AIDS-related baseline characteristics are tabulated in Table 7. There were no obvious between-group imbalances with respect to 1) mean CD4 counts (~442-469 cells/μL), 2) HIV RNA levels (data not shown), 3) HIV risk factors, or 4) mean BW. There were large variations in the characteristics related to BW, i.e. weight ranged from ~30 to 109 kg. Large variations in the average calorie intake in all treated patients (n=748), which generally was larger than the recommended daily dietary allowances, were noted. Median percentage difference between actual and recommended intake was between +27.6% and +31.7% across the groups (range from -24% to +543%).

Table 7

AIDS-Related Baseline Demographic Characteristics (Including Weight, CD4 Counts and HIV Risk Factors) of the ITT Population

Characteristic	Placebo	Half-Dose Serostim	Full Dose Serostim	All Patients	p-values[1]
CD4 Count (cells/μL)					
n	204	211	194	609	**0.6341**[2]
Mean (SD)	469.3 (296.1)	442.9 (279.2)	442.1 (277.8)	451.5 (284.4)	**0.5139**[2]
Median	428.0	391.0	433.0	415.0	
Range	(10.0, 1534.0)	(10.0, 1451.0)	(17.0, 2035.0)	(10.0, 2035.0)	
HIV Risk Factors,					
N	222	230	218	670	
Men who have sex with men, n (%)	171 (77.0)	180 (78.3)	170 (78.0)	521 (77.8)	**0.6058**[3]
Intravenous drug use, n (%)	15 (6.8)	12 (5.2)	17 (7.8)	44 (6.6)	**0.4433**[3]
Heterosexual sex with FIV infected person, n (%)	24 (10.8)	17 (7.4)	17 (7.8)	58 (8.7)	
Weight (kg)					
n	222	230	218	670	0.4324[4]
Mean (SD)	**66.2 (10.6)**	**65.3 (10.2)**	**66.5 (10.2)**	**66.0 (10.3)**	0.9030[4]
Median	65.8	65.5	65.4	65.6	
Range	(29.8, 108.9)	(37.4, 100.8)	(41.0, 103.6)	(29.8, 108.9)	

[1]The first p-value for footnote (2) is for the overall treatment effect, and the second p-value is for the comparison between the full dose Serostim group and the placebo group.
[2]p-value from an ANOVA on ranked data with effects for treatment and pooled center.

[3]p-value from CMH general association test.

[4]p-value from an ANOVA on raw data with effects for treatment and pooled center.

As can be seen in Table 8, ~86-87% of the patients in each treatment arm were receiving HAART at study onset (~57-61% were receiving PI-containing HAART). For the purpose of this study, HAART therapy was defined as treatment with 1) at least 2 PIs, or 2) at least 2 nucleoside reverse transciptase inhibitors (NRTIs) and at least 1 PI, or 3) at least 2 NRTIs and at least 1 non-nucleoside reverse transcriptase inhibitor (NNRTI).

The number and types of ongoing HIV-related illnesses reported at screening was assessed by treatment group in all treated patients (n=757). Virtually all patients (99.7%) had 1 or more HIV-related illnesses: 38.6% had 1 illness, 27.9% had 2 illnesses, 15.9% had 3 illnesses, and 7.5% had 4 illnesses. The 3 treatment groups were well balanced with respect to numbers of patients with 1 or more illnesses. The most frequent HIV-related diseases were peripheral neuropathy (19.2%), lymphadenopathy (14.7%), diarrhea (12.7%), herpes simplex infection (6.6%), oral candidiasis (6.2%) and seborrheic dermatitis (6.2%). A total of 206 (27.2%) of the treated patients reported "other" HIV-related illnesses at baseline including lipodystrophy/fat redistribution, hypercholesterolemia and/or hypertriglyceridemia, hypogonadism, depression, fatigue, condyloma acuminata and leukopenia.

Table 8
Baseline Antiretroviral Therapy Use by Treatment Group in the ITT Population

Antiretroviral	Placebo n=222 n (%)	Half-Dose Serostim n=230 n (%)	Full Dose Serostim n=218 n (%)	All Patients n=670 n (%)
At Least 1 Protease Inhibitor				
Yes	128 (57.7)	131 (57.0)	132 (60.6)	391 (58.4)
No	94 (42.3)	99 (43.0)	86 (39.4)	279 (41.6)
At Least 1 NRTI				
Yes	219 (98.6)	224 (97.4)	216 (99.1)	659 (98.4)
No	3 (1.4)	6 (2.6)	2 (0.9)	11 (1.6)
At Least 1 NNRTI				
Yes	95 (42.8)	106 (46.1)	93 (42.7)	294 (43.9)
No	127 (57.2)	124 (53.9)	125 (57.3)	376 (56.1)
HAART Patient				
Yes	194 (87.4)	197 (85.7)	189 (86.7)	580 (86.6)
No	28 (12.6)	33 (14.3)	29 (13.3)	90 (13.4)

VI.A.5.3 Treatment Compliance

Treatment compliance was assessed by patient-completed diary cards. During the 12 week, placebo controlled phase of the study, only 16 patients (2.1%) were discontinued because they missed more than 10 doses of study drug; during the 12-36 week extension phase of the study, only 7 patients (1.1%) were discontinued for the same reason, and another 14 patients (2.2%) were discontinued because they missed more than 7 doses in a row. Patients in the ITT population had to be 80% compliant with their dosing regimen in order to be included in the Sponsor's Evaluable Population, and 632 patients (~83% of the 757 patients enrolled and treated) were deemed to be eligible for the Evaluable Population including patients with "inconsistent" BWO measurements (n=77). Taken together, these observations suggest that dosing compliance was acceptable.

VI.A.5.3.1 Drug Accountability

Between 1997 and 2001, more than [redacted] vials of Serostim were dispensed worldwide in order to conduct this study. As described in Section VI.A.4.2.8, the Sponsor has always gone to great lengths to ensure drug accountability, and site investigators have usually demonstrated and documented compliance with regard to drug accountability. [redacted]

b(4)

[redacted]

b(4)

b(4)

VI.A.5.4 Concomitant Therapy

Having thoroughly reviewed the entire submission including the reasons for study drug discontinuation and the numerous narrative histories of patients with serious adverse events (SAEs), this Medical Officer is not aware of the use of any disallowed medications by the patients participating in this clinical trial - excepting 1 patient who was discontinued during the extension phase of the study for initiating a "new" therapy for AIDS-associated wasting. Most importantly, and as desired, 85-90% of patients were receiving HAART therapy, and the remainder non-HAART antiretroviral therapy. **As presently stated in the Serostim Package Insert, patients receiving Serostim for AIDS-associated wasting must always be treated with concomitant antiretroviral therapy because of the theoretical (but never clinically substantiated) possibility that rhGH could enhance HIV replication.** In addition, some patients were receiving secondary prophylactic therapy for AIDS-related opportunistic infections (after Amendment 1A deleted the exclusion of such patients from enrollment in 2/00). Other medications used by patients were generally those prescribed to treat frequently preexisting AIDS-related illnesses (see Section VI.A.2) or routine ailments.

VI.A.5.5 Efficacy Results for Study GF-9037 (equivalent to Integrated Summary of Efficacy [ISE] in that only 1 study was included in the Sponsor's submission)

VI.A.5.5.1 Datasets Analyzed

As explained in detail in Section VI.A.4.4.3.1.2, the BWO analyses presented in this Medical Officer's review were performed by the Division's Statistical Reviewer (and belatedly by the Sponsor) in the "maximized", preferred ITT population containing 670 patients (including patients with "inconsistent" BWO measurements). Similarly, the LBM (by BIS) analyses presented in this review were performed by the Division's Statistical Reviewer (and originally by the Sponsor as a "sensitivity" analysis) in the "maximized", preferred ITT population containing 650 patients (including patients with "inconsistent" LBM measurements).

b(4)

VI.A.5.5.2 Primary Efficacy Results (BWO) and Most Important Secondary Efficacy Parameter (LBM by BIS)

VI.A.5.5.2.1 Bicycle Ergometry Work Output (BWO)

The mean maximum BWO until exhaustion increased after 12 weeks by 2.57 kJ in the Serostim 0.1 mg/kg daily group (p<0.004) and by 2.53 kJ in the Serostim 0.1 mg/kg every other day group (p<0.004) compared with placebo (see Table 9). BWO improved ~9% in both active treatment arms, and decreased 1% in the placebo group. Of note, a significant treatment difference was also observed for full dose Serostim when sensitivity analyses were performed in the Sponsor's ITT population (excluding "inconsistent" BWO measurements) (n=570), and the Sponsor's Evaluable Population (excluding "inconsistent" BWO measurements) (n=555). Work until exhaustion was verified by analyzing the scores derived from the Borg RPE scale in the Sponsor's Evaluable Population (data not shown). Median values of 19 (maximum score = 20) were observed in all treatment groups at the end of the bicycle protocol both at baseline and after 12 weeks of treatment. This indicates that a satisfactory and uniform level of exhaustion had been obtained across all 3 treatment groups at both of these time points.

Table 9

Mean (Median) of BWO (kJ) After 12 Weeks of Treatment in the ITT Population (Including Patients With « Inconsistent » Measurements)[a]

	Placebo	Half-Dose Serostim	Full Dose Serostim
Bicycle Work Output (kJ)	n=222	n=230	n=218
Baseline	25.92 (25.05)	27.79 (26.65)	27.57 (26.30)
Change from Baseline	-0.05 (-0.25)	2.48 (2.30)	2.52 (2.40)
Difference from Placebo			
Mean (2-sided 95% C.I.)	-	**2.53**[b] (0.81, 4.25)	**2.57**[b] (0.83, 4.31)
Median	-	2.55	2.65

[a]Protocol-Defined ITT Population: Treated patients with both a baseline assessment and at least 1 post-baseline assessment (using an early termination post-baseline assessment if patient terminated prior to Week 12 - last observation carried forward [LOCF]).
ANOVA model with effects for treatment and pooled center.
[b]p<0.004 for difference from placebo in change from baseline using Hochberg multiple comparison adjustment.

The distribution of BWO responses in all 3 treatment groups is presented graphically in Figure 1. Approximately 34% and 36% of full dose Serostim-treated patients and half-dose Serostim-treated patients, respectively, were non-responders, i.e. BWO decreased or did not change after treatment with Serostim. On the other hand, approximately 46% of placebo-treated patients manifested an increase in BWO.

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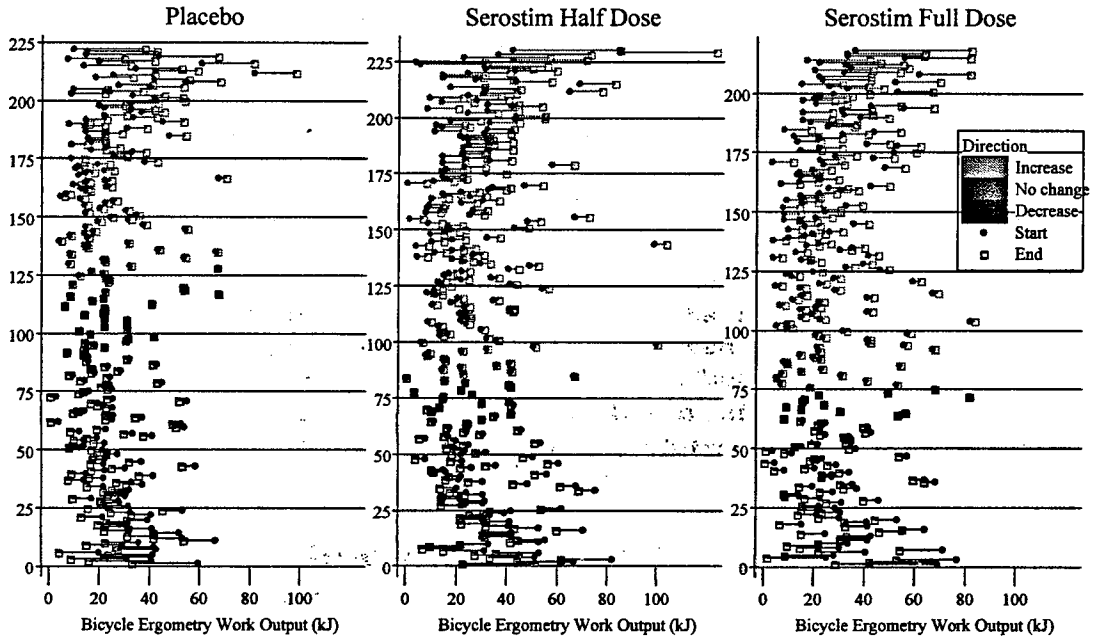
Figure 1

Per Patient Baseline (Start) to Week 12 (End) BWO (kJ) Sorted by the Value of Change (Most Negative Sort Value at Bottom and Most Positive Sort Value at Top)



VI.A.5.5.2.2 Lean Body Mass (LBM) by BIS

LBM increased after 12 weeks by 4.88 kg in the Serostim 0.1 mg/kg daily group (p<0.0001) and by 2.92 in the Serostim 0.1 mg/kg every other day group (p<0.0002) compared with placebo (see Table 10) **- a very clearcut dose-dependent response.** Of note, significant treatment differences were also observed for both doses of Serostim when sensitivity analyses were performed in the ITT population (excluding "inconsistent" LBM measurements) (n=606), and the Sponsor's Evaluable Population (excluding "inconsistent" LBM measurements) (n=587).

The distribution of LBM responses in all 3 treatment groups is presented graphically in Figure 2. **Approximately 9% and 15% of full dose Serostim-treated patients and half-dose Serostim-treated patients, respectively, were non-responders,** i.e. LBM decreased or did not change after treatment with Serostim. On the other hand, approximately 56% of placebo-treated patients manifested an increase in LBM.

Of note, BCM (by BIS) increased in a dose-dependent fashion after treatment with Serostim in the Sponsor's Evaluable Population (excluding "inconsistent" LBM measurements) (data not shown). The pairwise treatment differences (compared to placebo) in change from baseline in BCM for both doses of Serostim were highly statistically significant (p<0.0001), and, interestingly, about 50% of the treatment differences observed for LBM. Furthermore, LBM (by DEXA; at selected sites only)

also increased in a dose-dependent fashion after treatment with Serostim in the Sponsor's Evaluable Population (excluding "inconsistent" LBM measurements) (data not shown). The pairwise treatment differences (compared to placebo) in change from baseline in LBM (by DEXA) for both doses of Serostim were somewhat smaller than the treatment differences observed for LBM (by BIS), but still highly statistically significant (p<0.0001).

Table 10

Mean (Median) of LBM (kg) after 12 Weeks of Treatment in the ITT Population (Including Patients With « Inconsistent » Measurements)[a]

	Placebo	Half-Dose Serostim	Full Dose Serostim
Lean Body Mass (kg) (by BIS)	n=222	n=223	n=205
Baseline	50.04 (49.83)	49.04 (48.90)	49.61 (49.76)
Change from Baseline	0.97 (0.67)	3.89 (3.65)	5.84 (5.48)
Difference from Placebo			
Mean (2-sided 95% C.I.)	-	**2.92**[b] (1.41, 4.44)	**4.88**[c] (3.3, 6.42)
Median	-	2.98	4.81

[a]Protocol-Defined ITT Population: Treated patients with both a baseline assessment and at least 1 post-baseline assessment (using an early termination post-baseline assessment if patient terminated prior to Week 12 - LOCF).

ANOVA model with effects for treatment and pooled center.

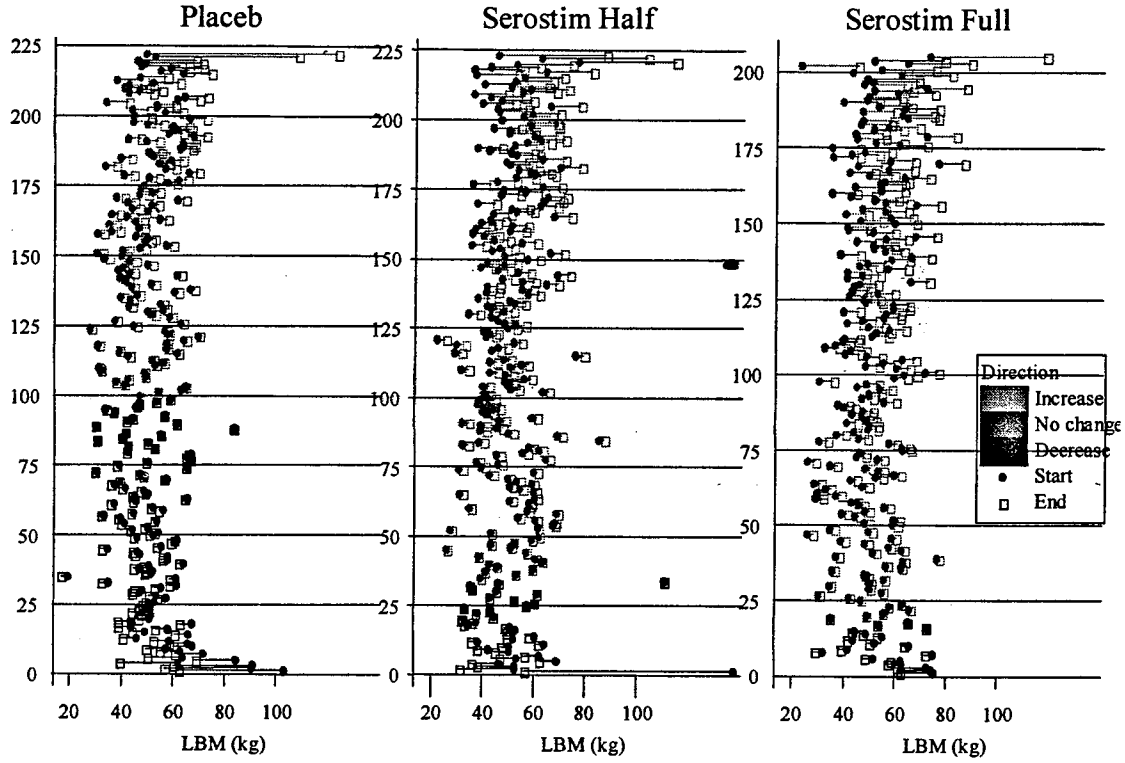
[b]p<0.0002 for difference from placebo in change from baseline using Hochberg multiple comparison adjustment.

[c]p<0.0001 for difference from placebo in change from baseline using Hochberg multiple comparison adjustment.

Figure 2

Per Patient Baseline (Start) to Week 12 (End) LBM (kg)

Sorted by the Value of Change (Most Negative Sort Value at Bottom and Most Positive Sort Value at Top)



VI.A.5.5.3 Subgroup/Covariate Analyses

VI.A.5.5.3.1 Gender

BWO: The mean differences from placebo in change from baseline in BWO for both active treatment groups was significant in men (and similar in magnitude to the combined study population), **but not in women** (see Table 11 below). In addition, as demonstrated in Table 12 below, female gender predicted a greater likelihood of a positive BWO response across all 3 treatment groups. **However, given the very small number of women in the study population, and the absence of a significant treatment-by-gender interaction in the ANOVA performed on the entire ITT study population comparing changes from baseline in BWO between each of the active treatment arms and the placebo group in men vs. women, these results (in particular, the lack of a response in women) must be interpreted with caution.**

Table 11

Mean (Median) of BWO (kJ) after 12 Weeks of Treatment by Gender

Population: ITT Including Inconsistent Measures Patients[a]

Gender		Placebo	Half-Dose Serostim	Full Dose Serostim
Male	Bicycle Work Output (kJ)	n=201	n=212	n=198
	Baseline	27.78 (26.55)	29.70 (27.80)	29.63 (27.90)
	Change from Baseline	0.23 (-0.25)	2.61 (2.30)	2.63 (2.45)
	Difference from Placebo			
	Mean (2-sided 95% C.I.)	-	**2.38**[b] (0.58, 4.19)	**2.40**[c] (0.56, 4.23)
	Median	-	2.55	2.70
Female	Bicycle Work Output (kJ)	n=21	n=18	n=20
	Baseline	13.78 (12.45)	12.34 (12.25)	13.40 (12.98)
	Change from Baseline	-0.08 (-0.10)	2.04 (2.25)	2.00 (2.00)
	Difference from Placebo			
	Mean (2-sided 95% C.I.)	-	2.13 (-3.76, 8.01)	2.08 (-3.65, 7.81)
	Median	-	2.35	2.10

[a]Protocol-Defined ITT Population: Treated patients with both a baseline assessment and at least 1 post-baseline assessment (using an early termination post-baseline assessment if patient terminated prior to Week 12 - LOCF).

ANOVA model with effects for treatment, gender, and their interaction.

[b]$p<0.010$ for difference from placebo in change from baseline using Hochberg multiple comparison adjustment.

[c]$p<0.011$ for difference from placebo in change from baseline using Hochberg multiple comparison adjustment.

Table 12

Gender of Patients Relative to Positive and Negative Changes in BWO (kJ) at Week 12

Population: ITT Including Inconsistent Measures Patients[a]

Gender	Change in Bicycle Work Output	Placebo n=222	Half-Dose Serostim n=230	Full Dose Serostim n=218
Male	n	201	212	198
	Positive	91 (45.3%)	132 (62.3%)	128 (64.7%)
	Negative	110 (54.7%)	80 (37.7%)	70 (35.3%)
Female	n	21	18	20
	Positive	11 (52.4%)	14 (77.8%)	15 (75.0%)
	Negative	10 (47.6%)	4 (22.2%)	5 (25.0%)
p-value for comparison within treatment groups[b]		0.535	0.19	0.354
p-value for comparison across treatment groups[c]		**0.001**		

[a]Protocol-Defined ITT Population: Treated patients with both a baseline assessment and at least 1 post-baseline assessment (using an early termination post-baseline assessment if patient terminated prior to Week 12 - LOCF).

[b]Based on CMH Test comparing responses by gender and treatment group.

[c]Based on CMH Test comparing responses by gender adjusting for treatment group.

LBM: The mean differences from placebo in change from baseline in LBM for both active treatment groups was significant in men (and similar in magnitude to the combined study population), but not in women (see Table 13 below). In addition, as demonstrated in Table 14 below, male gender predicted a greater likelihood of a positive LBM response only in the Serostim half-dose treatment arm. However, as noted above, given the very small number of women in the study population, and the absence of a significant treatment-by-gender interaction in the ANOVA performed on the entire ITT study population comparing changes from baseline in LBM between

each of the active treatment arms and the placebo group in men vs. women, these results (in particular, the lack of a response in women) must be interpreted with caution.

Table 13

Mean (Median) of LBM (kg) after 12 Weeks of Treatment by Gender

Population: ITT Including Inconsistent Measures Patients[a]

Gender		Placebo	Half-Dose Serostim	Full Dose Serostim
Male	Lean Body Mass (kg) (by BIS)	n=202	n=204	n=189
	Baseline	51.77 (51.19)	51.01 (50.19)	51.37 (50.98)
	Change from Baseline	1.04 (0.72)	4.22 (3.96)	6.06 (5.75)
	Difference from Placebo			
	Mean (2-sided 95% C.I.)	-	**3.18**[b] (1.59, 4.77)	**5.02**[b] (3.40, 6.65)
	Median	-	3.24	5.03
Female	Lean Body Mass (kg) (by BIS)	n=20	n=19	n=16
	Baseline	35.02 (34.40)	34.48 (34.32)	33.47 (32.55)
	Change from Baseline	0.48 (0.30)	1.19 (0.87)	3.59 (2.57)
	Difference from Placebo			
	Mean (2-sided 95% C.I.)	-	0.71 (-4.42, 5.85)	3.11 (-2.26, 8.49)
	Median	-	0.58	2.28

[a]Protocol-Defined ITT: Treated patients with both a baseline assessment and at least 1 post-baseline assessment (using an early termination post-baseline assessment if patient terminated prior to Week 12 - LOCF).

ANOVA model with effects for treatment, gender, and their interaction.

[b]$p<0.0001$ for difference from placebo in change from baseline using Hochberg multiple comparison adjustment.

Table 14

Gender of Patients Relative to Positive and Negative Changes in LBM (kg) at Week 12

Population: ITT Including Inconsistent Measures Patients[a]

Gender	Change in LBM	Placebo n=222	Half-Dose Serostim n=223	Full Dose Serostim n=205
Male	n	202	204	189
	Positive	113 (55.9%)	179 (87.7%)	172 (91.0%)
	Negative	89 (44.1%)	25 (12.3%)	17 (9.0%)
Female	n	20	19	16
	Positive	11 (55.0%)	10 (52.6%)	14 (87.5%)
	Negative	9 (47.4%)	9 (47.4%)	2 (12.5%)
p-value for comparison within treatment groups[b]		0.936	< 0.001	0.643
p-value for comparison across treatment groups[c]		< 0.001		

[a]Protocol-Defined ITT Population: Treated patients with both a baseline assessment and at least 1 post-baseline assessment (using an early termination post-baseline assessment if patient terminated prior to Week 12 - LOCF).

[b]Based on CMH Test comparing responses by gender and treatment group.

[c]Based on CMH Test comparing responses by gender adjusting for treatment group.

VI.A.5.5.3.2 Race/Ethnicity

BWO: The treatment-by-race interaction in the ANOVA performed on the entire ITT study population comparing changes from baseline in BWO between each of the active treatment arms and the placebo group in Caucasians vs. non-Caucasians was statistically significant (p=0.02 for the full dose group versus placebo, and p=~0.05 for the half-dose group versus placebo). Table 15 displays descriptive statistics of differences from placebo in change from baseline in BWO for both Serostim dosages in different ethnic groups. These data indicate that the interaction was qualitative in nature, i.e. the mean change from baseline in BWO was greater in Serostim-treated patients compared with placebo-treated patients amongst Caucasians and Asians; in contrast, the mean change from baseline in BWO was greater in placebo-treated patients compared with Serostim-treated patients amongst African Americans and Hispanics. ***This exploratory observation potentially will be discussed further in Section VI.A.5.5.6, Summary/Discussion of Efficacy.***

Table 15

Mean Difference from Placebo in Change from Baseline (SD) in BWO (kJ) by Race

Population: ITT Including Inconsistent Measures Patients[a]

Treatment	Caucasian			Hispanic			African American			Asian			Other		
	n	Mean	Diff[b]	n	Mean	Diff[b]	n	Mean	Diff[b]	n	Mean	Diff[b]	n	Mean	Diff[b]
Full Dose Serostim	157	3.81 (9.35)	**4.00**	30	-0.58 (11.71)	**-1.99**	26	-2.07 (8.12)	**-5.16**	5	6.74 (10.32)	**7.67**			
Half-Dose Serostim	175	3.23 (9.95)	**3.42**	31	0.66 (9.76)	**-0.75**	18	0.24 (6.82)	**-2.85**	4	2.18 (3.07)	**3.11**	2	-4.25 (3.61)	**-3.58**
Placebo	177	-0.19 (8.49)	-	20	1.41 (9.51)	-	18	3.09 (7.67)	-	4	-0.93 (2.10)	-	3	-0.67 (6.60)	-

[a]Protocol-Defined ITT Population: Treated patients with both a baseline assessment and at least 1 post-baseline assessment (using an early termination post-baseline assessment if patient terminated prior to Week 12 - LOCF).
[b]**Difference from placebo.**

LBM: The treatment-by-race interaction in the ANOVA performed on the entire ITT study population comparing changes from baseline in LBM between each of the active treatment arms and the placebo group in Caucasians vs. non-Caucasians was not statistically significant for either Serostim treatment group. Table 16 displays descriptive statistics of differences from placebo in change from baseline in LBM in different ethnic groups. The mean change from baseline in LBM was greater in Serostim-treated patients compared with placebo-treated patients amongst African Americans and Hispanics as well as Caucasians and Asians.

Table 16
Mean Difference from Placebo in Change from Baseline (SD) in LBM (kg) by Race
Population: ITT Including Inconsistent Measures Patients[a]

Treatment	Caucasian			Hispanic			African American			Asia			Other		
	n	Mean	Diff[b]	n	Mean	Diff[b]	n	Mean	Diff[b]	n	Mean	Diff[b]	n	Mean	Diff[b]
Full Dose Serostim	178	6.56	**5.03**	26	2.75	**3.24**	21	4.97	**7.34**	5	4.88	**4.85**			
Half-Dose Serostim	172	4.43	**2.90**	28	1.83	**2.32**	17	3.28	**5.65**	5	1.90	**1.87**	1	4.00	**4.78**
Placebo	178	1.53	-	20	-0.49	-	18	-2.37	-	5	0.03	-	1	-0.78	-

[a]Protocol-Defined ITT Population: Treated patients with both a baseline assessment and at least 1 post-baseline assessment (using an early termination post-baseline assessment if patient terminated prior to Week 12 - LOCF).
[b]**Difference from placebo.**

VI.A.5.5.3.3 Use of HAART

The majority of patients (~86-87% in all 3 treatment arms) were being treated with HAART at the time of enrollment in the study.

BWO: The treatment-by-HAART interaction in the ANOVA performed on the entire ITT study population comparing changes from baseline in BWO between each of the active treatment arms and the placebo group in HAART users vs. HAART non-users was weakly statistically significant (p=0.06 for the full dose group vs. placebo *and* the half-dose group vs. placebo). Table 17 displays descriptive statistics of differences from placebo in change from baseline in BWO for both Serostim dosages in HAART users and HAART non-users. These data indicate that the interaction was qualitative in nature, i.e. the mean change from baseline in BWO was greater in Serostim-treated patients compared with placebo-treated patients amongst HAART users; in contrast, the mean change from baseline in BWO was greater in placebo-treated patients compared with Serostim-treated patients amongst HAART non-users. These observations are supported to a limited extent by a comparison of the proportion of patients demonstrating a positive BWO response (a much cruder indicator than the actual difference in the change in BWO after treatment with either Serostim dosage vs. placebo) after treatment with both doses of Serostim and placebo between subjects receiving and not receiving HAART (see Table 18). In this regard, a significantly greater amount of HAART-treated patients receiving half-dose Serostim demonstrated a positive BWO response compared with non-HAART-treated patients receiving half-dose Serostim. Although not statistically significant, a similar trend was observed in patients receiving full dose Serostim. Nonetheless, given that there were very few patients (~10-13%) not receiving HAART, one must interpret these exploratory analyses very cautiously. *These observations will be further discussed in Section VI.A.5.5.6, Summary/Discussion of Efficacy.*

Table 17
Mean Difference from Placebo in Change from Baseline (SD) in BWO (kJ) by HAART Usage
Population: ITT Including Inconsistent Measures Patients[a]

Treatment	HAART Usage			No HAART Usage		
	n	Mean	Diff[b]	n	Mean	Diff[b]
Full Dose	189	2.96 (9.2)	**3.00**	29	-0.06 (13.0)	**-1.93**
Half-Dose	197	3.14 (9.6)	**3.18**	33	-0.82 (9.3)	**-2.69**
Placebo	194	-0.04 (8.4)	-	28	1.87 (8.7)	-

[a]Protocol-Defined ITT Population: Treated patients with both a baseline assessment and at least 1 post-baseline assessment (using an early termination post-baseline assessment if patient terminated prior to Week 12 - LOCF).
[b]**Difference from placebo.**

Table 18
HAART Usage Relative to Positive and Negative Changes in BWO (kJ) at Week 12
Population: ITT Including Inconsistent Measures Patients[a]

HAART	Change in Bicycle Work Output	Placebo n=222	Half-Dose Serostim n=230	Full Dose Serostim n=218
Patients on HAART	**n**	194	197	189
	Positive	86(44.3%)	131(66.5%)	126(66.7%)
	Negative	108(55.7%)	66(33.5%)	63(33.3%)
Patients not on HAART	**n**	28	33	29
	Positive	16(57.1%)	15(45.5%)	17(58.6%)
	Negative	12(42.9%)	18(54.6%)	12(41.4%)
Comparison of response with HAART usage or not (within treatment groups)[b]		0.204	0.020	0.397
Comparison of response with HAART usage or not (across treatment groups)[c]		0.259		

[a]Protocol-Defined ITT Population: Treated patients with both a baseline assessment and at least 1 post-baseline assessment (using an early termination post-baseline assessment if patient terminated prior to Week 12 - LOCF).
[b]Based on CMH Test comparing response with/without HAART usage by treatment group.
[c]Based on CMH Test comparing response with/without HAART usage adjusting for treatment group.

LBM: In contrast to the significant treatment-by-HAART interaction with respect to the change from baseline in BWO described above, the treatment-by-HAART interaction in the ANOVA performed on the entire ITT study population comparing change from baseline in LBM between each of the active treatment arms and the placebo group in HAART users vs. HAART non-users was not statistically significant. Furthermore, a comparison of the proportion of patients demonstrating a positive LBM response (a much cruder indicator than the actual difference in the change in LBM after treatment with either Serostim dosage vs. placebo) after treatment with both doses of Serostim and placebo between subjects receiving and not receiving HAART did not reveal a disproportionate number of positive LBM responders in the HAART-treated patients receiving either dose of Serostim (see Table 19).

Table 19

HAART Usage Relative to Positive and Negative Changes in LBM (kg) at Week 12

Population: ITT Including Inconsistent Measures Patients[a]

HAART	Change in LBM	Placebo n=222	Half-Dose Serostim n=223	Full Dose Serostim n=205
Patient on HAART	n	192	195	181
	Positive	115 (59.9%)	166 (85.1%)	165 (91.2%)
	Negative	77 (40.1%)	29 (14.9%)	16 (8.8%)
Patient not on HAART	n	30	28	24
	Positive	9 (30.0%)	23 (82.1%)	21 (87.5%)
	Negative	21 (70.0%)	5 (17.9%)	3 (12.5%)
Comparison of response with HAART usage or not (within treatment groups)[b]		0.002	0.682	0.562
Comparison of response with HAART usage or not (across treatment groups)[c]		<0.001		

[a]Protocol-Defined ITT Population: Treated patients with both a baseline assessment and at least 1 post-baseline assessment (using an early termination post-baseline assessment if patient terminated prior to Week 12 - LOCF).

[b]Based on CMH Test comparing response with/without HAART usage by treatment group.

[c]Based on CMH Test comparing response with/without HAART usage adjusting for treatment group.

VI.A.5.5.3.4 Body Weight (BW) (kg) and Body Mass Index (BMI) (kg/m^2) at Baseline

As demonstrated in Table 20 (BW) and Table 21 (BMI), a lower baseline BW and lower baseline BMI were significant predictors of a positive BWO response after treatment with full dose (but not half-dose) Serostim. However, as can be seen in Figure 3 (BW) and Figure 4 (BMI), regression analyses plotting baseline BWs and BMIs against actual changes in BWO do NOT demonstrate significant inverse linear relationships. These seemingly contradictory findings can be explained by the fact that a positive vs. negative BWO response is a much cruder/less sensitive indicator of response than the actual change in BWO (kJ).

Table 20
Baseline BW (kg) for Patients with Positive and Negative Changes in BWO (kJ) at Week 12
Population - ITT Including Inconsistent Measures Patients*

Change in Bicycle Work Output	Statistics	Placebo	Half-Dose Serostim	Full Dose Serostim
Positive	**n**	102	146	143
	Mean (SEM)	66.4(1.0)	64.5(0.8)	65.0(0.9)
	Range	(45.0, 93.1)	(37.4, 100.8)	(41.0, 103.6)
Negative	**n**	120	84	75
	Mean (SEM)	66.0(0.9)	66.6(1.1)	69.3(1.2)
	Range	(29.8, 108.9)	(44.9, 86.2)	(53.5, 88.3)
p-value for comparison within treatment groups**		0.7406	0.1308	**0.003**
p-value for comparison across treatment groups**		**0.0144**		

*Protocol-Defined ITT Population: Treated patients with both a baseline assessment and at least 1 post-baseline assessment (using an early termination post-baseline assessment if patient terminated prior to Week 12 - LOCF).
**Based on ANOVA model with effects for treatment, change in BWO (pos/neg), and their interaction.

Table 21
Baseline BMI (kg/m^2) for Patients with Positive and Negative Changes in BWO at Week 12
Population: ITT Including Inconsistent Measures Patients*

Changes in Bicycle Work Output	Statistics	Placebo	Half-Dose Serostim	Full Dose Serostim
Positive	**n**	102	146	143
	Mean (SEM)	21.3(0.3)	20.8(0.2)	20.9(0.2)
	Range	(15.9, 29.1)	(13.7, 29.3)	(15.3, 30.1)
Negative	**n**	120	84	75
	Mean (SEM)	21.3(0.3)	21.4(0.3)	21.9(0.3)
	Range	(12.1, 30.0)	(17.1, 27.9)	(18.2, 29.6)
p-value for comparison within treatment groups**		0.9443	0.0725	**0.0096**
p-value for comparison across treatment groups**		**0.009**		

*Protocol-Defined ITT Population: Treated patients with both a baseline assessment and at least 1 post-baseline assessment (using an early termination post-baseline assessment if patient terminated prior to Week 12 - LOCF).
**Based on ANOVA model with effects for treatment, change in BWO (pos/neg), and their interaction.

Figure 3

b(4)

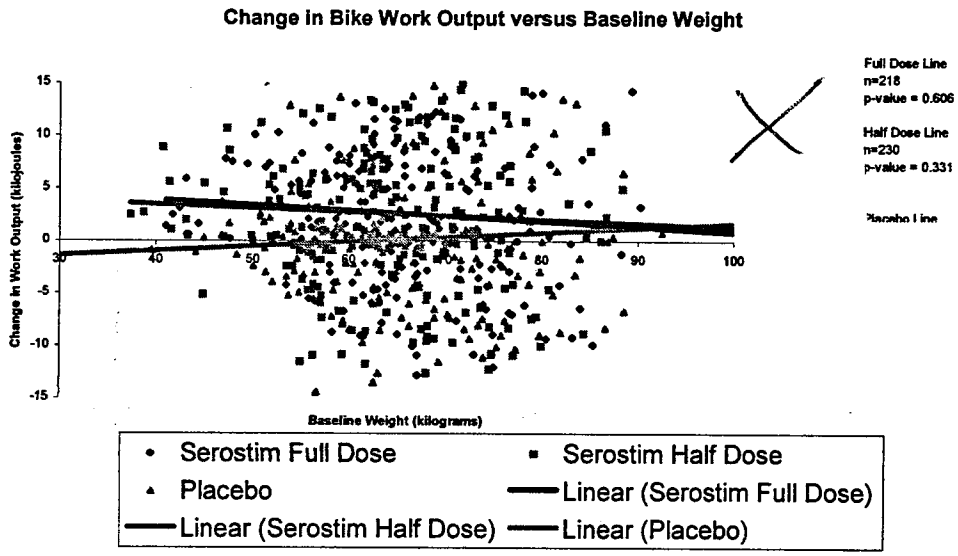
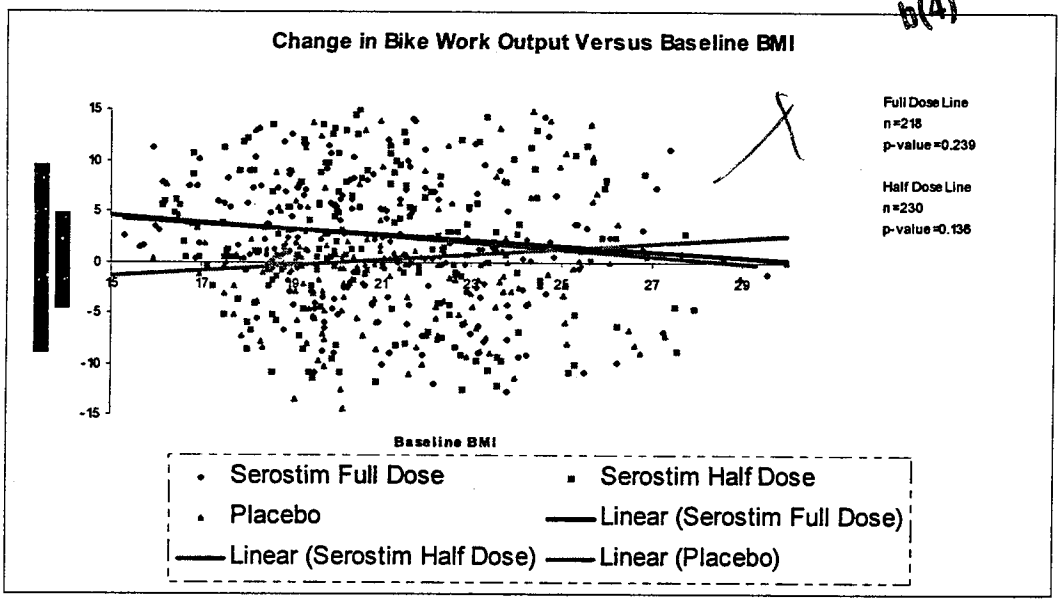


Figure 4

b(4)



VI.A.5.5.3.5 Other Covariates

There was no significant treatment-by-center interaction, nor were there any significant differences in mean values between centers. Age and baseline truncal fat mass/limb fat mass ratio were not predictors of a positive BWO or LBM response.

VI.A.5.5.4 Other Secondary Efficacy Results

VI.A.5.5.4.1 Total Fat Mass (by DEXA)

Total fat mass (by DEXA) decreased after 12 weeks by 1.75 kg in the Serostim 0.1 mg/kg daily group ($p<0.0001$) and by 1.28 kg in the Serostim 0.1 mg/kg every other day group ($p<0.0002$) compared with placebo (see Table 22) – a clearcut dose-dependent response. As seen in Table 23, the response in men was almost identical to the population taken as a whole. Surprisingly, there were also statistically significant, dose-dependent treatment effects in women, even though very few women had available total fat mass data to be analyzed! The decreases in total fat mass (by DEXA) were paralleled by dose-dependent decreases in truncal fat mass (by DEXA), limb fat mass (by DEXA) and the truncal fat mass/limb fat mass ratio.

Table 22
Mean (Median) of Total Body Fat (by DEXA) (kg) after 12 Weeks of Treatment
Population: ITT Including Inconsistent Measures Patients[a]

	Placebo	Half-Dose Serostim	Full Dose Serostim
Total Body Fat (by DEXA) (kg)			
Baseline	n=94 8.07 (7.33)	n=100 8.27 (8.03)	n=85 8.69 (8.28)
Change from Baseline	0.03 (0.01)	-1.25 (-1.23)	-1.72 (-1.51)
Difference from Placebo			
Mean (2-sided 95% C.I.)	-	**-1.28[b]** (-1.79, -0.77)	**-1.75[b]** (-2.28, -1.21)
Median	-	-1.24	-1.52

[a]Protocol-Defined ITT Population: Treated patients with both a baseline assessment and at least 1 post-baseline assessment (using an early termination post-baseline assessment if patient terminated prior to Week 12 - LOCF).
ANOVA model with effects for treatment and pooled center.
[b]$p<0.0001$ for difference from placebo in change from baseline using Hochberg multiple comparison adjustment.

Table 23
Mean (Median) of Total Body Fat by DEXA (kg)
after 12 Weeks of Treatment by Gender
Population: ITT Including Inconsistent Measures Patients[a]

Gender		Placebo	Half-Dose Serostim	Full-Dose Serostim
Male	Total Body Fat by DEXA (kg)	n=82	n=88	n=76
	Baseline	7.71 (7.13)	8.04 (7.82)	8.21 (7.91)
	Change from Baseline	0.00 (-0.07)	-1.24 (-1.26)	-1.64 (-1.48)
	Difference from Placebo			
	Mean (2-sided 95% C.I.)	-	**-1.24**[b] (-1.77, -0.70)	**-1.64**[b] (-2.19, -1.08)
	Median	-	-1.19	-1.40
Female	Total Body Fat by DEXA (kg)	n=12	n=12	n=9
	Baseline	9.89 (8.65)	11.35 (9.64)	15.01 (14.81)
	Change from Baseline	0.66 (0.55)	-0.94 (-0.95)	-1.90 (-1.80)
	Difference from Placebo			
	Mean (2-sided 95% C.I.)	-	**-1.60**[c] (-3.03, -0.18)	**-2.56**[d] (-4.10, -1.02)
	Median	-	-1.50	-2.36

[a]Protocol Defined ITT Population: Treated patients with both a baseline assessment and at least 1 post-baseline assessment (using an early termination post-baseline assessment if patient terminated prior to Week 12 - LOCF).

ANOVA model with effects for treatment, gender, and their interaction.

[b]p<0.0001 for difference from placebo in change from baseline using Hochberg multiple comparison adjustment.

[c]p<0.027 for difference from placebo in change from baseline using Hochberg multiple comparison adjustment.

[d]p<0.001 for difference from placebo in change from baseline using Hochberg multiple comparison adjustment.

VI.A.5.5.4.2 Body Weight (BW)

BW increased after 12 weeks by 2.1 kg in the Serostim 0.1 mg/kg daily group (p<0.0001) and by 1.49 kg in the Serostim 0.1 mg/kg every other day group (p<0.0002) compared with placebo (see Table 24) – a clearcut dose-dependent response. The treatment effect with respect to BW was approximately 50% of that observed in LBM. As seen in Table 25, the response in men was almost identical to the population taken as a whole. Neither dosage of Serostim resulted in a statistically significant increase in BW in women compared with placebo, but the number of women in the sample was very small.

Table 24
Mean (Median) of BW (kg) after 12 Weeks of Treatment
Population: ITT Including Inconsistent Measures Patients[a]

	Placebo	Half-Dose Serostim	Full Dose Serostim
BW (kg)	n=247	n=257	n=253
Baseline	65.35 (65.30)	65.08 (65.18)	65.75 (65.77)
Change from Baseline	0.69 (0.68)	2.18 (2.15)	2.79 (2.65)
Difference from Placebo			
Mean (2-sided 95% C.I.)	-	**1.49**[b] (1.02, 1.95)	**2.10**[b] (1.6, 2.57)
Median	-	1.47	1.97

[a]Protocol-Defined ITT Population: Treated patients with both a baseline assessment and at least 1 post-baseline assessment (using an early termination post-baseline assessment if patient terminated prior to Week 12 - LOCF).
ANOVA model with effects for treatment and pooled center.
[b]p<0.0001 for difference from placebo in change from baseline using Hochberg multiple comparison adjustment.

Table 25
Mean (Median) of BW (kg) after 12 Weeks of Treatment by Gender
Population: ITT Including Inconsistent Measures Patients[a]

Gender		Placebo	Half-Dose Serostim	Full Dose Serostim
Male	**BW (kg)**	n=224	n=235	n=229
	Baseline	66.74 (66.33)	66.29 (66.07)	67.28 (66.84)
	Change from Baseline	0.70 (0.66)	2.26 (2.28)	2.93 (2.81)
	Difference from Placebo			
	Mean (2-sided 95% C.I.)	-	1.56[b] (1.07, 2.06)	2.23[b] (1.74, 2.73)
	Median	-	1.61	2.15
Female	**BW (kg)**	n=23	n=22	n=24
	Baseline	54.27 (53.78)	53.74 (52.26)	53.53 (54.03)
	Change from Baseline	0.77 (0.86)	1.00 (0.75)	1.32 (1.32)
	Difference from Placebo			
	Mean (2-sided 95% C.I.)	-	0.23 (-1.33, 1.80)	0.55 (-0.99, 2.08)
	Median	-	-0.11	0.46

[a]Protocol-Defined ITT Population: Treated patients with both a baseline assessment and at least 1 post-baseline assessment (using an early termination post-baseline assessment if patient terminated prior to Week 12 - LOCF).
ANOVA model with effects for treatment, gender, and their interaction.
[b]p<0.0001 for difference from placebo in change from baseline using Hochberg multiple comparison adjustment.

VI.A.5.5.4.3 Six Minute Walk Test

The six minute walk test was performed at selected sites only. The difference from placebo in the increase from baseline in the distance traveled in 6 minutes was not statistically significant for either Serostim dose group (data not shown).

VI.A.5.5.4.4 Quality of Life (QOL) Assessment

VI.A.5.5.4.4.1 Bristol-Meyers Anorexia/Cachexia Recovery Instrument (BACRI)

The BACRI consists of 8 questions regarding an individual's perceptions of his/her well being since the initiation of treatment. Patients respond by making a mark on a visual analog scale (ranging from 0 to 100) between two extreme outcomes which are different for each question. A score of zero denotes a poor outcome, 100 a maximal improvement, and 50 no change. Question 7 by itself (a global treatment benefit item) and the BACRI-7 (a composite score for Questions 1, 2, 3, 4, 5, 6, and 8) were considered by the Sponsor to be the most meaningful assessments.

Question 7 - "Do you think this treatment has been of benefit to you?" - has the possible answer extremes "Not at all" at 0 and "Very much" at 100. The mean scores observed at Week 12 were 72.3±1.8 (mean±SEM) in the full dose Serostim group, 65.4±1.7 in the half-dose Serostim group, and 51.6±1.7 in the placebo group. Mean scores at Week 12 (mean baseline score was not obtained and therefore mean change in score after 12 weeks of treatment was not available) were compared utilizing a repeated measures ANOVA (with effects for treatment, pooled center, time, and treatment by time interaction), followed by Hochberg's mutliple (pairwise) comparison procedure. When the mean scores from either Serostim group were compared with the mean score from the placebo group, the difference was significant ($p<0.0001$); in addition, the difference between the mean scores observed in the full dose and half-dose Serostim groups was also significant ($p=0.004$), i.e. an apparent dose related improvement.

BACRI-7: The mean scores observed at Week 12 were 464.0±7.1 in the full dose Serostim group, 440.9±6.7 in the half-dose Serostim group, and 399.7±6.6 in the placebo group. When the mean scores from either Serostim group were compared with the mean score from the placebo group, the difference was once again significant ($p<0.0001$); in addition, the difference between the mean scores observed in the full dose and half-dose Serostim groups was also once again significant ($p=0.0155$), i.e. an apparent dose related improvement.

VI.A.5.5.4.4.2 Multidimensional Health Status Assessment (MHSA)

The MHSA consists of a series of questions which assess an individual's perception of his/her general health, mood, social behavior, attention, reasoning, problem solving, and bodily pain. Responses are ranked (i.e., excellent=1 through poor=5 with regard to a question about the state of general health; none=1 through very severe=6 with regard to a question about the amount of bodily pain), and a score is calculated.

When the Week 12 scores regarding the patient's perception of his/her state of general health (Module A, Question 1) from either Serostim group were compared with the score from the placebo group, the differences were significant. When the Week 12 scores regarding the patient's perception of his/her bodily pain (Module A, Question 2) from both Serostim groups were compared with the score from the placebo group, the difference was significant for the full dose Serostim group only (p=0.0012). However, as per Module B, Question 5, the increase in bodily pain did not interfere with the patients' normal work.

VI.A.5.5.4.4.3 Critique of Sponsor's QOL Assessments and Proposed Labeling Language by the Agency's Study Endpoints and Label Development Team (SEALD)

See Section VI.A.5.5.6.

VI.A.5.5.4.5 IGF-I Responses (ng/mL) - Efficacy Implications

Serum IGF-I and IGF-I standard deviation score (SDS) responses between baseline and Week 12 are presented in **Section VI.A.5.6.6.6.1 (under Safety Results).** No attempt was made by the Sponsor to correlate either 1) the raw mean increase in BWO (the primary efficacy variable) or the raw mean increase in LBM (the most important secondary efficacy variable) with the raw mean increase in serum IGF-I after 12 weeks of treatment with Serostim; or 2) the mean treatment differences on the increase from baseline in BWO or LBM with the mean treatment difference on the increase from baseline in serum IGF-I (or IGF-I SDS) after 12 weeks of treatment with either dose of Serostim vs. placebo. In fact, the mean treatment differences for IGF-I were not determined. In this regard, recent endocrine literature suggests that body composition changes and IGF-I responses after treatment of adult GHD patients with rhGH are **not** significantly correlated. **Therefore, the lack of such analyses are not important omissions by the Sponsor.**

VI.A.5.5.5 Efficacy Data from Open Label Extension Trial (in particular Weeks 12-24 and 0-24)

VI.A.5.5.5.1 BWO

Five hundred and forty eight patients completed 24 weeks of treatment with Serostim. Descriptive statistics for the changes between Week 0 and Week 24 in BWO are presented for 454 patients in 5 different protocol-directed dose groups (excluding 94 patients with "inconsistent" measurements) in Table 26. Most notably, the mean increase in BWO was greater in the patients treated with half-dose Serostim for 12 weeks during the placebo controlled phase who continued half-dose Serostim for the next 12 weeks (5.8 kJ) than in

the patients who received full dose Serostim continuously for 24 weeks (4.4 kJ). Similar changes in BWO are displayed graphically in Figure 5 for the 443 of these 454 patients who had "consistent" BWO measurements at baseline, Week 12 and Week 24 (an "equal n" plot). The change in BWO was similar at Week 12 in patients who received either full dose or half-dose Serostim (consistent with the formal statistical analysis presented earlier). **However, the additional increase in BWO between Week 12 and Week 24 was somewhat greater in the continuous half-dose patients than in the continuous full dose patients.**

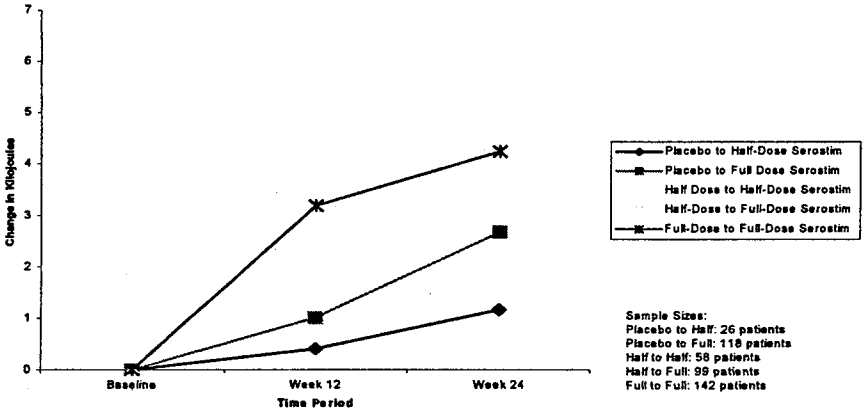
Table 26

BWO (kJ), Change from Baseline to Week 24
in All Treated Patients Excluding Inconsistent Measures Patients

Time Point	Statistics	Placebo to Half-Dose Serostim	Placebo to Full-Dose Serostim	Half-Dose to Half-Dose Serostim	Half-Dose to Full-Dose Serostim	Full-Dose to Full-Dose Serostim
Baseline	n	27	120	58	101	148
	Mean (SD)	30.4 (22.0)	27.3 (14.9)	29.9 (16.1)	28.8 (16.9)	28.1 (17.0)
	Median	23.8	22.7	25.8	24.4	23.1
	Range	(4.8, 98.0)	(3.8, 80.9)	(8.2, 82.1)	(3.4, 99.2)	(4.2, 82.0)
Endpoint	n	27	120	58	101	148
	Mean (SD)	31.7 (22.3)	29.1 (14.3)	35.8 (17.3)	33.6 (19.1)	32.4 (18.3)
	Median	23.9	27.8	31.5	30.5	30.6
	Range	(4.4, 98.1)	(3.2, 74.2)	(8.5, 81.3)	(5.2, 98.7)	(3.3, 84.4)
Change	n	27	120	**58**	101	**148**
	Mean (SD)	1.3 (10.2)	1.8 (7.9)	**5.8 (12.2)**	4.9 (12.9)	**4.4 (10.0)**
	Median	2.2	2.4	**4.7**	2.9	**2.4**
	Range	(-20.2, 24.8)	(-32.5, 29.7)	**(-30.2, 36.1)**	(-22.4, 57.0)	**(-33.7, 39.3)**

Figure 5

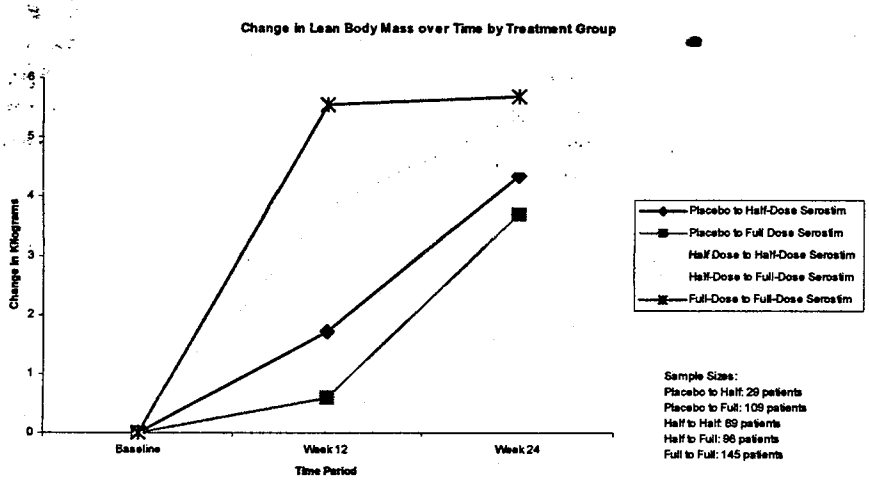
Change in Bicycle Work Output Over Time by Treatment Group



VI.A.5.5.5.2 LBM and BW

As depicted graphically in Figure 6, very modest additional increases in LBM were observed in patients treated continuously with both full dose and half-dose Serostim - compared with the more robust, dose-dependent increases in LBM observed during the 12 week, placebo controlled portion of the trial. A dose-dependent increase in BW was also maintained after 24 weeks of treatment.

Figure 6



VI.A.5.5.6 Efficacy - Summary/Discussion of Results

Study Objectives/Design:

The Sponsor conducted a 12 week, prospective, randomized, parallel group, double blind, placebo controlled, dose ranging (followed by a 12-36 week extension phase) in patients with human immunodeficiency virus (HIV)-/acquired immunodeficiency syndrome (AIDS)-associated catabolism/wasting to 1) evaluate the clinical efficacy of Serostim compared with placebo in stimulating an increase in the primary efficacy outcome parameter, bicycle ergometry work output (BWO) (as well as changes in multiple other secondary efficacy variables including, most importantly, an increase in lean body mass (LBM) and body weight (BW), and a decrease in total fat mass; 2) establish an optimal dose of Serostim; 3) assess the safety and tolerability of Serostim; and 4) ***confirm the results of Study 5341 conducted by the Sponsor in 1992-1993 which resulted in the accelerated approval of Serostim for the treatment of AIDS-associated wasting in 1996 (in this regard, Study GF-9037 was considered to be an obligatory Subpart H/Phase IV confirmatory study).*** Patients were randomized to full dose Serostim 0.1 mg/kg (up to 6 mg) daily, half-dose Serostim 0.1 mg/kg (up to 6 mg) every other day (alternating with placebo) and placebo during the 12 week, placebo controlled portion of the study. The primary objectives of the 12-36

week extension phase were to establish the durability of the clinical efficacy of Serostim, and to further assess the long-term safety and tolerability of Serostim.

Statistics:

The primary efficacy comparison was the change in BWO from baseline to Week 12 between the full dose Serostim group and the placebo group. ***Although not designated by the Sponsor in the original protocol as part of the primary efficacy objective, the difference in the change in BWO from baseline to Week 12 between the Serostim half-dose group and the placebo group was also considered to be of significant importance by the Division. If possible, BWO determinations were to be performed if patients prematurely discontinued from the study.*** The most important secondary efficacy comparison was the change in LBM (by BIS) from baseline to Week 12 between the full dose Serostim group and the placebo group, as well as between the half-dose Serostim group and the placebo group. Both the BWO and LBM analyses were performed in the intent-to-treat (ITT) population ***including*** patients with so-called "inconsistent" measurements (n=670 for BWO and n=650 for LBM).

Disposition:

A total of 757 patients were randomized and treated (full dose Serostim [n=253], half-dose Serostim [n=257] and placebo [n=247]). **~85% of treated patients completed the 12 week, placebo controlled portion of the study.** Five hundred and forty eight patients (~72% of the cohort originally randomized and treated) completed a total of 24 weeks on-study.

Demographics:

No statistically significant differences were observed across treatment groups with respect to multiple continuous and categorical demographic parameters, including age, sex, race (the majority of patients were Caucasian males), HIV RNA copies, CD4 T-cell counts, ongoing AIDS-related illnesses and BW. Most patients were homosexual, Caucasian males, and ~85% of patients in all treatment groups were receiving HAART therapy.

BWO Results from Placebo Controlled Portion of Study:

The mean maximum BWO until exhaustion increased after 12 weeks by 2.57 kJ in the Serostim 0.1 mg/kg daily group ($p<0.004$) and by 2.53 kJ in the Serostim 0.1 mg/kg every other day group ($p<0.004$) compared with placebo. Work until exhaustion was verified by analyzing the scores derived from the Borg RPE scale indicating that a satisfactory and uniform level of exhaustion had been obtained across all 3 treatment groups at both of these time points. Distribution analysis revealed that ~66% and 64% of full dose Serostim-

treated patients and half-dose Serostim-treated patients, respectively, were responders. On the other hand, ~46% of placebo-treated patients manifested an increase in BWO (compared with ~51% of placebo-treated patients in Study 5341 with respect to treadmill work output).

These results confirm the findings in the Sponsor's original, label-enabling Study 5341 which demonstrated a significant increase in treadmill work output after 12 weeks of treatment with Serostim 0.1 mg/kg/day (up to 6 mg) (of interest, ~84% of patients were responders with respect to treadmill work output in Study 5341), and also indicate that full dose and half-dose Serostim have almost identical effects with respect to stimulating an increase in BWO. The associated significant, dose proportional increase in LBM observed during this study (see ahead) enhances the validity of the BWO findings (even though this study did not confirm the statistically significant correlation between work output and LBM responses observed during Study 5341).

LBM Results from Placebo Controlled Portion of Study:

LBM increased after 12 weeks by 4.88 kg in the Serostim 0.1 mg/kg daily group ($p<0.0001$) and by 2.92 in the Serostim 0.1 mg/kg every other day group ($p<0.0002$) compared with placebo - a very clearcut dose-dependent response. Furthermore, LBM (by DEXA; at selected sites only) also significantly increased in a dose-dependent fashion after treatment with Serostim in the Sponsor's Evaluable Population.
Distribution analysis revealed that ~91% and 85% of full dose Serostim-treated patients and half-dose Serostim-treated patients, respectively, were responders. On the other hand, ~56% of placebo-treated patients manifested an increase in BWO (compared with ~51% of placebo-treated patients in Study 5341).

Of note, BCM (by BIS) increased in a dose-dependent fashion after treatment with Serostim in the Sponsor's Evaluable Population. Interestingly, the pairwise treatment differences (compared to placebo) in change from baseline in BCM for both doses of Serostim were ~50% of the treatment differences observed for LBM.

These results confirm the findings in the Sponsor's original, label-enabling Study 5341 which demonstrated a smaller (3.1 kg in Study 5341 vs. 4.88 kg in GF-9037), but still significant increase from baseline in LBM (compared to placebo) after 12 weeks of treatment with Serostim 0.1 mg/kg/day (up to 6 mg) (of interest, only ~65% of patients were responders with respect to LBM in Study 5341). It is somewhat reassuring that the between-group treatment differences on change from baseline in LBM by BIS and DEXA were similar. As stated above, the significant, dose proportional increase in LBM observed during this study enhances the validity of the BWO findings (even though this study did not confirm the statistically significant correlation between work output and LBM responses observed during Study 5341).

Comment Regarding BWO and LBM Results from Placebo Controlled Portion of Study:

In that 12 weeks of treatment with half-dose Serostim results in an identical BWO result as full dose Serostim, and a significant LBM result (~half as much as full dose Serostim), and substantially less adverse effects compared with full dose Serostim (see Section VI.A.5.6.1), it is the opinion of this Medical Officer that half-dose Serostim should be used more as initial therapy.

Analysis of Subgroups and Covariates:

Gender:

The mean differences from placebo in change from baseline in BWO and LBM for both active treatment groups was significant in men (and similar in magnitude to the combined study population), **but not in women. However, given the very small number of women in the study population, and the absence of a significant treatment-by-gender interaction in the ANOVA performed on the entire ITT study population comparing changes from baseline in BWO and LBM between each of the active treatment arms and the placebo group in men vs. women, the lack of a response in women must be interpreted with caution.**

Race/Ethnicity:

The treatment-by-race interaction in the ANOVA performed on the entire ITT study population comparing changes from baseline in BWO (but not LBM) between each of the active treatment arms and the placebo group in Caucasians vs. non-Caucasians (constituting ~25% of each treatment arm) was statistically significant. The interaction was qualitative in nature, i.e. the mean change from baseline in BWO was greater in Serostim-treated patients compared with placebo-treated patients amongst Caucasians and Asians; **in contrast, the mean change from baseline in BWO was greater in placebo-treated patients compared with Serostim-treated patients amongst African Americans and Hispanics.**

However, in that 1) there is no biologic plausibility for this observation; 2) this is a *post hoc* exploratory analysis; and 3) this interaction is not seen for LBM, this observation must be interpreted with caution. For the same reasons, this Medical Officer does not feel that an additional study comparing Caucasians and non-Caucasians is necessary nor is it essential to accrue BWO data (in addition to LBM data) in the Registry that the Sponsor plans to create for patients with AIDS-associated wasting treated with Serostim (see Section VI.A.5.5.8).

Use of HAART:

The treatment-by-HAART interaction in the ANOVA performed on the entire ITT study population comparing changes from baseline in BWO

(but not LBM) between each of the active treatment arms and the placebo group in HAART users vs. HAART non-users was weakly statistically significant. These data indicate that the interaction was qualitative in nature, i.e. the mean change from baseline in BWO was greater in Serostim-treated patients compared with placebo-treated patients amongst HAART users; **in contrast, the mean change from baseline in BWO was greater in placebo-treated patients compared with Serostim-treated patients amongst HAART non-users.**

Such an interaction is theoretically biologically plausible, i.e. HAART therapy by itself could result in improved BWO/LBM. **Nonetheless, given that 1) there were very few patients (~10-13%) not receiving HAART; 2) this is a *post hoc* exploratory analysis; and 3) this interaction is not seen for LBM, this observation must be interpreted with caution.**

Other Potential Covariates:

A lower baseline body weight and lower baseline BMI were significant predictors of a positive BWO response after treatment with full dose (but not half-dose) Serostim. However, regression analyses did NOT demonstrate significant inverse linear relationships. No other significant predictor of response was discovered amongst BWO and LBM responders.

Analysis of Other Secondary Efficacy Parameters During the Placebo Controlled Portion of the Study:

Total Fat Mass:

Total fat mass (by DEXA) decreased after 12 weeks by 1.75 kg in the Serostim 0.1 mg/kg daily group ($p<0.0001$) and by 1.28 kg in the Serostim 0.1 mg/kg every other day group ($p<0.0002$) compared with placebo - **a clearcut dose-dependent response.** The decreases in total fat mass were paralleled by dose-dependent decreases in truncal fat mass (by DEXA), limb fat mass (by DEXA) and the truncal fat mass/limb fat mass ratio.

The decreases in total fat mass observed in this study confirm similar results from Study 5341, and are readily explained by the powerful, well known lipolytic effect of rhGH.

BW:

BW increased after 12 weeks by 2.1 kg in the Serostim 0.1 mg/kg daily group ($p<0.0001$) and by 1.49 kg in the Serostim 0.1 mg/kg every other day group ($p<0.0002$) compared with placebo - **a clearcut dose-dependent response.** The treatment effect with respect to BW was ~50% of that observed in LBM.

The increases in BW observed in this study confirm similar results from Study 5341 (treatment difference was 1.6 kg for full dose Serostim vs. placebo).

QOL Measurements:

With regard to the BACRI: When the mean scores (Question 7 by itself and BACRI-7 composite score) from either Serostim group were compared with the mean score from the placebo group, the differences were significant. In addition, the differences between the mean scores observed in the full dose and half-dose Serostim groups were also significant, i.e. an apparent dose related improvement. The Sponsor therefore concluded that treatment with Serostim resulted in an improvement in an individual's perceptions of [redacted] and proposed the following wording for the Package Insert [redacted] b(4)

With regard to the MHSA: The Sponsor observed significant improvement in the patients' perceptions of their state of general health. In addition, although patients described a significant increase in bodily pain (with full dose Serostim compared with placebo), this increase in bodily pain did not interfere with their normal activities/work. [redacted] b(4)

As alluded to earlier, consultation was obtained by this Medical Officer from the Agency's SEALD team. The SEALD team reviewer was extremely critical of the QOL instruments utilized by the Sponsor, and the Sponsor's proposed wording for the Package Insert. Selected comments (some verbatim and some paraphrased by this Medical Officer) of the SEALD team reviewer are summarized below.

With regard to the BACRI:

- Documentation of the development and validation of the BACRI was **not included in the submission.** Since this documentation was not available for review, we **cannot determine conclusively that an** [redacted] b(4)
- Since the **BACRI does not capture any adverse impact of treatment, allowing a claim of** [redacted] **is unbalanced,** i.e. Serostim treatment results in well established adverse effects that are not captured by the BACRI.
- Utilization of Question 7 (a single global treatment benefit item) can be used to interpret other patient-reported findings (e.g., it gives us confidence that the BACRI-7 is a meaningful endpoint since the global item showed the same type of result), but it **does not**

provide support for claims [redacted] because the determinants of that perception cannot be ascertained. b(4)

- The literature does support the use of the BACRI-7 as a measure of subjective recovery from anorexia/cachexia symptoms (37).

With regard to the MHSA:

- Documentation of the development and validation of the MHSA was not included in the submission. [redacted] the absence of documentation of the psychometric and other measurement properties of this instrument. b(4)
- The MHSA demonstrated very small differences in mean scores at Week 12 between treatment groups.

With regard to both the BACRI and the MHSA:

- According to the emerging standards in patient-reported outcomes measurement, the BACRI and MHSA would not be called [redacted] measures, unless it could be documented that these measures captured all of the concepts defined by patients to represent the impact of treatment on their underlying condition. The BACRI does not capture any of the negative impact of treatment with rhGH. The MHSA does capture pain, but does not capture patient-reported symptoms associated with fluid retention or abnormal fasting blood glucose levels (well established adverse effects associated with rhGH therapy). Therefore, broad claims cannot be justified. b(4)
- Documentation of linguistic validation of the multiple language versions used in this trial was not referenced.

Labeling recommendations of the SEALD team reviewer and final QOL labeling language agreed to by the Division and the Sponsor:

- If BACRI results are used in labeling, the BACRI should be referenced by name and we suggest omitting [redacted] b(4)
- The only result that should be given is that of the BACRI-7 which was developed and validated to measure patients' perceptions of the impact of treatment on their anorexia/cachexia symptoms.
- [redacted] b(4)
- Taking into account the recommendations of the SEALD team reviewer, the final QOL labeling language agreed to by the Division and the Sponsor is as follows: Patients' perceptions of the impact of 12 weeks of treatment on their wasting symptoms as assessed by the Bristol-Meyers Anorexia/Cachexia Recovery Instrument improved with both doses of Serostim in Clinical Trial 2.

Efficacy Results During the Extension Phase of the Study (Descriptive Statistics Only):

BWO, LBM and BW:

Approximately 72% of the patients originally randomized and treated completed 24 weeks of treatment.

BWO: The increase in BWO in 200 patients (142 patients who received full dose Serostim continuously for 24 weeks and 58 patients who received half-dose Serostim continuously for 24 weeks) who had "consistent" BWO measurements at baseline, Week 12 and Week 24 was similar at Week 12 for patients who received either full dose or half-dose Serostim (consistent with the formal statistical analysis presented earlier). **However, the additional increase in BWO between Week 12 and Week 24 was somewhat greater in the continuous half-dose patients than in the continuous full dose patients.**

LBM: Dose-dependent increases in LBM at Week 12 were observed in 214 patients (145 patients who received full dose Serostim continuously for 24 weeks and 69 patients who received half-dose Serostim continuously for 24 weeks) who had "consistent" LBM measurements at baseline, Week 12 and Week 24. **However, the additional increase in LBM between Week 12 and Week 24 was very modest in patients treated continuously with both full dose and half-dose Serostim. The dose response effect was still apparent at Week 24.**

BW: A dose-dependent increase in BW was also maintained after 24 weeks of treatment.

The 24 week results for BWO, LBM and BW described above indicate that the effect of both doses of Serostim was maintained through 24 weeks, i.e., that the response achieved at Week 12 was durable.

VI.A.5.5.7 Efficacy - Conclusions

- ~85% of treated patients completed the 12 week, placebo controlled portion of the study - an acceptable completion rate.
- Most patients were homosexual, Caucasian males, and ~85% of patients in all treatment groups were receiving HAART therapy.
- **The BWO results in this study confirm the findings in the Sponsor's original, label-enabling Study 5341 which demonstrated a significant increase in treadmill work output after 12 weeks of treatment with Serostim 0.1 mg/kg/day (up to 6 mg) and also indicate that full dose and half-dose Serostim have almost identical effects with respect to stimulating an increase in BWO.**
- **The LBM results in this study confirm the findings in the Sponsor's original, label-enabling Study 5341 which demonstrated a smaller (3.1 kg in Study 5341 vs. 4.88 kg in GF-9037), but still significant increase from baseline in**

LBM (compared to placebo) after 12 weeks of treatment with Serostim 0.1 mg/kg/day (up to 6 mg). It is somewhat reassuring that the between-group treatment differences on change from baseline in LBM by BIS and DEXA were similar.

- The significant, dose proportional increase in LBM observed during this study enhances the validity of the BWO findings (even though this study did not confirm the statistically significant correlation between work output and LBM responses observed during Study 5341).
- **In that 12 weeks of treatment with half-dose Serostim results in an identical BWO result as full dose Serostim, and a significant LBM result (~half as much as full dose Serostim), and substantially less adverse effects compared with full dose Serostim, it is the opinion of this Medical Officer that half-dose Serostim should be used more as initial therapy.**
- Given the very small number of women in the study population, and the absence of a significant treatment-by-gender interaction in the ANOVA performed on the entire ITT study population, **the lack of a response in women must be interpreted with caution.**
- **The treatment-by-race interaction** in the ANOVA performed on the entire ITT study population comparing changes from baseline in BWO between each of the active treatment arms and the placebo group in Caucasians vs. non-Caucasians (constituting ~25% of each treatment arm) **was statistically significant.** The interaction was qualitative in nature. **However, in that 1) there is no biologic plausibility for this observation; 2) this is a post hoc exploratory analysis; and 3) this interaction is not seen for LBM, this observation must be interpreted with caution. For the same reasons, this Medical Officer does not feel that an additional study comparing Caucasians and non-Caucasians is necessary nor is it essential to accrue BWO data (in addition to LBM data)** b(4)
- The treatment-by-HAART interaction in the ANOVA performed on the entire ITT study population comparing changes from baseline in BWO between each of the active treatment arms and the placebo group in HAART users vs. HAART non-users was weakly statistically significant. The interaction was qualitative in nature. ***Such an interaction is theoretically biologically plausible, i.e. HAART therapy by itself could result in improved BWO/LBM. Nonetheless, given that 1) there were very few patients (~10-13%) not receiving HAART; 2) this is a post hoc exploratory analysis; and 3) this interaction is not seen for LBM, this observation must be interpreted with caution.***
- No significant predictors of response was discovered amongst BWO and LBM responders.
- The decreases in total fat mass observed in this study confirm similar results from Study 5341, and are readily explained by the powerful, well known lipolytic effect of rhGH. The decreases were dose-dependent.
- The increases in BW observed in this study confirm similar results from Study 5341. The increases were dose-dependent.

- The SEALD team reviewer found significant faults with the QOL instruments utilized by the Sponsor and recommended omitting the terms [redacted] from the Package Insert proposed by the Sponsor. This was accomplished (see ahead to Efficacy Recommendations). b(4)
- The 24 week results for BWO, LBM and BW indicate that the effect of both doses of Serostim was maintained through 24 weeks, i.e., that the response achieved at Week 12 was durable.

VI.A.5.5.8 Efficacy - Recommendations

- This Medical Officer strongly endorses the Sponsor's intention to create [redacted] b(4)

- See third bullet under Safety Recommendations. The CLINICAL STUDIES section of the most recently proposed Package Insert was modified by this Medical Officer to reflect that 12 weeks of treatment with half-dose Serostim results in an identical BWO result as full dose Serostim, and a significant LBM result (~half as much as full dose Serostim).

- The CLINICAL STUDIES section of the most recently proposed Package Insert was severely edited by this Medical Officer (after consultation with the Agency's SEALD team) to more accurately and appropriately reflect the results of the QOL assessments performed by the Sponsor.

b(4)

VI.A.5.6 Safety Results for Study GF [redacted] (equivalent to Integrated Summary of Safety [ISS] in that only 1 study was included in the Sponsor's submission)

VI.A.5.6.1 Database

All 757 patients in the study who were randomized to active treatment and received at least 1 injection of Serostim or placebo were included in the safety database. With respect to the safety data presented and analyzed in this study report, the datalock date was in 4/02.

VI.A.5.6.2 Disposition of Patients

See Section VI.A.5.1.1.

VI.A.5.6.3 Extent of Exposure

During the 12 week, placebo controlled portion of the study, the 253 patients randomized and treated with Serostim 0.1 mg/kg daily (up to 6 mg/day) received an average daily dose of 5.6 ± 0.7 mg and, taken as a group, were exposed to daily Serostim dosing for a total of 53.4 exposure years, while the 257 patients randomized and treated with Serostim 0.1 mg/kg (up to 6 mg/day) alternating with placebo received an average daily dose of 2.9 ± 0.3 mg and, taken as a group, were exposed to alternate day Serostim treatment for a total of 56.4 exposure years.

During the extension phase of the study, 521 patients received full dose Serostim therapy for a total of 150.5 exposure years, while 125 patients received alternate day Serostim treatment for a total of 73.2 exposure years.

VI.A.5.6.4 Demographics

See Section VI.A.5.2.

VI.A.5.6.5 Deaths

Six patients died during the study or very shortly after study completion: 2 patients during the placebo controlled portion of the study (secondary to "progression of underlying disease"/cirrhosis and a heroin overdose); 3 patients during the extension phase of the study (secondary to chest pain/cardiac arrest, septic shock, and cerebral lymphoma/nadir sepsis); and 1 patient 30 days after discontinuing study drug (secondary to pneumonia/respiratory failure). **None of these deaths were felt to be related to the administration of Serostim by the Sponsor or this Medical Officer.**

VI.A.5.6.6 Adverse Events

VI.A.5.6.6.1 Serious Adverse Events (SAEs)

VI.A.5.6.6.1.1 SAEs During the Placebo Controlled Phase of Study GF-9037 (Weeks 0-12)

A total of 37 SAEs were reported by 32 patients during the placebo controlled phase of the study. Seventeen SAEs were reported by 15 patients receiving full dose Serostim; 11 SAEs were reported by 9 patients receiving half-dose Serostim; and 9 SAEs were reported by 8 patients treated with placebo. Seven SAEs reported by 7 patients during the placebo controlled phase of the study may have resulted from AIDS-defining/related opportunistic infections and are discussed separately in Section VI.A.5.6.6.1.3 ahead. One patient receiving

half-dose Serostim reported severe gynecomastia as an SAE (see Section VI.A.5.6.6.5.6 ahead). Strangely, neither of the 2 patients discontinued during the placebo controlled phase of the study due to new onset diabetes mellitus and hyperglycemia, respectively, were designated as having a SAE. A review of all of the other SAEs reported during this portion of the study was not revealing.

VI.A.5.6.6.1.2 SAEs During the Extension Phase of Study GF-9037 (After Week 12)

Five hundred and forty eight patients received either full dose (~80%) or half-dose Serostim (~20%) for an additional 12 weeks, and 177 patients received either dose of Serostim for an additional 36 weeks. A total of 51 SAEs were reported by 34 patients during the extension phase of the study. Thirty two SAEs were reported by 22 patients receiving full dose Serostim, and 19 SAEs were reported by 12 patients receiving half-dose Serostim. More SAEs were reported by patients receiving full dose Serostim; however, as noted above, the vast majority of the patients (~80%) entering and completing the first 12 weeks of the extension phase were receiving full dose Serostim. Nine SAEs reported by 9 patients during the extension phase of the study may have resulted from AIDS-defining/related opportunistic infections and are discussed separately in Section VI.A.5.6.6.1.3 ahead. Four of the SAE patients reported during the extension phase were diagnosed with a malignancy (squamous cell carcinoma in situ, basal cell carcinoma, Hodgkin's lymphoma [in fact, diagnosed 6 months after completion of therapy], and acute myelogenous leukemia [in fact, diagnosed 7 months after completion of therapy]; 4 of the 5 malignancies diagnosed during the study; see Section VI.A.5.6.6.6.2 ahead; all of these patients were treated with full dose Serostim during the extension phase). Two SAE patients were discontinued from the study because of new onset diabetes mellitus requiring hospitalization (1 in the full dose group and 1 in the half-dose group; see Table 40 ahead). Surprisingly, 4 other patients (all receiving full dose Serostim) who were discontinued from the study during the extension phase because of glucose intolerance were not designated as having SAEs (see Table 40 ahead). A review of all of the other SAEs reported during this portion of the study was not revealing.

VI.A.5.6.6.1.3 SAEs (and Treatment Emergent Adverse Events [TEAEs]) Possibly Resulting From AIDS-Defining/Related Opportunistic Infections During Both the Placebo Controlled and Extension Phases of the Study

Seven SAEs reported by 7 patients during the placebo controlled phase of the study possibly resulted from AIDS-defining/related opportunistic infections (see Table 12.9 in the Sponsor's submission). As can be seen in Table 27, these infections did not occur predominantly in the Serostim-treated groups.

Eight SAEs reported by 8 patients during the extension phase of the study possibly resulted from AIDS-defining/related opportunistic infections (derived by this Medical Officer from Table 12.10 in the Sponsor's submission). Five SAEs were reported by patients receiving full dose Serostim (meningitis [2]; pneumonia [1]; pneumocystis carinii infection [1]; herpes zoster [1]) and 3 SAEs were reported by patients receiving half-dose Serostim (cryptococcal meningitis [1]; pneumonia [2]).

Table 27

SAEs Possibly Resulting From AIDS-Defining/Related Opportunistic Infections During the 12 Week, Placebo Controlled Phase of Study GF-9037

Diagnosis	Placebo		Serostim 0.1 mg/kg every other day		Serostim 0.1 mg/kg daily	
	Patients	Events	Patients	Events	Patients	Events
NEUROSYPHILIS	0	0	1	1	0	0
HERPES ZOSTER	1	1	0	0	0	0
PNEUMOCYSTIS CARINII INFECTION	1	1	0	0	0	0
PNEUMONIA	2	2	1	1	1	1

Table 28 compares the incidence of possibly AIDS-defining/related opportunistic infections reported as TEAEs during the placebo controlled phase of the study (see Table 12.7 in the Sponsor's submission). **With the apparent exception of herpes simplex infection, these infections did not occur predominantly in the Serostim-treated groups.**

The incidence of possibly AIDS-defining/related opportunistic infections reported as TEAEs during the non-placebo controlled extension phase of the study was not analyzed by this Medical Officer.

Table 28

TEAEs Possibly Resulting From AIDS-Defining/Related Opportunistic Infections During the 12 Week, Placebo Controlled Phase of Study GF-9037

Diagnosis	Placebo		Serostim 0.1 mg/kg every other day		Serostim 0.1 mg/kg daily	
	Patients	Events	Patients	Events	Patients	Events
CANDIDIASIS	7	7	8	10	5	5
PARASITIC INFECTION	1	1	0	0	3	3
CYTOMEGALOVIRUS INFECTION	0	0	0	0	1	1
HERPES SIMPLEX	2	2	7	7	6	6
HERPES ZOSTER	2	2	1	1	1	1
PNEUMOCYSTIS CARINII INFECTION	1	1	0	0	0	0
PNEUMONIA	3	3	5	5	3	3

VI.A.5.6.6.2 Adverse Events Leading to Discontinuation of Study Drug Treatment and Study Termination During Study GF-9037

VI.A.5.6.6.2.1 Adverse Events Leading to Discontinuation of Serostim or Placebo Treatment and Study Termination During the Placebo Controlled Phase of Study GF-9037 (Weeks 0-12)

Seven hundred and fifty seven patients were exposed to either full dose or half-dose Serostim (n=510), or placebo (n=247), during the 12 week, placebo controlled phase of Study GF-9037. A total of 46 patients were discontinued due to adverse events, 26 (10.3%) in the full dose Serostim group, 17 in the half-dose Serostim group (6.6%), and 3 (1.2%) in the placebo group. Table 29 (created by this Medical Officer) and Table 30 (from the Sponsor's submission) delineate the specific adverse events which led to discontinuation of these patients from the study.

In the opinion of this Medical Officer, 18 of the 26 patients who were discontinued from the full dose Serostim group (~69%) manifested adverse events which were more than likely related to Serostim therapy (2 patients with significant glucose intolerance [see Table 40 ahead]; 8 patients with important arthralgia/musculoskeletal pain/skeletal pain; 5 patients with consequential edema; and 7 patients with symptomatic carpal tunnel syndrome [n=5]/paraesthesias [n=2]). Four of these 18 patients manifested combinations of the abovedescribed, Serostim-related adverse effects. In addition, 2 of the 26 patients were discontinued from the full dose Serostim group because of significant hypertension, which may have been related to Serostim therapy.

In the opinion of this Medical Officer, 10 of the 17 patients who were discontinued from the half-dose Serostim group (~59%) manifested adverse events which were more than likely related to Serostim therapy (none with glucose intolerance; 6 patients with important arthralgia/myalgia; 2 patients with consequential edema; and 3 patients with symptomatic carpal tunnel syndrome [n=1]/paraesthesias [n=2]). One of these 10 patients was discontinued with arthralgia and edema.

More of these adverse events most likely related to Serostim therapy leading to discontinuation during the placebo controlled phase of the study occurred when either dose of Serostim was first initiated (e.g., study onset) than during more extended treatment with either half-dose or full dose Serostim.

It is apparent from these data that a dose response relationship exists across the 3 treatment groups with respect to the development of adverse events leading to study drug discontinuation, in particular adverse events most likely related to Serostim, i.e. administration of the full dose of Serostim resulted in larger

numbers of patients with musculoskeletal complaints, edema, carpal tunnel tunnel, and glucose intolerance than treatment with the half-dose of Serostim, and treatment with both doses of Serostim resulted in these kinds of adverse events much more frequently than placebo administration. See Section VI.A.5.8.1 for further discussion of this issue.

Table 29

Discontinuations Due to Adverse Events by Treatment Group up to Week 12

Patient Number	Disc. Study Day	Disposition Category	Specific Adverse Event	Likely Rel. to Serostim
Full Dose Serostim (n=26)				
	39	OTHER	DIABETES MELLITUS (severe)	YES
	42	ADVERSE EVENT	HYPERGLYCEMIA	YES
	57	ADVERSE EVENT	SKELETAL PAIN	YES
	61	PATIENT DECISION	MUSCULOSKELETAL PAIN (severe) NEUROPATHY (severe)	YES NO
	51	PERSISTENT TOXICITY ACCORDING TO THE DOSE ADJUSTMENT ALGORITHMS	ARTHRALGIA (began Day 31)	YES
	80	PATIENT DECISION	ARTHRALGIA	YES
	3	ADVERSE EVENT	ARTHRALGIA	YES
	29	PATIENT DECISION	ARTHRALGIA EDEMA, PERIPHERAL INSOMNIA	YES YES NO
	26	PATIENT DECISION	ARTHRALGIA (severe) EDEMA	YES YES
	49	PATIENT DECISION	ARTHRALGIA (severe) EDEMA, PERIPHERAL (severe; twice) CARPAL TUNNEL SYNDROME	YES YES YES
	77	ADVERSE EVENT	EDEMA, PERIPHERAL (severe; twice)	YES
	9	PATIENT DECISION	EDEMA, GENERALIZED NEUROPATHY PERIPHERAL	YES NO
	31	ADVERSE EVENT	CARPAL TUNNEL SYNDROME (severe)	YES
	68	OTHER	CARPAL TUNNEL SYNDROME	YES
	38	PERSISTENT TOXICITY ACCORDING TO THE DOSE ADJUSTMENT ALGORITHMS	CARPAL TUNNEL SYNDROME (began Day 18)	YES
	79	PATIENT DECISION	CARPAL TUNNEL SYNDROME (severe)	YES
	63	PATIENT DECISION	PARAESTHESIA	YES
	45	PERSISTENT TOXICITY ACCORDING TO THE DOSE ADJUSTMENT ALGORITHMS	PARAESTHESIA (began Day 36)	YES

b(6)

63	PERSISTENT TOXICITY ACCORDING TO THE DOSE ADJUSTMENT ALGORITHMS	HYPERTENSION (began Day 43)	POSSIBLY
20	ADVERSE EVENT	HYPERTENSION PALPITATIONS SWEATING INCREASED	POSSIBLY UNLIKELY POSSIBLY
17	PATIENT DECISION	TACHYCARDIA (Severe)	UNLIKELY
31	ADVERSE EVENT	TACHYCARDIA	UNLIKELY
26	PATIENT DECISION	TACHYCARDIA	UNLIKELY
12	PATIENT DECISION	DEPRESSION	UNLIKELY
64	PERSISTENT TOXICITY ACCORDING TO THE DOSE ADJUSTMENT ALGORITHMS	NAUSEA/VOMITING (began Day 3)	UNLIKELY
86	ADVERSE EVENT	SEPSIS INCREASED ALK PHOS	UNLIKELY

Half-Dose Serostim (n=17)

83	PERSISTENT TOXICITY ACCORDING TO THE DOSE ADJUSTMENT ALGORITHMS	MYALGIA (began Day 31)	YES
27	PERSISTENT TOXICITY ACCORDING TO THE DOSE ADJUSTMENT ALGORITHMS	ARTHRALGIA (began Day 9)	YES
42	PATIENT DECISION	ARTHRALGIA	YES
41	ADVERSE EVENT	ARTHRALGIA (severe) ARTHROSIS (severe)	YES YES
34	PATIENT DECISION	ARTHRALGIA GASTRITIS	YES NO
89	ADVERSE EVENT	ARTHRALGIA (severe) EDEMA, PERIPHERAL (twice)	YES YES
29	PATIENT DECISION	EDEMA, PERIPHERAL	YES
40	ADVERSE EVENT	CARPAL TUNNEL SYNDROME	YES
45	PATIENT DECISION	PARAESTHESIA (severe)	YES
72	ADVERSE EVENT	PARAESTHESIA DEPRESSION	YES NO
40	ADVERSE EVENT	PERIPHERAL NEUROPATHY (severe)	UNLIKELY
12	PATIENT DECISION	DIZZINESS GAIT ABNORMAL	UNLIKELY
12	PATIENT DECISION	ANOREXIA	UNLIKELY
28	PATIENT DECISION	ANOREXIA ABDOMEN ENLARGED	UNLIKELY
44	MISSING MORE THAN 10 TOTAL DOSES DURING WEEKS 0 - 12	PYELONEPHRITIS	UNLIKELY
57	ADVERSE EVENT	DEEP VEIN THROMBOPHLEBITIS	UNLIKELY
85	ADVERSE EVENT	DEPRESSION SUICIDE ATTEMPT (severe/life threatening)	UNLIKELY

Placebo (n=3)

80	PATIENT DECISION	HERPES ZOSTER (severe/life threatening)	N/A
20	PATIENT DECISION	EDEMA, GENERALIZED (severe) MYALGIA (severe)	N/A
82	ADVERSE EVENT	LEG PAIN PARAESTHESIA DEPRESSION	N/A

b(6)

Table 30

Discontinuations Due to Adverse events by Treatment Group up to Week 12

	Placebo (n=247)	Half-Dose Serostim (n=257)	Full Dose Serostim (n=253)	All Patients (n=757)
ADVERSE EVENT	**n (%)**	**n (%)**	**n (%)**	**n (%)**
TOTAL PATIENTS	**3 (1.2)**	**17 (6.6)**	**26 (10.3)**	**46 (6.1)**
BODY AS A WHOLE - GENERAL DISORDERS	1 (0.4)	4 (1.6)	9 (3.6)	14 (1.8)
ABDOMEN ENLARGED	0	1 (0.4)	0	1 (0.1)
CARPAL TUNNEL SYNDROME	**0**	**1 (0.4)**	**5 (2.0)**	**6 (0.8)**
LEG PAIN	1 (0.4)	0	0	1 (0.1)
EDEMA	**0**	**0**	**1 (0.4)**	**1 (0.1)**
EDEMA, PERIPHERAL	**0**	**2 (0.8)**	**3 (1.2)**	**5 (0.7)**
SWEATING INCREASED	0	0	1 (0.4)	1 (0.1)
CARDIOVASCULAR DISORDERS, GENERAL	0	0	2 (0.8)	2 (0.3)

HYPERTENSION				
CENTRAL/PERIPHERAL NERVOUS SYSTEM DISORDERS				
DIZZINESS				
GAIT ABNORMAL				
NEUROPATHY				
PERIPHERAL NEUROPATHY				
PARAESTHESIA				
GASTROINTESTINAL SYSTEM DISORDERS				
GASTRITIS				
NAUSEA				
VOMITING				
HEART RATE AND RHYTHM DISORDERS				
PALPITATION				
TACHYCARDIA				
METABOLIC AND NUTRITIONAL DISORDERS				
DIABETES MELLITUS				
HYPERGLYCEMIA				
EDEMA, GENERALIZED				
INCREASED ALKALINE PHOSPHATASE				
MUSCULOSKELETAL SYSTEM DISORDERS				
ARTHRALGIA				
ARTHROSIS				
MUSCULOSKELETAL PAIN				
MYALGIA				
SKELETAL PAIN				
PSYCHIATRIC DISORDERS				
ANOREXIA				
DEPRESSION				
INSOMNIA				
SUICIDE ATTEMPT				
RESISTANCE MECHANISM DISORDERS				
HERPES ZOSTER				
SEPSIS				
URINARY SYSTEM DISORDERS				
PYELONEPHRITIS				
VASCULAR (EXTRACARDIAC) DISORDERS				
DEEP VEIN THROMBOPHLEBITIS				

VI.A.5.6.6.2.2 Adverse Events Leading to Discontinuation of Full Dose or Half-Dose Serostim Treatment and Study Termination During the Extension Phase of Study GF-9037 (After Week 12)

During the extension phase, 65 patients were discontinued from the study (25 patients in the placebo to full dose group, 12 patients in the half-dose to full dose group, and 16 patients in the full dose to full dose group, but only 5 patients in the placebo to half-dose group and 7 patients in the half-dose to half-dose group. The reasons for discontinuation after Week 12 included arthralgia (15), peripheral edema (9), carpal tunnel syndrome (4) and hyperglycemia (n=6; see Table 40 ahead), and were therefore similar to the termination reasons observed during the first 12 weeks of the study. In addition, 6 patients were discontinued due to hypertriglyceridemia.

More of these adverse events most likely related to Serostim therapy leading to discontinuation during the extension phase of the study occurred when either dose of Serostim was first initiated (e.g., when placebo patients were switched to full dose or half-dose at the beginning of the extension phase) or after an increase in dose (e.g., when half-dose patients were switched to full dose at the

beginning of the extension phase under the amended protocol) than during more extended treatment with either half-dose or full dose Serostim.

These findings tend to support the observation that treatment with full dose Serostim results in more typical rhGH-related adverse effects than half-dose Serostim. However, once again, given that the majority (~80%) of the patients entering and completing the first 12 weeks of the extension phase were receiving full dose Serostim and the lack of a placebo group, these observations should be interpreted with caution.

VI.A.5.6.6.3 Analysis of Protocol-Directed Dose Interventions (Based on Observed Adverse Effects/Events)

VI.A.5.6.6.3.1 Analysis of Protocol-Directed Dose Interventions (Based on Observed Adverse Effects/Events) During the Placebo Controlled Phase of Study GF-9037 (Weeks 0-12)

During the placebo controlled phase of the study, 22.5% of patients in the full dose Serostim group, 10.5% of patients in the half-dose Serostim group, and 6.9% of patients in the placebo group required 1 or more dose reductions, and 11.9% of patients in the full dose Serostim group compared with 4.3% of patients in the half-dose Serostim group required 1 or more dose interruptions (see Table 31). As seen in Table 32, the most common reasons for dose reductions/interruptions during the placebo controlled phase of the study were similar to those which resulted in discontinuation (described above in Section VI.A.5.6.6.2.1), i.e. arthralgia/myalgia, edema, carpal tunnel syndrome and hyperglycemia. **Once again, a clearcut dose response is evident. See Section VI.A.5.8.1 for further discussion of this issue.**

Table 31

Number of Patients with Dose Reductions/Interruptions up to Week 12 in All Treated Patients*

	Placebo	Serostim 0.1 mg/kg qod	Serostim 0.1 mg/kg daily
	n=247	n=257	n=253
Variable	n (%)	n (%)	n (%)
Patients With 1 or More Dose Reductions			
Yes	17 (6.9)	27 (10.5)	57 (22.5)
No	230 (93.1)	230 (89.5)	196 (77.5)

Patients With 1 or More Doses Held			
Yes	**10 (4.0)**	**11 (4.3)**	**30 (11.9)**
No	237 (96.0)	246 (95.7)	223 (88.1)

*Patients could have more than 1 reason to be included in this table, e.g. a dose reduction followed by 1 or more doses held.

Table 32

Reasons for Dose Reductions/Interruptions up to Week 12 in All Treated Patients**

Variable	Placebo n=247 n (%)	Serostim 0.1 mg/kg qod n=257 n (%)	Serostim 0.1 mg/kg daily n=253 n (%)
Patients With 1 or More Dose Reductions			
Yes	**17 (6.9)**	**27 (10.5)**	**57 (22.5)**
No	**230 (93.1)**	**230 (89.5)**	**196 (77.5)**
Hyperglycemia***	**5*****	**2*****	**3*****
Edema, Peripheral	**0**	**3**	**19**
Arthralgias/Myalgias	**2**	**9**	**26**
Carpal Tunnel Syndrome	**0**	**1**	**7**
Gynecomastia	**0**	**1**	**1**
Hypertriglyceridema	**2**	**5**	**3**
Headache	0	0	2
Weight loss	3	2	0
Nausea/Vomiting	2	0	1
Others	5	7	5
Patients With 1 or More Doses Held			
Yes	**10 (4.0)**	**11 (4.3)**	**30 (11.9)**
No	**237 (96.0)**	**246 (95.7)**	**223 (88.1)**
Hyperglycemia	**0**	**0**	**1**
Edema, Peripheral	**0**	**2**	**9**
Arthralgias/Myalgias	**3**	**3**	**9**
Carpal Tunnel Syndrome	**0**	**0**	**1**
Gynecomastia	**0**	**0**	**1**
Hypertriglceridema	**0**	**0**	**0**
Headache	0	0	2
Weight loss	1	0	0
Nausea/Vomiting	0	1	1
Pneumonia	0	1	1
Other*	7	5	10

***Other includes: hypertension, palpitations, tachycardia, paroxysmal atrial fibrillation, non-compliance, incorrect dose, ran out of drug, difficulty injecting drug,**

****Patients may have reported more than 1 reason for the dose intervention.**

*****See Table 40 ahead.**

VI.A.5.6.6.3.2 Analysis of Protocol-Directed Dose Reductions (Based on Observed Adverse Effects/Events) During the Extension Phase of Study GF-9037 (After Week 12)

As seen in Table 33, a substantially larger number of patients receiving full dose Serostim during the extension phase of the study required 1 or more dose reductions or dose interruptions. However, once again, given that the majority (~80%) of the patients entering and completing the first 12 weeks of the extension phase were receiving full dose Serostim and the lack of a placebo group, these observations should be interpreted with caution.

Table 33

Number of Patients with Dose Reductions/Interruptions After Week 12 During the Extension Phase in All Treated Patients

Variable	Placebo to Half-Dose Serostim n=44 n (%)	Placebo to Full Dose Serostim n=182 n (%)	Half-Dose to Half-Dose Serostim n=81 n (%)	Half-Dose to Full Dose Serostim n=138 n (%)	Full-Dose to Full Dose Serostim n=201 n (%)
Patients With 1 or More Dose Reductions					
Yes	5 (11.4)	41 (22.5)	12 (14.8)	14 (10.1)	26 (12.9)
No	39 (88.6)	141 (77.5)	69 (85.2)	124 (89.9)	175 (87.1)
Patients With 1 or More Doses Held					
Yes	2 (4.5)	18 (9.9)	3 (3.7)	10 (7.2)	12 (6.0)
No	42 (95.5)	164 (90.1)	78 (96.3)	128 (92.8)	189 (94.0)

*Patients could have more than 1 reason to be included in this table, e.g. a dose reduction followed by 1 or more doses held.

VI.A.5.6.6.4 Treatment-Emergent Adverse Events (TEAEs)

VI.A.5.6.6.4.1 TEAEs During the Placebo Controlled Phase of Study GF-9037 (Weeks 0-12)

During the placebo controlled phase of the study, 608 adverse events were reported in 188 patients (76.1% of 247 patients) treated with placebo, 796 adverse events in 197 patients (76.7% of 257 patients) treated with half-dose Serostim, and 971 adverse events in 216 patients (85.4% of 253 patients) treated with full dose Serostim. In each group, the vast majority of adverse events were deemed mild to moderate in severity. SAEs have already been discussed in Section VI.A.5.6.6.1. Table 34 lists clinical adverse events which occurred during the first 12 weeks of Study GF-9037 in at least 5% of the patients in any 1 of the 3 treatment groups, without regard to causality assessment. **In this table, adverse events occurring more frequently in the Serostim-treated groups and considered by this Medical Officer to be more than likely related to the effects of Serostim are highlighted in bold and summarized as follows: arthralgia** (36.4% in the full dose Serostim group, 24.5% in the half-dose Serostim group and 11.3% in the placebo group), **myalgia** (30.4% in the full dose Serostim group, 17.9% in the half-dose Serostim group and 11.7% in the placebo group), **peripheral edema** (26.1% in the full dose Serostim group, 11.3% in the half-dose Serostim group and 2.8% in the placebo group), **paraesthesia** (7.9% in the full dose Serostim group, 7.4% in the half-dose Serostim group and 4.5% in the

placebo group). Of note, the incidence of carpal tunnel syndrome and glucose intolerance during the 12 week, placebo controlled portion of Study GF-9037 was <5% in both Serostim treatment groups, and, therefore, these adverse events do not appear in Table 34. In this regard, during the placebo controlled period, 12 patients (4.7%) in the full dose Serostim group, 5 patients (1.9%) in the half-dose Serostim group and no patients in the placebo group manifested carpal tunnel syndrome. In addition, during the placebo controlled phase of the study, the incidence of hyperglycemia reported as an adverse event was 3.6% for the placebo group, 1.9% for the Serostim 0.1 mg/kg qod group and 3.2% for the Serostim 0.1 mg/kg daily group (see Section VI.A.5.6.6.5.2 ahead for a detailed analysis of glucose intolerance during Study GF-9037).

As was apparent in the earlier analyses of adverse events leading to study drug discontinuation (see Section VI.A.5.6.6.2) and protocol-directed dose interventions (see Section VI.A.5.6.6.3), review of the TEAE data also reveals a dramatic dose response relationship across the 3 treatment groups, in particular with regard to adverse events most likely related to Serostim. See Section VI.A.5.8.1 for further discussion of this issue.

In addition, please see the relevant subsections of Section VI.A.5.6.6.5 regarding adverse events previously associated with rhGH therapy discussed in the preceding paragraph.

Table 34

Adverse Events During the First 12 weeks of Study GF-9037 Occurring in at Least 5% of the Patients in Any 1 of the 3 Treatment Groups (Without Causality Assessment)

	Placebo	Serostim 0.1 mg/kg qod	Serostim 0.1 mg/kg daily
	n=247	n=257	n=253
Body System Preferred Term	%	%	%
MUSCULOSKELETAL SYSTEM DISORDERS			
ARTHRALGIA	11.3	24.5	36.4

MYALGIA	**11.7**	**17.9**	**30.4**
ARTHROSIS	**3.6**	**7.8**	**10.7**
GASTROINTESTINAL SYSTEM DISORDERS			
DIARRHEA	10.1	10.1	5.5
NAUSEA	4.9	5.4	9.1
PSYCHIATRIC DISORDERS			
INSOMNIA	6.1	3.9	5.9
BODY AS A WHOLE - GENERAL DISORDERS			
EDEMA, PERIPHERAL	**2.8**	**11.3**	**26.1**
HEADACHE	9.3	10.1	12.6
FATIGUE	4.5	3.5	5.1
RESPIRATORY SYSTEM DISORDERS			
RHINITIS	6.5	5.1	4.0
UPPER RESPIRATORY TRACT INFECTION	5.7	4.3	3.6
BRONCHITIS	5.3	2.3	4.7
ENDOCRINE DISORDERS			
GYNECOMASTIA	**0.4**	**3.5**	**5.5**
CENTRAL/PERIPHERAL NERVOUS SYSTEM DISORDERS			
PARAESTHESIA	**4.5**	**7.4**	**7.9**
HYPOESTHESIA	**2.4**	**1.6**	**5.1**
METABOLIC AND NUTRITIONAL DISORDERS			
EDEMA, GENERALIZED	**1.2**	**1.2**	**5.9**

VI.A.5.6.6.4.2 TEAEs During the Extension Phase of Study GF-9037 (After Week 12)

During the extension phase of Study GF-9037, the incidence and types of TEAEs reported were not different from those observed during the 12 week, placebo controlled portion of the study.

VI.A.5.6.6.5 Potential Adverse Events/Effects Previously Associated with rhGH Therapy in Adults

VI.A.5.6.6.5.1 General

None of the more severe but unusual adverse events associated with rhGH therapy in children and potentially applicable to adults (e.g., benign intracranial hypertension, proliferative retinopathy, hypercalcemia, or pancreatitis) was reported during this study.

VI.A.5.6.6.5.2 Altered Glucose Homeostasis

VI.A.5.6.6.5.2.1 Changes in Mean Fasting Blood Glucose and Shift Tables

Given that treatment with rhGH may result in insulin resistance, impaired glucose tolerance, and occasionally overt diabetes mellitus (38-39), especially in patients with HIV-/AIDS-associated cachexia (26-28), (see Section VI.A.5.8.1 ahead for further discussion of this issue),

individuals with known diabetes mellitus (as per original protocol) and impaired glucose tolerance (as per Amendment 3) were excluded from the study. Glucose metabolism was monitored by measurement of fasting blood glucose levels at the 4, 8, 12, 16, 20, 24, and 48 week visits. Levels of glycated hemoglobin and insulin were *not* obtained during Study GF-9037.

As seen in Table 35, mean fasting blood glucose levels were normal at baseline in the placebo, half-dose Serostim and full dose Serostim treatment arms, and mildly increased in a dose proportional manner by approximately 2, 6, and 10 mg/dL, respectively, after 12 weeks of treatment (99 of 757 treated patients apparently did not have fasting blood glucose levels available at Week 12).

The number and percentages of patients with fasting blood glucose levels 110-126 mg/dL, >126-250 mg/dL and >250 mg/dL at baseline, and at Week 4, Week 8 and Week 12 by treatment group are shown in Table 36. Approximately 7-8% of patients in each treatment group had fasting blood glucose levels between 110-126 mg/dL (i.e., impaired fasting sugar) at baseline. Five patients (2.0% of 253) in the full dose Serostim group, 3 patients (1.2% of 256 [1 treated patient apparently did not have a fasting blood glucose level available at baseline]) in the half-dose Serostim group, and 5 patients (2.0% of 247) in the placebo group had fasting blood glucose levels >126-250 mg/dL at baseline (**i.e., overt diabetes mellitus was present and these patients should not have been enrolled in the study**). Five of the 8 "misenrolled" patients in the Serostim groups are further discussed in Table 40. No patients in any treatment group had fasting blood glucose levels >250 mg/dL at baseline.

As seen in Table 36, **fasting blood glucose levels increased early after treatment with both doses of Serostim, particularly in the full dose Serostim group, i.e a dose response was apparent.** At Week 4, 6.4% of placebo-treated patients (no change from baseline), 13.5% of half-dose Serostim-treated patients (up from 7.8%), and 18% of full dose Serostim-treated patients (up from 7.1%) had fasting blood glucose levels 110-126 mg/dL. In addition, at Week 4, 4.3% of placebo-treated patients (up from 2.0%), 3.7% of half-dose Serostim-treated patients, and 9.2% of full dose Serostim-treated patients had fasting blood glucose levels >126-250 mg/dL. Furthermore, 3 patients in the full dose Serostim-treated group, and none in the other 2 groups had fasting blood glucose levels >250 mg/dL. **At Weeks 8 and 12, the percentage of half-dose Serostim-treated patients with fasting blood glucose levels 110-126 mg/dL and >126-250 mg/dL remained about the same, while the percentage of full dose Serostim-treated patients with fasting blood glucose levels 110-126 mg/dL and >126-250 mg/dL declined modestly.**

Fasting blood glucose levels were also monitored throughout the extension phase of the study. As seen in Table 37, mean change from baseline to Week 24 was greater in the patients continued on full dose Serostim between Weeks 12 and 24 (11.1 mg/dL) than the mean change

from baseline to Week 24 in the patients continued on half-dose Serostim between Weeks 12 and 24 (2.7 mg/dL). Data from Week 48 are not shown because of the small sample size.

The number and percentages of patients with fasting blood glucose levels 110-126 mg/dL, >126-250 mg/dL and >250 mg/dL at baseline (baseline for patients in the 2 groups switched from placebo to Serostim was the Week 12 value; baseline for patients in the 3 groups continued on either dose of Serostim was the Week 0 value), and at Week 16, Week 20 and Week 24 by treatment group are shown in Table 38. In the 2 groups switched from placebo to either dose of Serostim between Weeks 12 and 24, the glycemic response was similar to that observed during the placebo controlled portion of the study (an early increase in the number of patients with abnormal sugars, especially those switched to full dose Serostim, which then stabilized or declined). **In the groups continued on either full dose or half-dose Serostim, the number of patients with abnormal sugars (110-126 mg/dL or >126-250 mg/dL) at Weeks 16, 20 and 24 was similar to the number of patients with abnormal sugars at Week 12 (see Table 36), i.e. there was no progressive increase in the number of patients with abnormal sugars.** Data from Week 48 are not shown because of the small sample sizes.

Table 35
Fasting Glucose: Change from Baseline to Week 12
All Treated Patients
(except for 99 of 757 patients who apparently did not have fasting glucose values available at Week 12)

Laboratory Parameter	Statistics	Baseline Placebo	Baseline Half-Dose Serostim	Baseline Full Dose Serostim	Week 12 Placebo	Week 12 Half-Dose Serostim	Week 12 Full Dose Serostim	Change Placebo	Change Half-Dose Serostim	Change Full Dose Serostim
Fasting Glucose (mg/dL)	n	225	226	207	225	226	207	225	226	207
	Mean (SD)	92.6 (13.8)	92.0 (12.2)	90.4 (14.2)	94.6 (20.0)	97.6 (16.7)	100.2 (20.8)	**2.0 (21.0)**	**5.6 (16.6)**	**9.7 (21.4)**
	Median	91	91	89	92	96	97	0	6	8
	Range	(51, 154)	(59, 137)	(53, 175)	(53, 283)	(59, 197)	(52, 246)	(-67, 198)	(-35, 112)	(-32, 165)

Table 36
Fasting Glucose*: Patient Count and Percentage of Abnormal Values by Visit and Treatment Group
Population: All Treated Patients
Week 0 to Week 12

Time Point	Treatment Group: Placebo Pts	Placebo 110-126	Placebo >126-250	Placebo >250	Half-Dose Serostim Pts	Half-Dose Serostim 110-126	Half-Dose Serostim >126-250	Half-Dose Serostim >250	Full Dose Serostim Pts	Full Dose Serostim 110-126	Full Dose Serostim >126-250	Full Dose Serostim >250
Baseline	247	18 (7.3)	**5 (2.0)**	0 (0.0)	256	20 (7.8)	**3 (1.2)**	0 (0.0)	253	18 (7.1)	**5 (2.0)**	0 (0.0)
Week 4	233	**15 (6.4)**	**10 (4.3)**	0 (0.0)	244	**33 (13.5)**	**9 (3.7)**	**0 (0.0)**	228	**41 (18.0)**	**21 (9.2)**	**3 (1.3)**
Week 8	225	18 (8.0)	8 (3.6)	0 (0.0)	233	**31 (13.3)**	**12 (5.2)**	0 (0.0)	218	**37 (17.0)**	**16 (7.3)**	**1 (0.5)**
Week 12	225	16 (7.1)	8 (3.6)	1 (0.4)	226	**28 (12.4)**	**10 (4.4)**	0 (0.0)	207	**29 (14.0)**	**12 (5.8)**	0 (0.0)

*mg/dL

Table 37
Fasting Glucose: Change from Baseline* to Week 24
All Treated Patients

Laboratory Parameter	Statistics	Change, Week 24 - Baseline: Placebo To Half-Dose Serostim	Placebo To Full Dose Serostim	Half-Dose to Half-Dose Serostim	Half-Dose to Full Dose Serostim	Full Dose to Full Dose Serostim
Fasting Glucose (mg/dL)	n	37	133	71	105	155
	Mean (SD)	4.8 (36.8)	6.0 (25.9)	**2.7 (18.0)**	5.9 (15.2)	**11.1 (19.6)**
	Median	1	6	2	6	9
	Range	(-52, 197)	(-191, 92)	(-37, 55)	(-27, 76)	(-50, 125)

*Baseline for patients in the 2 groups switched from placebo to Serostim was the Week 12 value; baseline for patients in the 3 groups continued on either dose of Serostim was the Week 0 value.

Table 38

Fasting Glucose*: Patient Count and Percentage of Abnormal Values by Visit and Treatment Group
Population: All Treated Patients
Baseline** to Week 24

	Treatment Group											
	Placebo to Half-Dose				Placebo to Full Dose				Half-Dose to Half-Dose			
Time Point	Pts	110-126	>126-250	>250	Pts	110-126	>126-250	>250	Pts	110-126 mg/dL	>126-250 mg/dL	>250 mg/dL
Baseline**	42	3 (7.1)	1 (2.4)	0 (0.0)	175	12 (6.9)	7 (4.0)	1 (0.6)	81	8 (9.9)	1 (1.2)	0 (0.0)
Week 16	42	**7 (16.7)**	**3 (7.1)**	**1 (2.4)**	152	**21 (13.8)**	**21 (13.8)**	**2 (1.3)**	78	**9 (11.5)**	**7 (9.0)**	0 (0.0)
Week 20	44	3 (6.8)	3 (6.8)	0 (0.0)	47	**8 (17.0)**	**8 (17.0)**	0 (0.0)	73	**10 (13.7)**	**3 (4.1)**	0 (0.0)
Week 24	39	3 (7.7)	1 (2.6)	1 (2.6)	138	**28 (20.3)**	9 (6.5)	0 (0.0)	71	**10 (14.1)**	**4 (5.6)**	0 (0.0)

	Treatment Group							
	Half-Dose to Full Dose				Full-Dose to Full Dose			
Time Point	Pts	110-126	>126-250	>250	Pts	110-126	>126-250	>250
Baseline**	138	7 (5.1)	1 (0.7)	0 (0.0)	201	12 (6.0)	4 (2.0)	0 (0.0)
Week 16	106	**14 (13.2)**	**6 (5.7)**	0 (0.0)	170	**33 (19.4)**	**16 (9.4)**	0 (0.0)
Week 20	9	0 (0.0)	0 (0.0)	0 (0.0)	85	**17 (20.0)**	**9 (10.6)**	0 (0.0)
Week 24	105	11 (10.5)	2 (1.9)	0 (0.0)	155	**26 (16.8)**	**12 (7.7)**	0 (0.0)

*mg/dL

**Baseline for patients in the 2 groups switched from placebo to Serostim was the Week 12 value; baseline for patients in the 3 groups continued on either dose of Serostim was the Week 0 value.

VI.A.5.6.6.5.2.2 Dose Interventions During the Placebo Controlled Portion of Study GF-9037

Table 39 depicts the number of patients requiring dose interventions because of elevated fasting blood glucose levels during the placebo controlled portion of the study. Surprisingly, a clear cut dose response was not observed, i.e. the number of dose reductions in the full dose Serostim group was not different from the number of dose reductions effected in the half-dose Serostim and placebo groups. However, of note, 2 patients in the full dose Serostim treatment arm (and none in the other groups) were discontinued because of hyperglycemia (see Table 40 ahead).

Table 39
Dose Interventions
During the Placebo Controlled Portion of Study GF-9037

Dose Intervention Category	Treated Patients	Patients with Intervention for Elevated Glucose	Subsequent Elevated Glucose	No Further Elevated Glucose
Dose Reduced for Elevated Glucose				
Full Dose Serostim	253	3	1	2
Half-Dose Serostim	257	2	1	1
Placebo	247	5	3	2
Dose Interrupted for Elevated Glucose				
Full Dose Serostim	253	1	0	1
Half-Dose Serostim	257	0	0	0
Placebo	247	0	0	0
Dose Discontinued for Elevated Glucose				
Full Dose Serostim	253	2		
Half-Dose Serostim	257	0		
Placebo	247	0		

Dose Reductions: Full-Dose Serostim - Patients [redacted] Half-Dose Serostim - Patient [redacted] Placebo- Patients [redacted] b(6)

Dose Interruptions: Full-Dose Serostim - Patient [redacted]

Dose Discontinued: Full-Dose Serostim - Patient [redacted] b(6)

VI.A.5.6.6.5.2.3 An Analysis of 1) Patients with Fasting Blood Glucose >160 mg/dL At Any Time During the Study, and 2) Patients Discontinued During Either Phase of the Study Because of Glucose Intolerance

A tabulation (see Table 40 below)(as well as case histories/narratives and complete fasting blood glucose profiles) of patients with any single fasting blood glucose level >160 mg/dL at any time during the study (12 week randomized placebo controlled phase and/or extension phase) requiring an intervention as per the original or more conservative 5/01 amended protocol (i.e., dose reduction,

interruption, or discontinuation - see below and also Section VI.A.4.2.5 for glycemic intervention criteria) were provided by the Sponsor at the request of this Medical Officer. 160 mg/dL was the fasting blood glucose level requiring dose reduction in the original protocol and neatly stratifies patients with high fasting blood glucose levels.

In addition, the Sponsor provided a tabulation/listing WITHOUT CASE HISTORIES/NARRATIVES of 29 patients (data not shown) with fasting blood glucose levels >160 mg/dL at least once, or patients with fasting blood glucose levels >140 mg/dL two or more times, at some time during the study, who did NOT have interventions performed. Of note, the patients who did not have interventions frequently had non-fasting blood draws. As a result, these elevated glucose values were often dismissed as not clinically significant (NCS), and interventions were not performed as per protocol-directed criteria.

For ease of reference, the glucose intervention criteria as per protocol are again summarized (also see Section VI.A.4.2.5 earlier):

- Original Protocol
    - Dose Reduction criterion: Fasting glucose >160 mg/dL but <400 mg/dL.
        - If no resolution within 14 days of Dose Reduction, then Dose Interruption. If no resolution within 7 days of Dose Interruption, then Discontinuation.
    - Discontinuation Criterion*: Fasting glucose ≥400 mg/dL.
        - If no resolution within 7 days of Dose Interruption, then Discontinuation.
- Amendment 3 (applies *only* to 48 patients enrolled after 8May03):
    - Dose Reduction criterion: Fasting glucose >126 mg/dL or 2 hour postprandial glucose >200 mg/dL
        - If no resolution within 14 days of Dose Reduction, then Dose Interruption. If no resolution within 7 days of Dose Interruption, then Discontinuation.
    - Discontinuation Criteria*: Fasting glucose ≥140 mg/dL or 2 hour postprandial glucose ≥240 mg/dL
        - If no resolution within 7 days of Dose Interruption, then Discontinuation.

Table 40

Patients Treated With Full Dose or Half-Dose Serostim With Any Single Fasting Blood Glucose Level >160 mg/dL At Any Time During the Study Requiring an Intervention As Per the Original or Amended Protocol

Patient #	Treatment	Action
+++	Full dose	dose reduction; *early discontinuation*
	Full dose	*early discontinuation; new onset type 2 diabetes mellitus*
	Placebo to full dose	*early discontinuation; hospitalized with new onset type 2 diabetes mellitus; SAE reported*
	Placebo to full dose	dose reductions; *early discontinuation; new onset type 2 diabetes mellitus* (as per this Medical Officer)
	Placebo to half-dose	dose reduction; *early discontinuation; hospitalized with new onset type 2 diabetes mellitus requiring insulin; SAE reported*
	Placebo to full dose	preexisting type 2 diabetes mellitus; dose reduction; *early discontinuation*
	Placebo to full dose	prior history of hyperglycemia; *early discontinuation*
	Placebo to full dose	persistent hyperglycemia while receiving placebo; similar degree of hyperglycemia while receiving full dose Serostim; dose reduction; *early discontinuation*
	Full dose to full dose	dose interruption due to hyperglycemia; dose reduction due to joint aches; early discontinuation because of non-compliance
	Full dose to full dose	dose reduction; early discontinuation because of non-compliance
	Placebo to half-dose	dose reduction; early discontinuation not related to increased glucose
	Full dose to full dose	dose reduction, enrolled after Amendment 3 effected on 5/8/01
	Full dose to full dose	prior history of hyperglycemia; dose reduction
	Half dose	prior history of hyperglycemia; dose reduction
	Placebo to full dose	prior history of hyperglycemia; dose reduction
++	Full dose to full dose	dose reduction; persistent hyperglycemia in the 220-250 mg/dL range during a 12 week full dose extension phase, but no early discontinuation; blood glucose allegedly "normal" 1 month off drug
	Full dose	dose reduction
	Full dose to full dose	dose reduction
	Half dose to half-dose	dose reduction
	Half dose to half-dose	dose reduction
	Half dose to half-dose	dose reduction
	Placebo to full dose	dose reduction
	Placebo to full dose	dose reduction
	Placebo to full dose	dose reduction
	Placebo to full dose	dose reduction

b(6)

+ *Patients with new onset type 2 diabetes mellitus leading to early discontinuation:* 1) Patient [redacted] After 8 weeks of full dose Serostim during the randomized, placebo controlled phase, was *discontinued* from the study because of sustained symptomatic hyperglycemia in excess of 340 mg/dL, and required antihyperglycemic therapy for new onset type 2 diabetes mellitus; 2) Patient [redacted] After 12 weeks of placebo followed by only 4 weeks of full dose Serostim during the extension phase, was *discontinued* from the study because of serum glucoses in the 440-490 mg/dL range, and required inpatient antihyperglycemic therapy for new onset type 2 diabetes mellitus; 3) Patient [redacted] - After 12 weeks of placebo followed by 20 weeks of full dose Serostim during the extension phase, manifested sustained serum glucoses in the 190-360 mg/dL range, did not respond to dose reductions, and was eventually *discontinued*. Eleven weeks post Serostim discontinuation, serum glucose was remarkably elevated at 436 mg/dL; 4) Patient [redacted] After 12 weeks of placebo followed by only 4 weeks of half-dose Serostim during the extension phase, was *discontinued* from the study because of a serum glucose in excess of 480 mg/dL, and required inpatient insulin therapy for new onset type 2 diabetes mellitus. b(6)

++ *Patients with preexisting type 2 diabetes mellitus or hyperglycemia which worsened during Serostim treatment leading to early discontinuation:* 1) Patient [redacted] with preexisting type 2 diabetes mellitus was enrolled in violation of the protocol and was *discontinued* with hyperglycemia (sustained serum glucoses in excess of 300 mg/dL) after 12 weeks of placebo followed by 6 weeks of full dose Serostim during the extension phase. Post-study serum glucoses ranged from 132 to 174 mg/dL compatible with a diagnosis of preexisting type 2 diabetes mellitus; 2) Patient [redacted] with a preexisting history of hyperglycemia was *discontinued* because of hyperglycemia (serum glucose 260 mg/dL) after 12 weeks of placebo followed by only 4 weeks of full dose Serostim during the extension phase. Post-study serum glucose was 197 mg/dL, potentially compatible with a diagnosis of preexisting type 2 diabetes mellitus; 3) Patient [redacted] was *discontinued* because of hyperglycemia (serum glucose 189 mg/dL) unresponsive to dose reduction after 12 weeks of placebo followed by 10 weeks of full dose Serostim during the extension phase. Of note, similar degrees of hyperglycemia were observed when the patient was receiving placebo. Post-study serum glucose was 138 mg/dL 6 weeks off Serostim, potentially compatible with a diagnosis of preexisting type 2 diabetes mellitus. b(6)

+++ Patients with a prior history of hyperglycemia who required an on-study dose reduction with a satisfactory glycemic response: Patients [redacted] and [redacted] b(6)

++++ Patient [redacted] - After 4 weeks of full dose Serostim during the randomized, placebo controlled phase, manifested sustained glucoses in excess of 300 mg/dL, did not respond to dose reductions, and was eventually *discontinued*; serum glucose normalized within 2 weeks of Serostim discontinuation. b(6)

+++++ Patient [redacted] manifested persistent hyperglycemia (220-250 mg/dL) during a 12 week, full dose extension phase, but was not discontinued from the study. Blood glucose allegedly was "normal" 1 month off drug. b(6)

With regard to the 25 patients listed in Table 40, interventions related to excessive hyperglycemia included: 1) dose reduction (n=21; fasting blood glucose levels usually normalized after dose reduction, i.e. the elevations were transient; 3/21 had preexisting hyperglycemia); 2) dose interruption (n=1); and 3) early discontinuation (n=8; fasting blood glucose levels remained elevated after dose reduction [dose interruption] and/or fasting blood glucose levels exceeded the threshold for protocol-driven dose interruption/discontinuation).

The 8 patients who were discontinued because of hyperglycemia are discussed in more detail in the footnote to Table 40 above (1 during the placebo controlled phase and 7 during the extension phase; 7 while receiving full dose Serostim and 1 while receiving half-dose Serostim). Four of these patients [redacted] manifested de novo diabetes mellitus on-study - 1 while receiving full dose Serostim during the placebo controlled phase of the study, 2 while receiving full dose Serostim b(6)

during the extension phase, and 1 while receiving half-dose Serostim during the extension phase. Three other patients were previously known to be 1) diabetic by history, 2) "hyperglycemic" by history, and 3) persistently hyperglycemic while receiving placebo during the randomized, placebo controlled phase of the study, respectively. Of note, all 3 of these patients were receiving full dose Serostim at the time sustained hyperglycemia became apparent!!

Six of the 25 patients in Table 40 had a prior history of glucose intolerance (i.e., 4 patients with preexisting hyperglycemia [patients (redacted) 1 patient with persistent hyperglycemia while receiving placebo [patient (redacted) and 1 patient with preexisting type 2 diabetes mellitus [patient (redacted) Three of these 6 patients (patients (redacted) and (redacted) are amongst the 8 patients who discontinued from the study because of hyperglycemia. b(6) b(6)

In terms of anti-retroviral therapy regimen, all 25 of these patients were receiving combination therapy with 1 or more NRTIs, and either a PI or a NNRTI or both.

Of the 47 patients enrolled in Study GF-9037 after the more restrictive intervention criteria for elevated blood glucose had been effected in Amendment 3 on 8May03: 1) 1 patient (patient (redacted) included in Table 40 above) had a serum glucose >160 mg/dL and required a dose reduction (in fact, that patient should have been discontinued under the new criteria); 2) 4/7 patients with fasting blood glucose levels >126 mg/dL but <160 mg/dL were successfully treated with dose reductions; 3) 3/7 patients with fasting blood glucose levels >126 mg/dL but <160 mg/dL were not treated with dose reductions because they were very close to completing the study; and 4) no patients were discontinued due to hyperglycemia, i.e. no patients manifested either a) fasting blood glucose level ≥140 mg/dL which did not resolve within 7 days of dose interruption leading to discontinuation, or b) fasting blood glucose >126 mg/dL which did not resolve within 14 days of dose reduction leading to dose interruption, and which then did not resolve within 7 days of dose interruption leading to discontinuation. b(6)

See Section VI.A.5.8.1 ahead for a summary/discussion of this Medical Officer's concerns regarding glucose intolerance during this trial.

VI.A.5.6.6.5.3 Arthralgia/Myalgia/Edema/Carpal Tunnel Syndrome-Paraesthesias

See Section VI.A.5.6.6.4 and Table 34 above. As expected, arthralgia, myalgia, various kinds of edema and carpal tunnel syndrome/paraesthesias all occurred more frequently in Serostim-treated patients compared with placebo-treated patients in a dose-dependent fashion.

VI.A.5.6.6.5.4 Acromegaloid Features - In Particular Chin/Jaw Prominence

No cases were reported.

VI.A.5.6.6.5.5 Gynecomastia

Gynecomastia was reported in 14 male patients (5.5%) in the full dose group, 9 male patients (3.5%) in the half-dose group (reported as a SAE in 1 patient), and 1 male patient (0.4%) in the placebo group during the placebo controlled portion of the study. During the extension phase of the study, gynecomastia was reported in 37 patients treated with full dose Serostim and 4 patients treated with half-dose Serostim. **A dose response effect is clearly evident.**

Additionally, there were 13 patients (13 events) in the full dose Serostim group and 5 patients (7 events) in the half-dose Serostim group with events coded as **breast neoplasm, male** (corresponding to an overall incidence rate of 5.9 per 100 person-years). These included breast and nipple lumps, breast nodules and areolar nodularity/cysts. Occasionally, these breast abnormalities were reported to be tender or painful; 80% were considered mild in severity by the reporting investigator; none of the 20 breast abnormalities were associated with signs or symptoms suggestive of malignancy, or led the treating investigator to perform any additional diagnostic procedures, including biopsy. **No malignancies were reported in these patients.** All of these events occurred in patients actively receiving Serostim therapy - 75% within 3 months of Serostim treatment initiation, including some within a few weeks. As described above, **almost twice as many events occurred in patients receiving full dose Serostim suggesting a dose response relationship.** One hundred percent of these events resolved during the study, the majority within 4 months (while the patients were still receiving Serostim treatment?).

See Section VI.A.5.8.1 ahead for further discussion of these findings.

VI.A.5.6.6.5.6 Anti-GH Antibodies and Allergy

Anti-rhGH antibodies were not detected during the study (at Weeks 12 and 48).

Allergy - There were no reports of allergic reactions attributable to rhGH.

VI.A.5.6.6.6 Other Issues Related to rhGH Therapy (Including IGF-I Response and Incidence of Malignancy)

VI.A.5.6.6.6.1 IGF-I Response - Safety Implications

Mean serum IGF-I levels (see Table 41 below for age-/sex-dependent reference ranges) were converted to mean serum IGF-I SDS, a much more accurate measure of IGF-I than raw serum IGF-I levels, which allows comparison of IGF-I responses irrespective of age and gender. IGF-I SDS were calculated by the Sponsor utilizing the following formula:

Patient's actual serum IGF-I value minus age-/sex-matched population mean divided by the age-/sex-matched population standard deviation (of the population mean). Information regarding the age-/sex-matched population means and standard deviations was provided to the Sponsor by the manufacturer of the IGF-I radioimmunoassay test kit

b(4)

Table 41
IGF-I Ranges, Male and Female
(0-90%)

AGE (years)	IGF-I RANGE
20-30	130-302
30-40	123-387
40-50	116-272
50-60	110-260
60-70	103-251

As seen in Table 42, mean baseline values of serum IGF-I SDS were slightly decreased (-0.6 to -0.8), and very similar across the 3 treatment groups. After 12 weeks of treatment, there was a dose-dependent increase in mean serum IGF-I SDS, i.e. 0.1 in the placebo group, 2.2 in the half-dose Serostim group, and 3.1 in the full dose Serostim group. These changes are graphically depicted in Figure 7.

Table 43 is a shift table demonstrating the change from baseline to Week 12 in mean serum IGF-I SDS by treatment group. **A dose-dependent response is clearly evident.** In patients with baseline mean serum IGF-I SDS -2 to <-1, no patients receiving placebo attained post-treatment mean serum IGF-I SDS >+2, **9 and 5** patients receiving half-dose Serostim

attained post-treatment mean serum IGF-I SDS >+2 to +3 and >+3, respectively, and 11 and 14 patients receiving full dose Serostim attained post-treatment mean serum IGF-I SDS >+2 to +3 and >+3, respectively. In patients with baseline mean serum IGF-I SDS -1 to +1, 2 and 3 patients receiving placebo attained post-treatment mean serum IGF-I SDS >+2 to +3 and >+3, respectively, 33 and 17 patients receiving half-dose Serostim attained post-treatment mean serum IGF-I SDS >+2 to +3 and >+3, respectively, and 24 and 55 patients receiving full dose Serostim attained post-treatment mean serum IGF-I SDS >+2 to +3 and >+3, respectively. Figure 8, an equal N stacked bar graph reflecting the distribution of mean serum IGF-I SDS at baseline and Week 12 by treatment group graphically depicts the shift table findings, in particular the fact that ~40% of patients receiving full dose Serostim attained mean serum IGF-I SDS >+3 (in contrast to ~15% of patients receiving half-dose Serostim).

If sustained, IGF-I SDS >+2 or, indeed, >+3, could be associated with clinical acromegaloid phenomena and, theoretically, oncogenic sequelae. However,

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Table 42

IGF-I SDS: Change from Baseline to Week 12 in All Treated Patients

		Baseline			Week 12			Change		
IGF-I SDS	Statistics	Placebo	Half-Dose Serostim	Full Dose Serostim	Placebo	Half-Dose Serostim	Full Dose Serostim	Placebo	Half-Dose Serostim	Full Dose Serostim
	n	204	193	181	204	193	181	204	193	181
	Mean (SD)	-0.7 (1.3)	-0.8 (1.1)	-0.6 (1.2)	-0.6 (1.4)	1.4 (1.4)	2.4 (1.7)	0.1 (1.0)	2.2 (1.3)	3.1 (1.7)
	Median	-0.6	-0.8	-0.6	-0.6	1.4	2.7	0.1	2.1	3.3
	Range	(-5.2, 2.7)	(-4.9, 1.6)	(-3.5, 4.4)	(-4.4, 5.1)	(-3.0, 4.6)	(-3.6, 6.2)	(-2.3, 5.3)	(-2.5, 5.6)	(-3.4, 6.4)

Figure 7

Mean IGF-1 SDS By Treatment Group for Baseline and Week 12
for Patients with Both a Baseline and Week 12 Measurement
(Placebo:204; Half-Dose Serostim: 193; Full-Dose Serostim: 181)

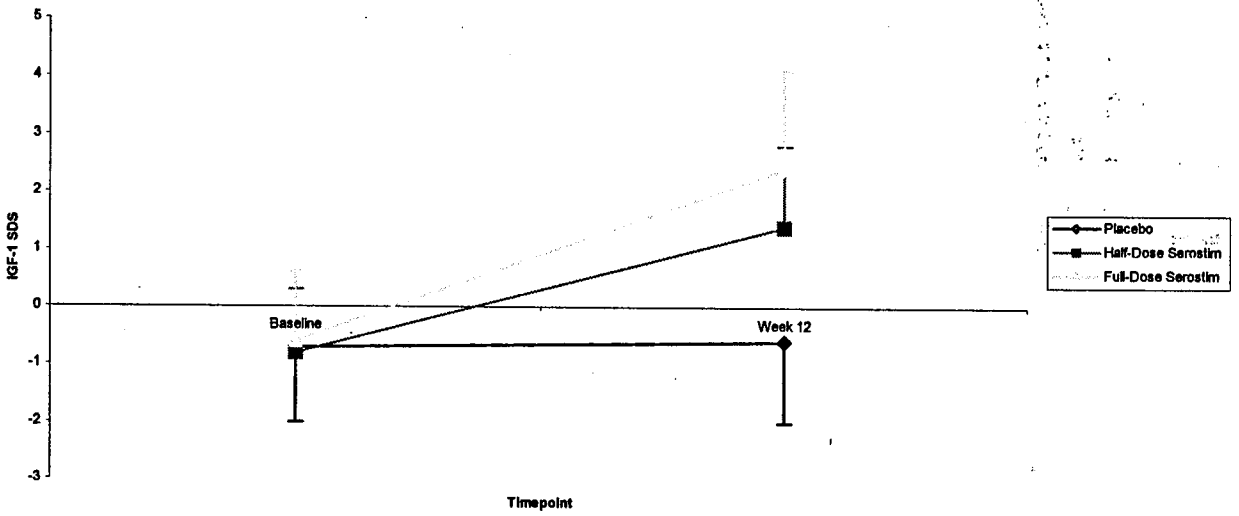

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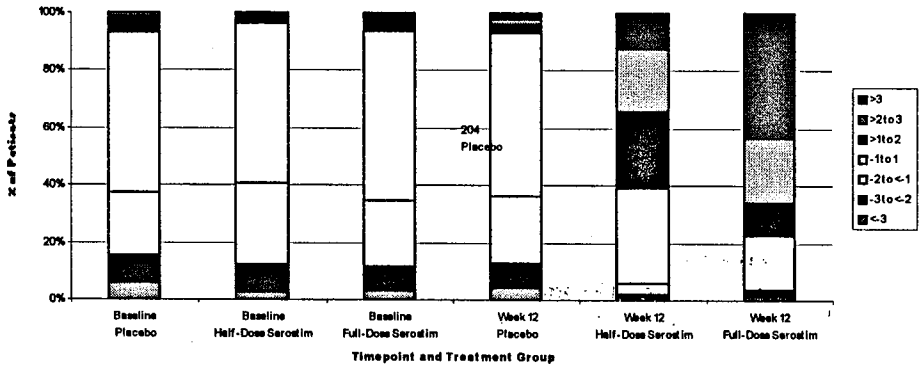
Table 43

IGF-I SDS - Shift Table and Change from Baseline to Week 12 in All Treated Patients

Baseline Mean IGF-I SDS	Mean IGF-I SDS at Week 12 Endpoint Placebo							Mean IGF-I SDS at Week 12 Endpoint Half-Dose Serostim							Mean IGF-I SDS at Week 12 Endpoint Full Dose Serostim						
	<-3	-3 - <-2	-2 - <-1	-1 - +1	>+1 - +2	>+2 - +3	>+3	<-3	-3 - <-2	-2 - <-1	-1 - +1	>+1 - +2	>+2 - +3	>+3	<-3	-3 - <-2	-2 - <-1	-1 - +1	>+1 - +2	>+2 - +3	>+3
<-3	5	5	2	0	0	0	0	0	1	2	2	0	0	0	0	0	0	5	1	0	0
-3 to <-2	2	9	4	4	1	0	0	0	1	4	**12**	2	0	0	2	2	0	1	**4**	**5**	2
-2 to <-1	2	2	**24**	**16**	0	0	0	0	2	0	**24**	**14**	**9**	**5**	1	1	1	**8**	**6**	**11**	**14**
-1 to +1	0	1	**17**	**87**	4	2	3	0	0	0	**25**	**33**	**33**	**17**	0	0	0	**19**	**9**	**24**	**55**
>+1 to +2	0	0	1	8	1	2	0	0	0	1	1	3	0	2	0	0	0	0	2	1	7
>+2 to +3	0	0	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1
>+3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0

Figure 8

IGF-1 SDS by Treatment Group and Timepoint
for Patients with Both a Baseline and Week 12 Measurement
(Placebo:204; Half-Dose Serostim: 193; Full-Dose Serostim: 181)



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VI.A.5.6.6.6.2 Effect on Serostim on the Incidence of Malignancy, In Particular HIV-/AIDS-Related Malignancies

Five malignancies were reported during the entire study:

- Disseminated **cerebral lymphoma** (which resulted in 1 of the 6 **deaths** reported during the study; diagnosed after receiving half-dose Serostim for 81 days during the placebo controlled phase followed by full dose Serostim for 108 days during the extension phase)
- Hodgkin's **lymphoma** (SAE; diagnosed 6 months off therapy after receiving full dose Serostim for 84 days during the extension phase following placebo in the placebo controlled phase)
- Basal cell carcinoma in situ (SAE; diagnosed after receiving full dose Serostim for 170 days during the placebo controlled/extension phases; successfully resected)
- Acute myelogenous leukemia (SAE; diagnosed 7 months off therapy after receiving full dose Serostim for 54 days during the extension phase)
- Squamous cell carcinoma in situ (SAE; diagnosed after receiving full dose Serostim for 108 days during the placebo controlled/extension phases; successfully resected)

In the opinion of this Medical Officer, only the 2 cases of lymphoma (both patients were receiving full dose Serostim at the time of diagnosis) could <u>possibly</u> have been AIDS-related malignancies.

In addition:

- No new cases of Kaposi's sarcoma or exacerbation of preexisting Kaposi's sarcoma were reported.
- No changes in pigmented nevi were noted.
- No cases of breast carcinoma, colon carcinoma, osteogenic sarcoma or leukemia were diagnosed.

VI.A.5.6.6.6.3 Effect of Serostim on HIV-/AIDS-Related Parameters

VI.A.5.6.6.6.3.1 HIV RNA Levels (viral load) and CD4 T-cell counts

Tables 44 and 46 show the results of the measurements of viral load (HIV RNA) and CD4 lymphocytes at baseline and Week 12. The median differences in change from baseline for both of these endpoints were not significant for either of the Serostim groups compared to placebo. In addition, when study patients receiving or not receiving HAART were analyzed separately, the same result was observed (see Table 45). Furthermore, the median change from baseline for viral load was not significantly different within treatment groups when patients receiving or not receiving HAART were compared (see Table 45).

Note: See Table 8 with regard to the very frequent and well balanced usage of HAART across all 3 treatment groups at baseline, and Section VI.A.5.5.3.3 with regard to the impact of HAART usage on efficacy.

Table 44

HIV-1 RNA (copies/mL) - Change from Baseline to Week 12 by Treatment Group in All Serostim Treated Patients (Treated Concurrently with HAART or non-HAART Antiretroviral Therapy)

			Half-Dose	Full Dose
Time Point	**Statistics**	**Placebo**	**Serostim**	**Serostim**
Baseline	**n**	135	142	118
	Median	1056.50	839.00	668.00
	Range	(400.00, 989091.00)	(94.00, 573847.00)	(400.00, 750000.00)
Change from Baseline to Week 12	**n**	135	142	118
	Median	0.00	0.00	0.00
	Range	(-454462.00, 425595.00)	(-485905.00, 486314.00)	(-406553.00, 151707.00)
	p-value[1]	0.5574	0.0919	0.0155
	Treatment Comparison vs. Placebo			
	Median Difference from Placebo in Change from Baseline		**0.00**	**0.00**
	95% Confidence Interval		**(0.00, 0.00)**	**(0.00, 0.00)**
	p-value[2]		**0.4281**	**0.3045**

[1]p-value from an ANOVA on ranked data with effects for treatment and pooled center.
[2]Based on Hochberg's multiple comparison procedure. Both pairwise comparisons (i.e., full dose Serostim vs. placebo and half-dose Serostim vs. placebo) are not statistically significant at the 0.05 level.

Table 45

Change in HIV-1 RNA (copies/mL) - Change from Baseline to Week 12 by HAART Usage
Population: All Treated Patients

HAART	Statistics	Placebo	Half-Dose Serostim	Full Dose Serostim	p-value[2] for Half-Dose vs. Placebo	p-value[2] for Full Dose vs. Placebo
Patients on HAART	n	116	124	109	0.4227	0.2918
	Median	0	0	0		
	Range	(-454462, 425595)	(-485905, 408647)	(-406553, 151707)		
Patients Not on HAART	n	19	18	9	0.8888	0.0836
	Median	0	0	0		
	Range	(-90008, 16295)	(-380726, 486314)	(-144, 132244)		
p-value[1] for Comparison Within Treatment Group:		0.563	0.4260	0.229		

[1]p-value from an ANOVA on ranked data with effects for treatment group, HAART usage and their interaction
[2]Based on Hochberg's multiple comparison procedure. Both pairwise comparisons (i.e., full dose Serostim vs. placebo and half-dose Serostim vs. placebo) are not statistically significant at the 0.05 level.

Table 46

CD4 Lymphocytes (cells/μL): Change from Baseline to Week 12 by Treatment Group in All Treated Patients
(Treated Concurrently with HAART or non-HAART Antiretroviral Therapy)

Time Point	Statistics	Placebo	Half-Dose Serostim	Full Dose Serostim
Baseline	n	202	201	175
	Median	457.00	414.00	411.50
	Range	(10.00, 1534.00)	(10.00, 1451.00)	(17.00, 2035.00)
Change from Baseline to Week 12	n	202	201	175
	Median	12.00	17.50	19.00
	Range	(-716.00, 332.00)	(-501.00, 459.00)	(-371.00, 720.00)
	p-value[1]	0.1081	0.0154	0.0276
	Treatment Comparison vs. Placebo			
	Median Difference from Placebo in Change from Baseline		5.50	7.00
	95% Confidence Interval		(-16.00, 26.00)	(-17.00, 29.00)
	p-value[2]		0.5797	0.5797

[1]p-value from an ANOVA on ranked data with effects for treatment and pooled center.
[2]Based on Hochberg's multiple comparison procedure. Both pairwise comparisons (i.e., full dose Serostim vs. placebo and half-dose Serostim vs. placebo) are not statistically significant at the 0.05 level.

VI.A.5.6.6.6.3.2 Effect of Serostim on the Incidence of Potentially AIDS-Defining/Related Opportunistic Infections

See Section VI.A.5.6.6.1.3 regarding the lack of difference in the incidence of AIDS-defining/related serious opportunistic infections across the various treatment groups during both phases of the study.

VI.A.5.6.6.6.3.3 Effect of Serostim on the Incidence of Potentially AIDS-Defining/Related Malignancies

See Section VI.A.5.6.6.6.2 above.

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VI.A.5.6.6.7 Other Clinical Laboratory Evaluations Including Blood Chemistry/Hematology (With Particular Emphasis on Plasma Triglyceride Levels), and Urinalysis

The mean changes from baseline for all of the above laboratory parameters (including hematology, electrolytes, renal function, liver tests, and lipids [including triglycerides]) were not clinically significant in any of the treatment groups, and there were no significant differences between treatment groups.

In this regard, the mean plasma triglyceride level at baseline ranged from 200-223 mg/dL across the 3 treatment groups, and, after 12 weeks of therapy, increased modestly in the placebo and half-dose Serostim groups (~13-15 mg/dL), and decreased slightly in the full dose Serostim group (~5 mg/dL). Of note, protocol-driven dose reductions were effected in 3 patients in the full dose Serostim group and 5 patients in the half-dose Serostim group (compared to 2 patients in the placebo group) during the placebo controlled phase of the study, **and 6 patients were discontinued due to hypertriglyceridemia during the extension phase of the study.**

In addition, a review of individual laboratory data for selected parameters by this Medical Officer revealed very few outliers or values of clinical import.

VI.A.5.6.6.8 Vital Signs

The mean changes from baseline for blood pressure, pulse, and temperature were not clinically significant in either treatment group, and there were no significant differences between treatment groups. In addition, a review of individual vital sign data by this Medical Officer revealed very few values of clinical import.

VI.A.5.7 Safety Update (SU)

Not applicable. Study was complete at the time of datalock and submission.

VI.A.5.8 Safety - Summary/Discussion of Results, Conclusions, and Recommendations

VI.A.5.8.1 Safety - Summary/Discussion of Results

All 757 patients in the study who were randomized to active treatment and received at least 1 injection of rhGH or placebo were included in the safety database.

Exposure:

During the 12 week, placebo controlled portion of the study, the 253 patients randomized and treated with Serostim 0.1 mg/kg daily (up to 6 mg/day) received an average daily dose of 5.6 ± 0.7 mg, while the 257 patients randomized and treated with Serostim 0.1 mg/kg (up to 6 mg/day) alternating with placebo received an average daily dose of 2.9 ± 0.3 mg.

Deaths:

None of the 6 deaths which occurred during the study were felt to be related to the administration of Serostim by the Sponsor or this Medical Officer. One of these patients developed disseminated cerebral lymphoma during the extension phase of the study and died secondary to nadir sepsis.

SAEs :

A total of 37 SAEs were reported by 32 patients during the placebo controlled phase of the study. Seven SAEs reported by 7 patients during the placebo controlled phase of the study may have resulted from AIDS-defining/related opportunistic infections and are discussed later in this section. One patient receiving half-dose Serostim reported severe gynecomastia as an SAE. Strangely, neither of the 2

patients discontinued during the placebo controlled phase of the study due to new onset diabetes mellitus and hyperglycemia, respectively, were designated as having a SAE. Gynecomastia and glucose intolerance as consequences of Serostim therapy are discussed later in this section. A review of all of the other SAEs reported during the placebo controlled phase of the study revealed none related to Serostim treatment.

Five hundred and forty eight patients received either full dose (~80%) or half-dose Serostim (~20%) for an additional 12 weeks, and 177 patients received either dose of Serostim for an additional 36 weeks. A total of 51 SAEs were reported by 34 patients during the extension phase of the study. More SAEs were reported by patients receiving full dose Serostim; however, the vast majority of the patients (~80%) entering and completing the first 12 weeks of the extension phase were receiving full dose Serostim. Nine SAEs reported by 9 patients during the extension phase of the study may have resulted from AIDS-defining/related opportunistic infections and are discussed later in this section. Four of the SAE patients reported during the extension phase were diagnosed with a malignancy and are discussed later in this section. All 4 patients were treated with full dose Serostim during the extension phase. Two SAE patients were discontinued from the study because of new onset diabetes mellitus requiring hospitalization (1 in the full dose group and 1 in the half-dose group). Surprisingly, 4 other patients (all receiving full dose Serostim) who were discontinued from the study during the extension phase because of glucose intolerance were not designated as having SAEs. Glucose intolerance as a consequence of Serostim therapy is discussed later in this section. A review of all of the other SAEs reported during the extension phase of the study revealed none related to Serostim treatment.

Discontinuations Due to Adverse Events :

A total of 46 patients were discontinued due to adverse events during the placebo controlled phase of the study, 26 (10.3%) in the full dose Serostim group, 17 in the half-dose Serostim group (6.6%), and 3 (1.2%) in the placebo group. In the opinion of this Medical Officer, 18 of the 26 patients who were discontinued from the full dose Serostim group (~69%), and 10 of the 17 patients who were discontinued from the half-dose group (~59%) manifested adverse events which were more than likely related to Serostim therapy.

The most common reasons for these discontinuations were consequential/symptomatic arthralgia/musculoskeletal pain/skeletal pain, edema and carpal tunnel syndrome/paraesthesias. In addition, 2 patients with significant glucose intolerance were discontinued during the placebo controlled phase.

It is apparent from these data that a dose response relationship exists across the 3 treatment groups with respect to the development of adverse events leading to

study drug discontinuation, in particular adverse events most likely related to Serostim, i.e. administration of the full dose of Serostim resulted in larger numbers of patients with musculoskeletal complaints, edema, carpal tunnel syndrome, and glucose intolerance than treatment with the half-dose of Serostim, and treatment with both doses of Serostim resulted in these kinds of adverse events much more frequently than placebo administration.

During the extension phase, 65 patients were discontinued from the study. The reasons for discontinuation after Week 12 were similar to the termination reasons observed during the first 12 weeks of the study.

More of these adverse events most likely related to Serostim therapy leading to discontinuation during either phase of the study occurred when either dose of Serostim was first initiated (e.g., study onset or when placebo patients were switched to full dose or half-dose at the beginning of the extension phase) or after an increase in dose (e.g., when half-dose patients were switched to full dose at the beginning of the extension phase under the amended protocol) than during more extended treatment with either half-dose or full dose Serostim.

Protocol-Directed Dose Reductions/Interruptions Due to Adverse Events :

During the placebo controlled phase of the study, 22.5% of patients in the full dose Serostim group, 10.5% of patients in the half-dose Serostim group, and 6.9% of patients in the placebo group required 1 or more dose reductions. **Once again, a clearcut dose response is evident.** The most common reasons for dose reductions during the placebo controlled phase of the study were similar to those which resulted in study discontinuation.

TEAEs:

During the placebo controlled phase of the study, 608 adverse events were reported in 188 patients treated with placebo, 796 adverse events in 197 patients treated with half-dose Serostim, and 971 adverse events in 216 patients treated with full dose Serostim. The most common TEAEs were those most likely related to treatment with rhGH: arthralgia (36.4% in the full dose Serostim group, 24.5% in the half-dose Serostim group and 11.3% in the placebo group), myalgia (30.4% in the full dose Serostim group, 17.9% in the half-dose Serostim group and 11.7% in the placebo group), peripheral edema (26.1% in the full dose Serostim group, 11.3% in the half-dose Serostim group and 2.8% in the placebo group), and paraesthesia (7.9% in the full dose Serostim group, 7.4% in the half-dose Serostim group and 4.5% in the placebo group).

Yet again, a clearcut dose response is apparent. Adverse events including arthralgia/myalgia, peripheral edema, and carpal tunnel syndrome/paraesthesia were more frequent during Serostim treatment than during placebo treatment,

and more frequent in the full dose group than the half-dose group. These kinds of events are well known during rhGH treatment, and thought to be related to the effects of rhGH on fluid homeostasis and interstitial matrix.

As previously discussed, this dose response relationship is also evident when one examines the adverse events 1) leading to study discontinuation and 2) requiring protocol-driven dose interventions.

rhGH-Related Adverse Events/Effects:

Well Known rhGH-Related Adverse Events/Effects, i.e. Arthralgia/Myalgia, Edema, Carpal Tunnel Syndrome/Paraesthesia:

Already discussed.

Severe But Unusual rhGH-Related Adverse Events/Effects:

None of the more severe but unusual adverse events associated with rhGH therapy **in children and potentially applicable to adults** (e.g., benign intracranial hypertension, proliferative retinopathy, hypercalcemia, or pancreatitis) was reported during this study.

Glucose Intolerance/Hyperglycemia:

Five patients in the full dose Serostim group, 3 patients in the half-dose Serostim group, and 5 patients in the placebo group had fasting blood glucose levels >126-250 mg/dL at baseline **(i.e., overt diabetes mellitus was present and these patients should not have been enrolled in the study).**

Mean changes in fasting blood glucose levels during the placebo controlled phase were dose-dependent, and ranged from 2 to 10 mg/dL. Shift table analysis during the 12 week, placebo controlled phase of the study **indicates that the number of patients with elevated fasting blood glucose levels increased soon after Serostim therapy initiation** (in the full dose Serostim group much more often than the half-dose Serostim group, i.e. at Week 4, 6.4% of placebo-treated patients, 13.5% of half-dose Serostim-treated patients, and 18% of full dose Serostim-treated patients had fasting blood glucose levels 110-126 mg/dL, and 4.3% of placebo-treated patients, 3.7% of half-dose Serostim-treated patients, and 9.2% of full dose Serostim-treated patients had fasting blood glucose levels >126-250 mg/dL), **and then seemed to plateau** (at Weeks 8 and 12).

In patients treated with full dose Serostim for 24 weeks, mean change in fasting blood glucose was 11.1 mg/dL, i.e. **mean fasting blood glucose did not increase further during the second 12 weeks of full dose Serostim**

therapy. In the groups continued on either full dose or half-dose Serostim for an additional 12 weeks during the extension phase, the number of patients with abnormal sugars at Weeks 16, 20 and 24 was similar to the number of patients with abnormal sugars at Week 12, i.e. there was no progressive increase in the number of patients with abnormal sugars.

Twenty nine patients manifested a fasting blood glucose level >160 mg/dL at least once, or a fasting blood glucose level >140 mg/dL on 2 or more occasions, at some time during the study, but did not have per protocol interventions performed. Twenty five patients manifested a fasting blood glucose level >160 mg/dL at some time during the trial resulting in an intervention including 21 patients who required dose reduction (fasting blood glucose levels usually normalized), and 8 patients who were discontinued from the study because of hyperglycemia (2 during the placebo controlled phase and 6 during the extension phase). Of note, 7 of these 8 patients were receiving full dose Serostim when they were terminated including the 2 patients discontinued during the placebo controlled phase of the study. Four of these 8 patients manifested de novo diabetes mellitus on-study - 1 while receiving full dose Serostim during the placebo controlled phase of the study, 2 while receiving full dose Serostim during the extension phase, and 1 while receiving half-dose Serostim during the extension phase. Three other patients were previously known to be diabetic or hyperglycemic by history.

It is clear from the data summarized above that glucose intolerance was common during this study, and, in some patients, resulted in substantial hyperglycemia. These findings are not at all surprising. It is well established (from many clinical trials and extensive post-marketing experience) that treatment of GHD adults (and children) with rhGH may result in insulin resistance, impaired glucose tolerance, and occasionally overt diabetes mellitus (38-39). Patients with HIV-/AIDS-associated cachexia treated with rhGH appear to be at greater risk for glucose intolerance due to multiple reasons, including the potential diabetogenic effects of PIs (rhGH use in the treatment of AIDS-asociated wasting was recently reviewed in references 26-28; also see Serono Study Report 5341 and its associated publication in reference 29). Furthermore, in this regard, the ***PRECAUTIONS*** section of the Package Insert for Serostim required modification in CY 2000 to alert prescribing physicians to the potential of Serostim-induced glucose intolerance - based on multiple cases of new onset diabetes mellitus/impaired glucose tolerance reported during post-marketing surveillance since approval of Serostim for treatment of AIDS-associated wasting in 1996.

Gynecomastia:

Gynecomastia was reported in 14 male patients in the full dose group, 9 male patients in the half-dose group, and only 1 male patient in the placebo group during the placebo controlled portion of the study; during the extension phase, 37 male patients receiving full dose Serostim manifested gynecomastia compared

with only 4 patients receiving half-dose Serostim. A dose response effect is evident.

Dose related gynecomastia has previously been reported as a possible rhGH-induced adverse reaction in children with GHD (40) and adults without GHD (41). The mechanism of action is not clearly understood. In the opinion of this Medical Officer, in the case of male patients with HIV-/AIDS-associated wasting, the effects of "refeeding" and increase in LBM on serum levels of testosterone and estradiol (and their ratio) may have been contributory. In addition, HAART products have been clearly associated with gynecomastia, including PIs such as indinavir and saquinavir, both of which were administered during Study GF-9037 (42-43).

Additionally, there were 13 patients (13 events) in the full dose Serostim group and 5 patients (7 events) in the half-dose Serostim group with events coded as breast neoplasm, male, including tender areolar and nipple nodularity. Breast malignancy was not diagnosed in any of these patients.

The absence of signs/symptoms of malignancy, the presence of a dose response relationship, the occurrence of 75% of these events within 3 months of therapy, and the fact that none of these events continued to worsen during the study (in fact, 100% of these events fully resolved during the study, usually within 4 months) suggest that these events most likely are a reflection of rhGH-induced gynecomastia (as previously reported), and not breast malignancy.

Although possible correlation has recently been observed between the serum IGF-I level and the incidence of breast carcinoma, there are no data in the Medline database at the present time linking breast malignancy and short-term (or, for that matter, long-term) exposure to rhGH.

Immunogenicity:

Anti-rhGH antibodies were not detected during the study (at Weeks 12 and 48).

Other rhGH-Related Issues :

IGF-I SDS:

In patients with baseline mean serum IGF-I SDS -1 to +1, 2 and 3 patients receiving placebo attained post-treatment mean serum IGF-I SDS >+2 to +3 and >+3, respectively, **33 and 17 patients receiving half-dose Serostim attained post-treatment mean serum IGF-I SDS >+2 to +3 and >+3, respectively, and 24 and 55 patients receiving full dose Serostim attained post-treatment mean serum IGF-I SDS >+2 to +3 and >+3, respectively. ~40% of patients receiving full dose Serostim attained mean serum IGF-I SDS >+3 (in contrast to ~15% of patients receiving half-dose Serostim). It is clear that that the IGF-I response is dose-dependent.**

If sustained, IGF-I SDS >+2 or, indeed, >+3, could be associated with clinical acromegaloid phenomena (which did not occur during this study) and, theoretically, oncogenic sequelae. However,

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Malignancy:

In the opinion of this Medical Officer, of the 5 malignancies which occurred during the study, only the 2 cases of lymphoma (both patients were receiving full dose Serostim at the time of diagnosis) could possibly have been AIDS-related malignancies.

In addition, no new cases of Kaposi's sarcoma or exacerbation of preexisting Kaposi's sarcoma were reported, no changes in pigmented nevi were noted, and no cases of breast carcinoma, prostatic carcinoma, colon carcinoma, osteogenic sarcoma or leukemia were diagnosed.

HIV-related Issues:

Viral Load and CD4 T-lymphocyte Counts:

The median differences in change from baseline for both viral load (HIV RNA) and CD4 T-cell counts were not significant for either of the Serostim groups compared to placebo (when patients were analyzed as a group or separately as per HAART usage).

Nonetheless, as clearly stated in the existing Package Insert, practitioners prescribing Serostim for HIV-/AIDS-associated wasting always need to concurrently administer HAART or some other antiretroviral therapy because of the theoretical risk of rhGH-induced HIV propagation (30).

AIDS-Related Opportunistic Infections Recorded as SAEs or TEAEs:

Seven SAEs reported by 7 patients during the placebo controlled phase of the study possibly resulted from AIDS-defining/related opportunistic infections. **These infections did not occur predominantly in the Serostim-treated groups.**

Eight SAEs reported by 8 patients (5 receiving full dose Serostim and 3 receiving half-dose Serostim) during the extension phase of the study possibly resulted from AIDS-defining/related opportunistic infections.

In Study 5341, there was also no increase in the incidence of AIDS-associated opportunistic infections in patients receiving full dose Serostim compared with patients treated with placebo. In addition,

the types of AIDS-indicator diseases reported during the study were similar for the 2 treatment groups.

VI.A.5.8.2 Safety - Conclusions

- None of the 6 deaths which occurred during the study were felt to be related to the administration of Serostim by the Sponsor or this Medical Officer.
- Except for 2 patients with significant hyperglycemia and 1 patient with severe gynecomastia, none of the 88 SAEs reported by 66 patients during the entire study were felt to be related to the administration of Serostim by the Sponsor or this Medical Officer.
- A total of 46 patients were discontinued due to adverse events during the placebo controlled phase of the study. **A dose response relationship was apparent across the 3 treatment groups with respect to the frequency of adverse events leading to study drug discontinuation, in particular adverse events most likely related to Serostim.**
  - More of these adverse events most likely related to Serostim therapy leading to discontinuation during either phase of the study occurred when either dose of Serostim was first initiated (e.g., study onset or when placebo patients were switched to full dose or half-dose at the beginning of the extension phase) or after an increase in dose (e.g., when half-dose patients were switched to full dose at the beginning of the extension phase under the amended protocol) than during more extended treatment with either half-dose or full dose Serostim.
- **A dose response relationship was apparent across the 3 treatment groups with respect to the frequency of adverse events requiring protocol-directed dose reductions, in particular adverse events most likely related to Serostim.**
- **A dose response relationship was apparent across the 3 treatment groups with respect to the frequency of TEAEs, in particular adverse events most likely related to Serostim.**
  - **Adverse events including arthralgia/myalgia, peripheral edema, and carpal tunnel syndrome/paraesthesia were more frequent during Serostim treatment than during placebo treatment, and more frequent in the full dose group than the half-dose group. These kinds of events are well known during rhGH treatment, and thought to be related to the effects of rhGH on fluid homeostasis and interstitial matrix.**
- None of the more severe but unusual adverse events associated with rhGH therapy in children and potentially applicable to adults (e.g., benign intracranial hypertension, proliferative retinopathy, hypercalcemia, or pancreatitis) was reported during this study.
- **Glucose intolerance was common during this study, and, in some patients, resulted in substantial hyperglycemia.**
  - Mean changes in fasting blood glucose levels during the placebo controlled phase were dose-dependent, and ranged from 2 to 10 mg/dL.

- Shift table analysis during the 12 week, placebo controlled phase of the study indicates that the number of patients with elevated fasting blood glucose levels increased soon after Serostim therapy initiation (in the full dose Serostim group much more often than the half-dose Serostim group), and then seemed to plateau.
- In patients treated with full dose Serostim for 24 weeks, mean fasting blood glucose did not increase further during the second 12 weeks of full dose Serostim therapy.
- In the groups continued on either full dose or half-dose Serostim for an additional 12 weeks during the extension phase, there was no progressive increase in the number of patients with abnormal sugars.
- Twenty five patients manifested a fasting blood glucose level >160 mg/dL at some time during the trial resulting in an intervention.
  - 21 patients required dose reduction (fasting blood glucose levels usually normalized).
  - 8 patients were discontinued from the study because of hyperglycemia (2 during the placebo controlled phase and 6 during the extension phase). Of note, 7 of these 8 patients were receiving full dose Serostim when they were terminated including the 2 patients discontinued during the placebo controlled phase of the study. Four of these 8 patients manifested de novo diabetes mellitus on-study - 1 while receiving full dose Serostim during the placebo controlled phase of the study, 2 while receiving full dose Serostim. during the extension phase, and 1 while receiving half-dose Serostim during the extension phase. Three other patients were previously known to be diabetic or hyperglycemic by history.
- A significant number of patients manifested gynecomastia during the study. A dose response effect was evident.
  - rhGH-induced gynecomastia has previously been reported in adults and children, and the mechanism is not clear.
  - Gynecomastia was reported in 14 male patients in the full dose group, 9 male patients in the half-dose group, and only 1 male patient in the placebo group during the placebo controlled portion of the study; during the extension phase, 37 male patients receiving full dose Serostim manifested gynecomastia compared with only 4 patients receiving half-dose Serostim.
  - Additionally, there were 13 patients (13 events) in the full dose Serostim group and 5 patients (7 events) in the half-dose Serostim group with events coded as breast neoplasm, male.
    - The absence of signs/symptoms of malignancy, the presence of a dose response relationship, the occurrence of 75% of these events within 3 months of therapy, and the fact that none of these events continued to worsen during the study (in fact, 100% of these events fully resolved during the study, usually within 4 months) suggest that these events most likely are a reflection of rhGH-induced gynecomastia, and not breast malignancy.

- **~40% of patients receiving full dose Serostim attained mean serum IGF-I SDS >+3 (in contrast to ~15% of patients receiving half-dose Serostim). It is clear that the IGF-I response is dose-dependent.**
  - If sustained, IGF-I SDS >+2 or, indeed, >+3, could be associated with clinical acromegaloid phenomena (which did not occur during this study) and, theoretically, oncogenic sequelae. **However,**

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- In the opinion of this Medical Officer, of the 5 malgnancies which occurred during the study, **only the 2 cases of lymphoma** (both patients were receiving full dose Serostim at the time of diagnosis) **could possibly have been AIDS-related malignancies.**
- The median differences in change from baseline for both viral load (HIV RNA) and CD4 T-cell counts were not significant for either of the Serostim groups compared to placebo.
  - **Nonetheless, as clearly stated in the existing Package Insert, practitioners prescribing Serostim for HIV-/AIDS-associated wasting always need to concurrently administer HAART or some other antiretroviral therapy because of the theoretical risk of rhGH-induced HIV propagation.**
- Seven SAEs reported by 7 patients during the placebo controlled phase of the study possibly resulted from AIDS-defining/related opportunistic infections. **These infections did not occur predominantly in the Serostim-treated groups.**

VI.A.5.8.3 Safety Recommendations

- This Medical Officer strongly endorses the Sponsor's intention to

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Substantial instances of glucose intolerance reported during post-marketing surveillance since the 1996 launch of Serostim in patients with AIDS-associated wasting led to an important modification of the PRECAUTIONS section of the Serostim Package Insert in CY 2000.

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- The Division strongly endorses the Sponsor's intention to

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- In that 12 weeks of treatment with half-dose Serostim results in an identical BWO result as full dose Serostim, and a significant LBM

result (~half as much as full dose Serostim), and substantially less adverse effects compared with full dose Serostim, half-dose Serostim should be used more as initial therapy, especially in patients already diagnosed with diabetes mellitus/impaired glucose intolerance, edema forming diseases such as congestive heart failure, cirrhosis and nephrosis, and musculoskeletal disease, or at significant risk for these diseases. In this regard, a) the ADVERSE REACTIONS section of the most recently proposed Package Insert was modified by this Medical Officer to more clearly reflect the substantially greater amount of rhGH-related adverse effects after treatment with full dose Serostim compared with half-dose Serostim, and b) the DOSAGE AND ADMINISTRATION section of the most recently proposed Package Insert was modified by this Medical Officer to make prescribing physicians more aware that half-dose Serostim may well be a reasonable alternative to full dose Serostim in certain patients.

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VI.A.5.10 Edited Labeling

This Medical Officer extensively edited the entire Package Insert originally submitted by the Sponsor, in particular the Clinical Studies, Indications and Usage, Precautions, Adverse Reactions, and Dosage and Administration sections. Subsequently, several productive, interactive labeling teleconferences between the Division and the Sponsor transpired in June/July 2003. **The Package Insert attached below represents the end product of these teleconferences and is acceptable to both the Division and the Sponsor.**

[redacted] b(4)

12 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Medical- 20-604
5027

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/s/

Robert Perlstein
8/27/03 05:43:14 PM
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David Orloff
8/27/03 05:46:44 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-604/S027

STATISTICAL REVIEW(S)

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

Statistical Review and Evaluation
CLINICAL STUDIES

NDA:	20-604/SE8-027
Name of drug:	Serostim™ [somatropin (rDNA origin) for injection]
Applicant:	Serono, Inc
Indication:	Treatment of HIV-associated catabolism/wasting
Documents reviewed:	Electronic submission \\CDSESUB1\N20604\S_027\2002-10-31
Project manager:	Monika Johnson (HFD-510)
Clinical reviewer:	Robert Perlstein, M.D. (HFD-510)
Dates:	Received October 31, 2002; user fee (10 month) August 31, 2003
Statistical reviewer:	Lee-Ping Pian, Ph.D. (HFD-715)
Statistics team leader:	Todd Sahlroot, Ph.D. (HFD-715)
Biometrics division director:	Ed Nevius, Ph.D. (HFD-715)

Keywords: NDA review, clinical studies, analysis of covariance

1 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 CONCLUSIONS AND RECOMMENDATIONS

1.2 OVERVIEW OF CLINICAL PROGRAM AND STUDIES REVIEWED

This Subpart H supplemental application for Serostim contained a Phase 4 confirmatory study in fulfillment of the conditional approval granted under Subpart H on August 23, 1996. The Phase 4 study was to verify and describe the clinical benefit of Serostim in treatment of HIV-associated catabolism/wasting.

Study 9037 was a randomized, parallel group, double-blind, placebo-controlled, dose-ranging, multicenter study to compare the efficacy and safety of r-hGH versus placebo in the treatment of HIV-associated catabolism/wasting for 12 weeks. The study was initiated in August 1997 and was completed in February 2002

The primary efficacy comparison was the change in bicycle ergometer work output from baseline to Week 12 between the Serostim® full dose group and the placebo group. Secondary dose-finding comparisons were the change in LBM as measured by BIS from Baseline to Week 12 between the two Serostim® treatment groups and the placebo group.

The sponsor stated in the Discussion and Overall Conclusions section that "A total of 770 patients were enrolled in 56 investigative sites in 9 countries. Fifty-seven percent of the patients were enrolled in the USA, 32% in European countries, 10% in Australia and 1% in Thailand. The patients in the evaluable patient population, i.e., patients who were 80% compliant to the treatment, were mostly homosexual (78%) men (91%), aged 40 (median; range 21-77 years) receiving HAART (87.6%). Thus, the patients were representative of patients with HIV-infection and AIDS associated wasting, and the patients were appropriately treated with antiretroviral therapies. There were 111 withdrawals during the double-blind study phase, mostly from the Serostim dose groups and primarily due to AEs or patient decision, which in some cases was related to AEs. Six hundred and forty-six of 757 treated patients completed this period and continued into the extension phase."

The results from the primary efficacy analysis were "Treatment with Serostim resulted in improvements in maximum work output. The median increase after 12 weeks was 2.35 kJ in the half-dose group and 2.60 kJ in the full-dose group (within group p-values < 0.0001). The median treatment effect was 2.85 kJ compared to placebo ($p<0.0001$)." The results from the secondary efficacy analysis were "The BIS measurements demonstrated a dose-dependent increase in LBM. The median increase was 3.33 kg in the half-dose group and 5.21 kg in the full-dose group during the 12 weeks of double-blind treatment. Both changes were statistically significant relative to the change in the placebo group ($p<0.0001$)."

The sponsor's overall conclusion was "this study demonstrates that Serostim treatment was effective to improve physical function. Serostim® at a dosage of 0.1 mg/kg/day was superior to 0.1 mg/kg every other day in the treatment of HIV-associated wasting. Beneficial and dose-dependent effects were observed on body weight and composition and quality of life." The effects obtained by dosing every other day were similar in magnitude to those obtained by dosing every day over an extended treatment duration of 24 to 48 weeks. A dosage regimen of 0.1 mg/kg every other day was slightly better tolerated and accompanied with fewer adverse events than 0.1 mg/kg/day."

Both Serostim 0.1 mg/kg every day and Serostim 0.1 mg/kg every other day were superior to placebo in the primary efficacy comparison for ergometer maximum work output (kilojoules). However, Serostim 0.1 mg/kg every day was not superior to Serostim 0.1 mg/kg every other day. The study was not designed for a head-to-head comparison of the 2 dose groups but to placebo group.

The subgroup analysis in gender, race, etc., was not performed.

1.3 STATISTICAL EVALUATION OF EVIDENCE ON EFFICACY / SAFETY

1.3.1 SPONSOR'S RESULTS AND CONCLUSIONS

The sponsor's primary analysis was based on the evaluable population which was defined as all patients included in the ITT population who completed the Week 12 evaluations and were at least 80% compliant with their dose regimen. The 'ITT' population for the bicycle ergometry work output primary endpoint excluding the inconsistent ergometer readings comprised 570 patients and the evaluable population 555 patients. The sponsor presented results for the primary efficacy variable, change from baseline to week 12 for bicycle work output (kilojoules) using the evaluable patient population. The analysis of variance on ranked data included treatment and pooled center as fixed factors. The median change for bicycle work output increased by 2.35 kJ (baseline, 26.45 kJ, n=190) in the half-dose Serostim group and by 2.60 kJ (baseline, 26.35 kJ, n=166) in the full-dose Serostim group while the median change of the placebo group was –0.25 kJ (baseline, 25.2, n=199). The primary efficacy comparison between the full-dose Serostim group to the placebo group was statistically significant ($p<0.001$) with a median difference of 2.85 kJ and a 95% confidence interval of 1.40 kJ to 4.20 kJ (Table 3).

Table 1 Bicycle work output (kilojoules), change from baseline to week 12 by treatment group for the Evaluable Patient Population.

Time Point	Statistics	Placebo	Half-Dose Serostim*	Full-Dose Serostim*
Baseline	n	199	190	166
	Median	25.20	26.45	26.35
	Range	(2.90, 81.30)	(0.00, 99.20)	(3.20, 82.00)
Change from Baseline to Week 12	n	199	190	166
	Median	-0.25	2.35	2.60
	Range	(-26.70, 27.90)	(-22.60, 46.30)	(-40.70, 46.30)
Treatment Comparison versus Placebo				
Change from Baseline to Week 12	Median Difference			2.85
	95% Confidence Interval			(1.40, 4.20)
	p-value[2]			<0.0001

(1) Bicycle observations whose values are inconsistent with time on the bike and the bicycle protocol are excluded from the analysis.

(2) p-value from an ANOVA on ranked data with effects for treatment (trt) and pooled center (p-centr)

The sponsor concluded "The results from the assessment of physical function by bicycle ergometry showed statistically and clinically significant improvements during Serostim® 6mg daily treatment. The median treatment effect was 2.85 kJ ($p<0.0001$ versus placebo)."

1.3.2 STATISTICAL METHODOLOGIES

Interim analyses
Two interim analyses were performed using the O'Brien-Fleming procedure when 1/3 and 2/3 of the patients had completed 12 weeks of treatment or withdrew during the double blind period. The adjusted α values for the 2 interim analyses and the final analyses of bicycle ergometer work output were 0.0005, 0.014, and 0.045. The 2 purposes of the interim analyses were to recalculate the sample size if the estimated variance is imprecise and to stop the enrollment if a statistically significant difference was obtained between the full dose Serostim group and the placebo group in bicycle ergometer work output. Table 2 displays a summary of the interim analyses.

Table 2 Summary of interim analyses in bicycle ergometer work output

	1st Interim	2nd Interim
n	244	488
Date	October/November 2000	November 2001
Difference from placebo	not significant	2.2 kJs (p=0.0012)

Based on the 2 interim analyses the sponsor did not amend the protocol to change the sample size. The study was not stopped based on the 2nd interim analysis because the last patient had already been randomized on September 26, 2001 prior to the interim analysis.

Efficacy analysis

The primary efficacy comparison was the change in bicycle ergometer work output from baseline to week 12 between the full dose Serostim group and the placebo group. For all other outcomes except bicycle ergometer work output, Hochberg's multiple comparison procedure was used to compare each of the 2 Serostim treatment groups to the placebo group.

The analysis of variance was performed on the ranked data (nonparametric test) since the ANOVA model assumptions were not satisfied. Medians, pairwise treatment differences (Hodges-Lehmann method), p-value, and confidence intervals (Moses method) were presented.

The comparison between half dose Serostim and placebo on the primary endpoint was not in the primary analysis plan. This reviewer applied Hochberg's multiple comparison procedure to compare each of the 2 dose groups to the placebo group.

This reviewer performed parametric tests, which are robust to deviations from the normal distribution assumption, as long as the sample size is large. With over 200 patients in each treatment group, the central limit theorem will ensure that parametric tests work well even if the population distribution is non-normal.

1.3.3 DETAILED REVIEW OF INDIVIDUAL STUDIES

Study GF 9037

1.3.3.1

The study was initiated in the US in 1997, and expanded in 1999 to include Europe, Australia and Asia.

The selected dose in full dose Serostim group was the same as that of the previous phase 3 study, 0.1 mg/kg/day with a maximum daily dose of 6 mg/day. The objective of the study was to confirm the effects observed from treatment with this dose and secondly to assess effects at a half dose regimen of an injection of the full dose every other day.

The primary efficacy comparison was the change in bicycle ergometer work output from Baseline to Week 12 between the Serostim® full dose group and the placebo group. Secondary dose-finding comparisons were the change in LBM as measured by BIS from Baseline to Week 12 between the two Serostim® treatment groups and the placebo group.

Patient Disposition

A total of 770 patients were randomized and 757 patients treated. Patient randomization by geographic region is shown in Table 3.

Table 4 shows patient disposition during the placebo-controlled, double-blind 12 weeks study period and during the open-label extension by treatment group and for all patients.

Table 3 Patient randomization by geographic region

Region	Placebo (n=255) n (%)	Half-Dose Serostim* (n=259) n (%)	Full-Dose Serostim* (n=256) n (%)	All Patients (n=770) n (%)
USA	144 (56.5)	147 (56.8)	146 (57.0)	437 (56.8)
Europe	82 (32.2)	82 (31.7)	82 (32.0)	246 (31.9)
Australia	26 (10.2)	27 (10.4)	26 (10.2)	79 (10.3)
Asia	3 (1.2)	3 (1.2)	2 (0.8)	8 (1.0)

Table 4 Patient disposition

Disposition During First 12 Weeks	Placebo		Half-Dose Serostim*		Full-Dose Serostim*	All Patients
Number of Randomized Patients	255		259		256	770
Number of Treated Patients	247		257		253	757
Number of Treated Patients who Discontinued Prior to Week 12	21		38		52	111
Number of Treated Patients who Completed Week12	226		219		201	646
Disposition During the Extension	**Placebo to Half-Dose Serostim***	**Placebo to Full-Dose Serostim***	**Half-Dose to Half-Dose Serostim***	**Half-Dose to Full-Dose Serostim***	**Full-Dose to Full-Dose Serostim***	**All Patients**
Number of Treated Patients in Extension Period	44	182	81	138	201	646
Number of Treated Patients Completing 24 Weeks of Treatment	34	145	73	122	174	548
Number of Treated Patients Completing 48 Weeks of Treatment	30	29	62	0	56	177

Of the 757 treated patients, 670 (89%) patients were assessed at baseline and at least once during follow up for bicycle ergometer work output before 98 days (ITT population). Table 5 displays demographic characteristics of the ITT population for the change in bicycle ergometer work output.

Table 4 Descriptive statistics at baseline

		Placebo	Half-Dose Serostim	Full-Dose Serostim	All Patients
Age (yrs)	n	222	230	218	670
	Mean (SD)	40.6 (8.0)	41.0 (8.4)	40.8 (8.1)	
	Median	40.0	40.0	39.5	40.0
	Range	(21, 68)	(24, 77)	(24, 73)	(21, 77)
Sex, n (%)	Male	201 (91%)	212 (92%)	198 (91%)	611 (91%)
	Female	21 (9%)	18 (8%)	20 (3%)	59 (9%)
Race, n(%)	White	177 (80%)	175 (76%)	157 (72%)	509 (76%)
	Black	18 (8%)	18 (8%)	26 (12%)	62 (9%)
	Asia	4 (2%)	4 (.6%)	5 (.8%)	13 (2%)
	Hispanic	20 (9%)	31 (13%)	30 (14%)	81 (12%)
	Other	3 (1%)	0	2 (.9%)	5 (.8%)

Treatment groups were similar in mean BMI, weight and height at baseline. Mean BMI was 21.2 (SD=2.8) kg/m^2, mean weight was 66.0 (SD=10.3) kg, and the mean height was 141 (SD=51) cm at baseline.

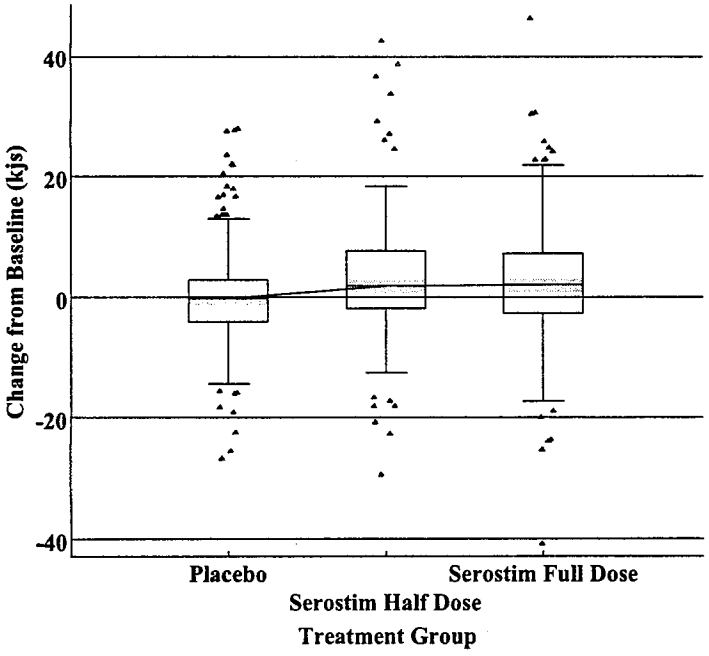
Primary Efficacy Outcome

Table 6 displays descriptive statistics of bicycle ergometer work output and Figure 1 the boxplot of the change from baseline bicycle ergometer work output for the ITT population.

Table 5 Descriptive statistic of bicycle ergometer work output

		Placebo	Half-Dose Serostim	Full-Dose Serostim
	n	222	230	218
Baseline (kJ)	Mean (SD)	26.5 (14.5)	28.3 (17.4)	38.1 (16.9)
	Median	22.45	24.05	23.35
	Range	(2.9, 81.3)	(0, 99.2)	(3.2, 82.0)
Endpoint (kJ)	Mean (SD)	26.7 (15.6)	30.9 (18.3)	30.7 (17.9)
	Median	22.15	27.25	26.55
	Range	(0.4, 98)	(0.0, 123.1)	(0.2, 83.7)
Change (kJ)	Mean (SD)	0.20 (8.43)	2.57 (9.65)	2.57 (9.81)
	Median	-0.2	2.1	1.9
	Range	(-26.7, 27.9)	(-29.4, 42.6)	(-40.7, 46.3)

Figure 1 Boxplot of change in bicycle ergometer work output



This reviewer performed analysis of variance on the primary efficacy variable with treatment and center as fixed factors in the model (Table 5).

Table 6 Results of ANOVA on Change from baseline bicycle ergometer work output (kJ) - ITT

	Placebo	Half-Dose Serostim	Full-Dose Serostim
n	222	230	218
Baseline (kJ) LSM (SE)	25.92 (1.09)	27.79(1.07)	27.57 (1.10)
Change (kJ) LSM (SE)	-0.05 (0.65)	2.48 (0.63)	2.52 (0.66)
Difference from Placebo LSM (CI)	-	2.53 (0.81, 4.25)	2.57 (0.83, 4.31)
p-value*		0.004	0.004

*Hochberg step-up procedure

The p value (0.004) from each of the 2 treatment comparisons versus placebo were adjusted using Hochberg step-up procedure. In addition, this p value is less than the 0.045 significance level for the final analysis of the interim analysis using the O'Brien-Fleming multiple testing procedure. Therefore, it is concluded that both the full dose and the half dose were statistically significant better than placebo in change from baseline bicycle ergometer work output.

1.4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Race

The overall treatment-by-race interaction was statistically significant ($p<0.01$) for change from baseline bicycle ergometer work output. The interaction term used 2 categories for treatment (Serostim, placebo) and 2 categories for race (Caucasian, Hispanic and Black). Table 7 displays the descriptive statistics by treatment and race. The interaction was qualitative in nature. The mean change from baseline ergometer work output in patients on Serostim was better in patients on placebo in Whites, but the placebo was better in Hispanics and Blacks. However, the finding is exploratory and requires clinical assessment.

Table 7 Mean (SD) change from baseline bicycle ergometer work output (kJ) by race

Treatment	White			Hispanic			Black			Asia			Other		
Serostim	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD
Full Dose	157	3.81	9.35	30	-0.58	11.71	26	-2.07	8.12	5	6.74	10.32			
Half Dose	175	3.23	9.95	31	0.66	9.76	18	0.24	6.82	4	2.18	3.07	2	-4.25	3.61
Placebo	177	-0.19	8.49	20	1.41	9.51	18	3.09	7.67	4	-0.93	2.10	3	-0.67	6.60

1.5 CONCLUSIONS AND RECOMMENDATIONS

Serostim 0.1 mg/kg/day daily injection (full dose) and every other day injection (half dose) for 12 weeks were statistically significantly superior to placebo ($p<0.01$) in the change from baseline in bicycle ergometer work output (kJ). The least square mean differences from placebo were 2.53 kJ and 2.57 kJ, respectively, for the half dose group and full dose group. The corresponding confidence intervals were (0.81, 4.25) and (0.83, 4.31), respectively. Therefore, both doses confirmed the clinical efficacy of Serostim in HIV –associated catabolism/wasting.

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/s/

Lee-Ping Pian
8/14/03 04:16:15 PM
BIOMETRICS

Todd Sahlroot
8/20/03 11:56:14 AM
BIOMETRICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-604/S027

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY FOR NDA # 20-604 SUPPL #_____

Trade Name Serostim™ Generic Name [somatropin (rDNA origin) for injection]

Applicant Name Serono Laboratories, Inc. HFD # 510 CSO: Pauls

Approval Date If Known_____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /X/ NO /__/

b) Is it an effectiveness supplement?

YES /__/ NO /__/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /X/ NO /__/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /__/ NO /_X_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use?

YES /__/ NO /_X_/

If yes, NDA #_____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /__/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X_/ NO /__/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 19-640 Humatrope [somatropin (rDNA)]

NDA# 19-676 and 20-168 Nutropin " "

NDA# 19-721 Norditropin " "

+ NDAs 20-280 (Genotropin) and 19-774 (Biotropin)

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /__/ NO /__/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /X/ NO /__/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /X/ NO /__/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /__/ NO /X/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /__/ NO /_X_/ However, Orphan Drug Exclusivity previously granted.

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /__/ NO /_X_/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

5341

_____ _____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /__/ NO /_X_/

Investigation #2 YES /__/ NO /__/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /__/ NO /_X_/

Investigation #2 YES /__/ NO /_X_/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

5341 _____

7033 _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 38,087 YES /X/ ! NO /__/ Explain: _____

Investigation #2

IND # 38,087 YES /__/ ! NO /__/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /__/ Explain _____ ! NO /__/ Explain _____

Investigation #2

YES /__/ Explain _____ ! NO /__/ Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /__/ NO /X/

If yes, explain: _____

Lana L. Pauls, M.P.H.

Signature

Date 3/28/96

Title: Regulatory Health Project Manager

Solomon Sobel, M.D.

Signature of Office/
Division Director

Date 4/12/96

cc: Original NDA Division File HFD-85 Mary Ann Holovac

13. PATENT INFORMATION

Reference is made to Serostim® NDA 20-604 for complete patent information.

16. DEBARMENT CERTIFICATION

Debarment Certification Statement.

In accordance with Section 306(k)(1) of the Federal, Drug, and Cosmetic Act, the undersigned hereby certifies that Serono, Inc. did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) [section 306 (a) or (b)], in connection with this application.

Rosann J. Reinhart
Executive Director, Regulatory Affairs

23-OCT-02
Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: June 30, 2002

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☑ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	See section 19.1 and 19.2 attached	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Pamela Williamson Joyce	Vice President, US Regulatory Affairs
FIRM/ORGANIZATION: Serono, Inc.	
SIGNATURE	DATE: October 30, 2002

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

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19. FINANCIAL DISCLOSURE

19.1 FINANCIAL DISCLOSURE OBTAINED FROM THE FOLLOWING INVESTIGATORS AND SUBINVESTIGATORS

Site #	Investigator	Sub-Investigator	Address	Number of patients enrolled
	Anthony LaMarca, M.D.			
	Anthony LaMarca, M.D.			
	Tlaloc Alferez, M.D.			
	David Brand, M.D.			
	Gregg Coodley, M.D., F.A.C.P.			
	Adrian Dobs, M.D., M.H.S.			
	Jeffrey Fessel, M.D.			

b(6)

b(6)

Site #	Investigator	Sub-Investigator	Address	Number of patients enrolled
	Deborah Goldsmith, M.D.			
	Abby Shevitz, M.D.			
	Kedarnath Javaly, M.D.			
	Donald Kotler, M.D.			
	W. Christopher Matthews,			
	Ardis Moe, M.D.			

b(6)

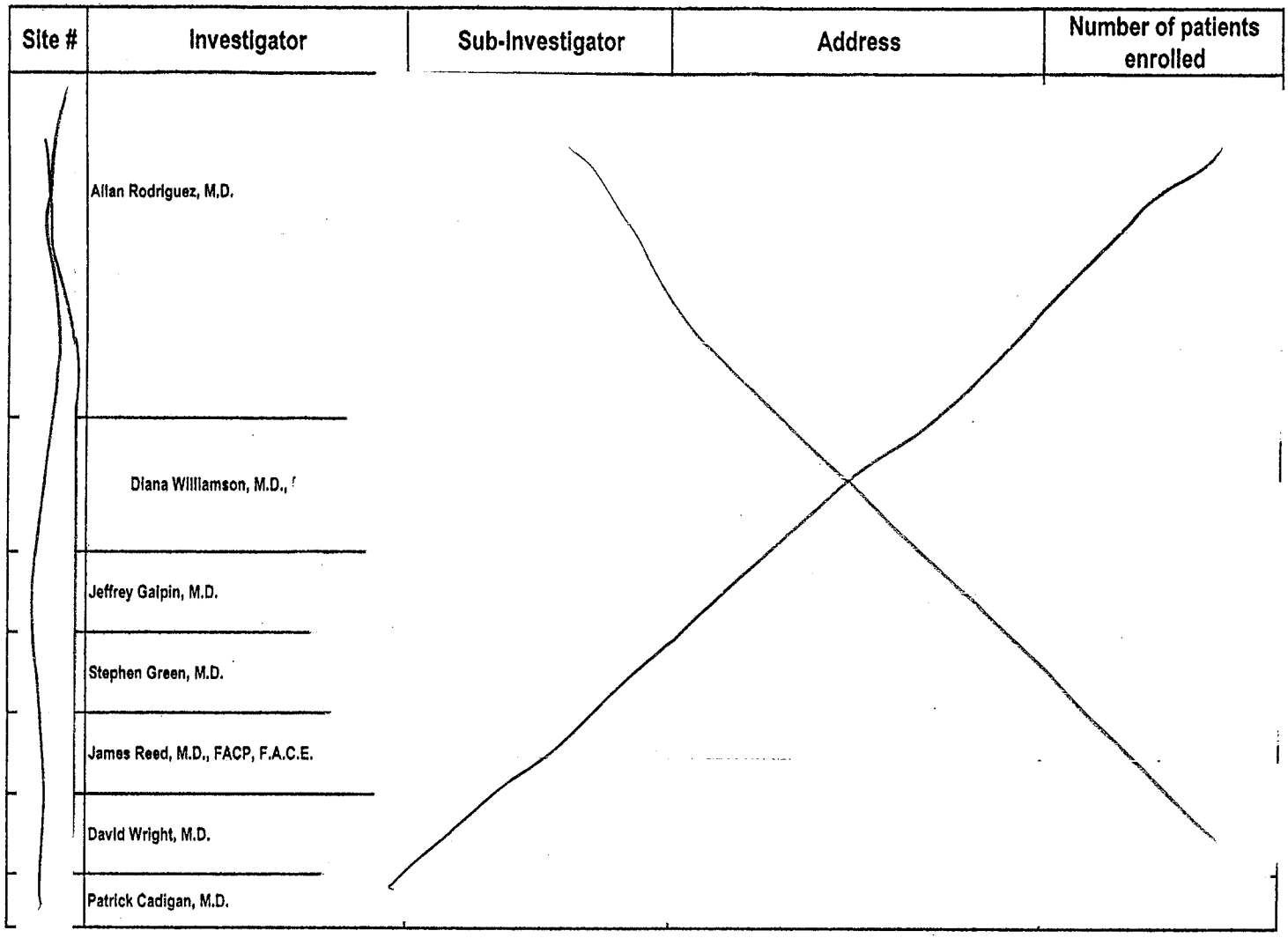
b(6)

Site #	Investigator	Sub-Investigator	Address	Number of patients enrolled
	Patricia Salvato, M.D.			
	Jamie Von Roenn, M.D.			
	Leonard Calabrese, D.O.			
	Christopher Lahart, M.D.			
	William Woodward, D.O. former Khoury, M.D.			
	Donald Northfelt, M.D.			
	Eric Daar, M.D.			
	David Paar, M.D.			
	Barry Rodwick, M.D.			
	Michael Somero, M.D.			

b(6)

b(6)

b(6)



Site #	Investigator	Sub-Investigator	Address	Number of patients enrolled
	Allan Rodriguez, M.D.			
	Diana Williamson, M.D.,			
	Jeffrey Galpin, M.D.			
	Stephen Green, M.D.			
	James Reed, M.D., FACP, F.A.C.E.			
	David Wright, M.D.			
	Patrick Cadigan, M.D.			

b(6)

Country	Site #	Name	Function	Address	Number of Patients Enrolled
		Dr. Robert Finlayson	Principal Investigator		
		Dr. Roger Garsia	Principal Investigator		
		Dr. David Cooper	Principal Investigator		
		Dr. Anthony Alworth	Principal Investigator		
		Dr. Norman Roth	Principal Investigator		
		Prof. Georg Stingl	Principal Investigator		

b(6)

b(6)

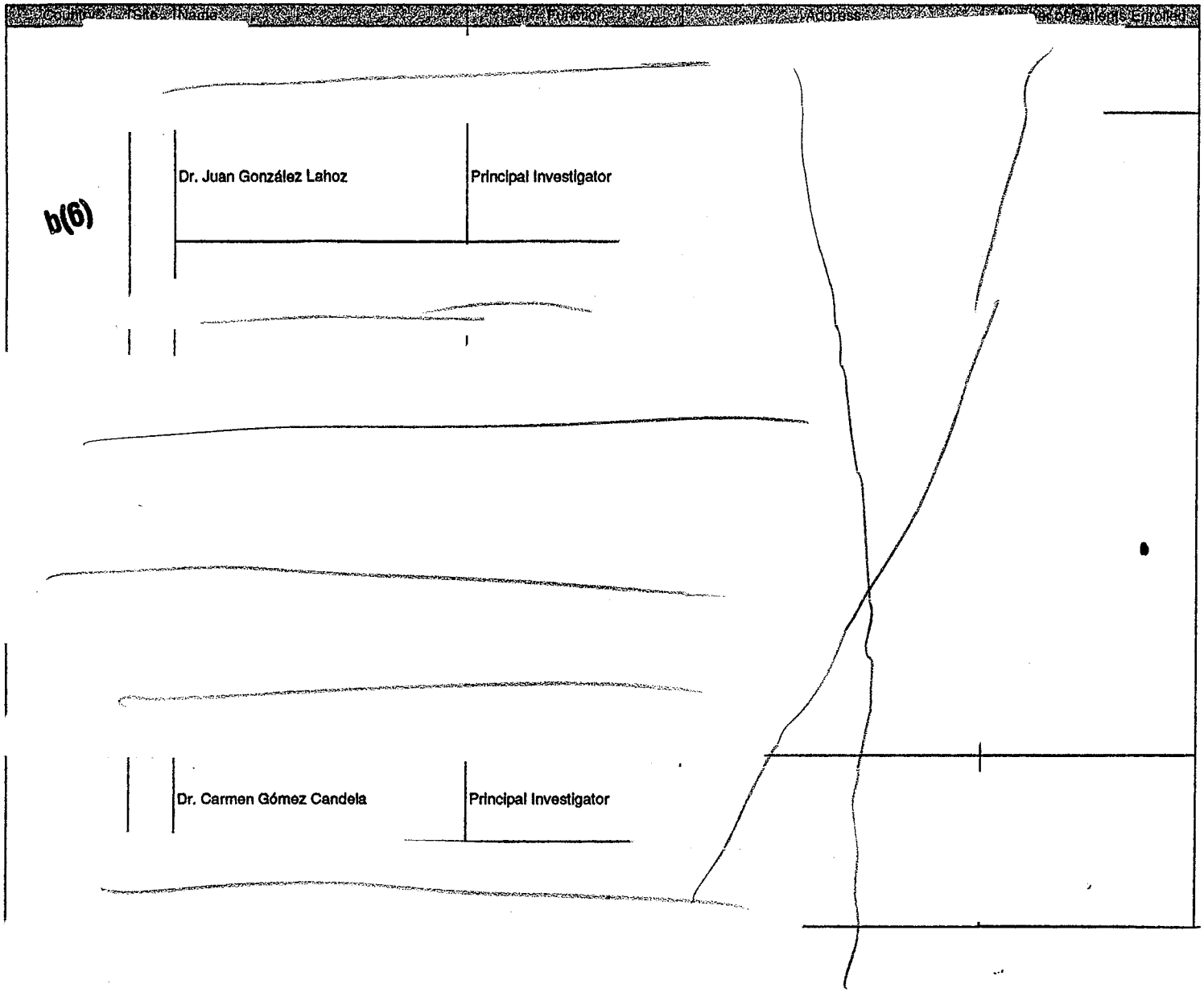
Country	Last Name	First Name	Position	Address	Number of Patients Enrolled
	Prim. Dr. Norbert Vetter		Principal Investigator		
	Dr. Johan Wandall		Principal Investigator		
	Dr. Thierry Saint Marc		Principal Investigator		
	Prof. Jean-Claude Melchior		Principal Investigator		
	Dr. Isabelle Poizot-Martin		Principal Investigator		

b(6)

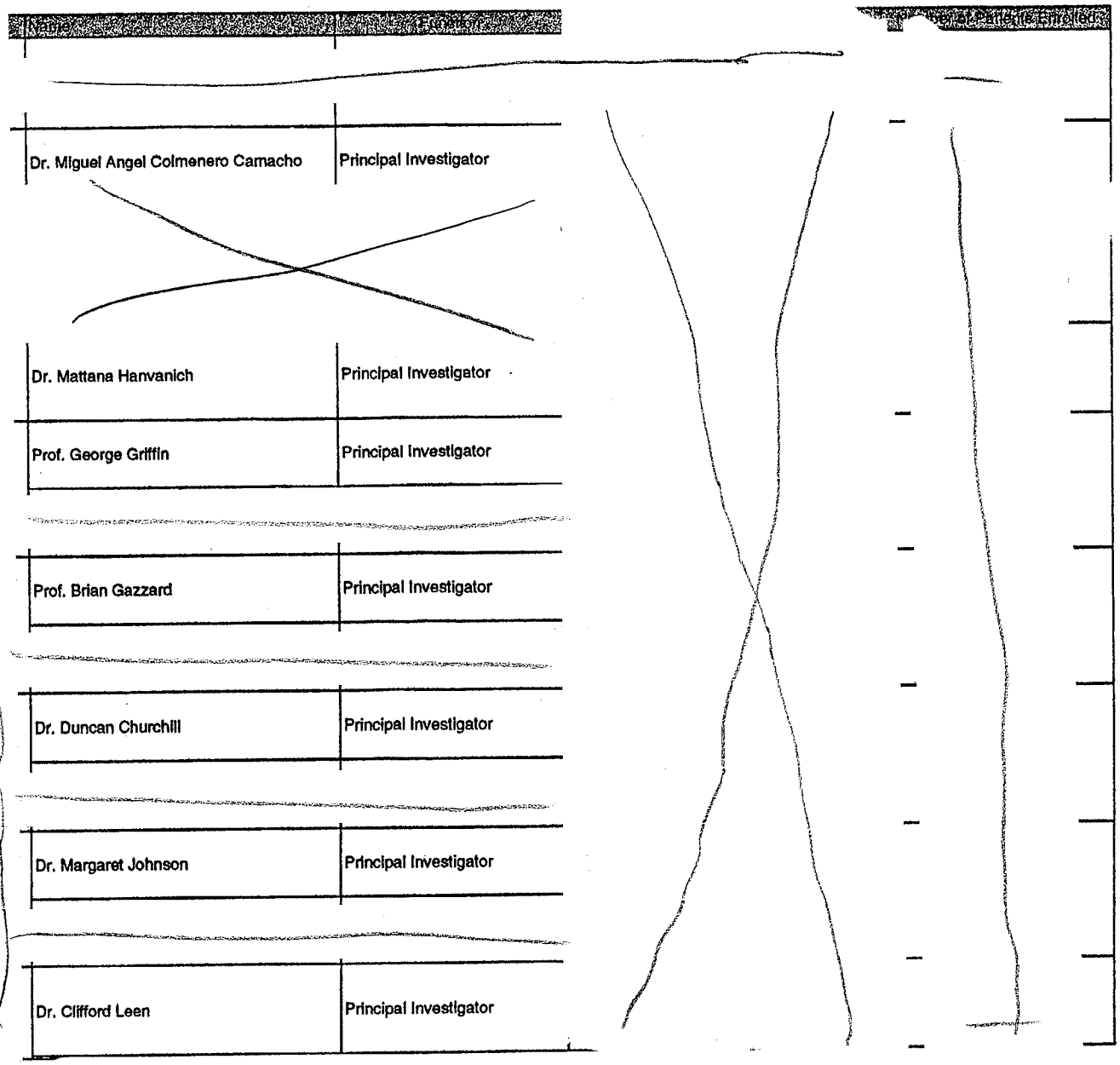
b(6)

Country	Site	Name	Function	Address	Number of Patients Enrolled
			Principal Investigator		
		Dr. Hans Jaeger	Principal Investigator		
		Dr. med. Heribert Knechten	Principal Investigator		
b(6)		Dr. med. Rockstroh Juergen	Principal Investigator	Medizinische Klinik, Universitäts klinik Bonn, Sigmund-Freud-strasse 25, Bonn D-53105	
		Dr. Med Schlomo Staszewski	Principal Investigator	ZIM, Infektionsambulanz, Uniklinik Frankfurt, Theodor Stern Kai 7, Frankfurt D-60596	
		Dr. Med Martin Hartmann	Principal Investigator		
		Dr. Bonaventura Clotet Sala	Principal Investigator		

b(6)


Country
Site
Name
Function
Address
# of Patients Enrolled
b(6)
Dr. Juan González Lahoz
Principal Investigator
Dr. Carmen Gómez Candela
Principal Investigator

b(6)


Name
Position
Dr. Miguel Angel Colmenero Camacho
Principal Investigator
Dr. Mattana Hanvanich
Principal Investigator
Prof. George Griffin
Principal Investigator
Prof. Brian Gazzard
Principal Investigator
Dr. Duncan Churchill
Principal Investigator
Dr. Margaret Johnson
Principal Investigator
Dr. Clifford Leen
Principal Investigator

b(6)

b(6)

Country	Site	Name	Function	Address	Number of Patients Enrolled

b(6)

Appears This Way
On Original

7 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

✓ Personal Privacy (b6)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative- 20-604
S027

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE:	July 15, 2003
TO:	Monika Johnson, Pharm.D., Regulatory Project Manager Robert Perlstein, M.D., Medical Officer, Clinical Reviewer Division of Metabolic & Endocrine Drug Products, HFD-510
THROUGH:	Khin Maung U, M.D., Branch Chief Good Clinical Practice Branch 1, HFD-46 Division of Scientific Investigations
FROM:	Andrea Slavin, RN, Consumer Safety Officer Good Clinical Practice Branch 1, HFD-46 Division of Scientific Investigations
SUBJECT:	Evaluation of Domestic Inspections
NDA:	20-604/S-027
SPONSOR:	Serono, Inc.
DRUG:	Serostim® [somatropin (rDNA origin) for injection]
CHEMICAL CLASSIFICATION:	Type 5, P
THERAPEUTIC CLASSIFICATION:	Growth Hormone
INDICATIONS:	Treatment of AIDS wasting
CONSULTATION REQUEST DATE:	January 22, 2003
GOAL DATE TO PROVIDE INSPECTION SUMMARY:	August 1, 2003
PDUFA GOAL DATE:	September 1, 2003

I. BACKGROUND:

This was the sponsor's confirmatory Phase 4 study for the AIDS wasting indication for Serostim®. This was a multicenter clinical trial conducted at 61 centers in 10 countries. The study compared full-dose growth hormone to half-dose growth hormone to placebo in subjects with AIDS wasting. The objectives of the study were to confirm the clinical efficacy of Serostim® compared with placebo, based on an endpoint of exercise function change, and to establish an optimal dose of Serostim®, based on the endpoint of lean body mass (LBM) change. The study population consisted of male and female subjects, at least 18 years of age, with clearly documented HIV infection and AIDS wasting. The subjects were maintained on antiretroviral therapy for their HIV infection. The study encompassed a 4-week run-in phase, and a 12-week double-blind treatment phase. Subjects were randomized to

receive full dose (0.1mg/kg/day up to 6mg/daily), half-dose (0.1mg/kg/day up to 6mg on alternate days) Serostim® or placebo administered subcutaneously. Subjects were re-randomized at week 12 to either full-dose or half-dose Serostim® and were then followed up to week 48. The protocol was amended on February 29, 2000 (Amendment 1A). This Amendment shortened the length of treatment to 24 weeks. Subjects who completed the 12-week double-blind phase, were eligible to enroll in a 12-week open-label phase. During the open-label phase, all subjects received full-dose Serostim®.

RESULTS (by site):

Name	City, State	Country	Protocol	Insp. Date	EIR Recd.	Classn.
Anthony LaMarca, MD	Fort Lauderdale, FL	USA	9037	5/5-13/2003	5/22/03	VAI
Patrick Cadigan, MD	Fort Lauderdale, FL	USA	9037	5/15-22/2003	6/19/03	VAI-RR
W. C. Mathews, MD	San Diego, CA	USA	9037	5/27-6/11/2003	7/10/03	VAI-RR

Study Protocol: 9037: "A Randomized, Parallel Group, Double-Blind, Placebo-Controlled, Dose-Ranging, Multicenter Study of Serostim®, Mammalian Cell-Derived Recombinant Human Growth Hormone (r-hGH[m]) in the Treatment of HIV-Associated Catabolism/Wasting"

Sites:
Basis for site selection: The sites were selected by the medical officer.

(1) **Anthony LaMarca, MD**
Therafirst Medical Center
4011 North Federal Highway
Fort Lauderdale, FL 33308

Inspection Dates: May 5-13, 2003

Methodology: Inspection assignments were issued to the field office.

a. What was inspected

The inspection confirmed that all subjects signed and dated consent forms prior to enrolling in the study. The site enrolled ⁄ subjects. Seventeen subjects' records were audited for data integrity with an emphasis on cycle ergometry at the baseline and week 12 visits. Data in source documents and case report forms were compared to data in sponsor-provided data listings. No major discrepancies were noted. b(4)

b. Limitations of inspection: None

c. General observations/commentary

No FDA 483 was issued.

No significant deviations were noted. There were some discrepancies noted between data in source documents/ case report forms, and what was reported to the IRB pertaining to subject withdrawals. In addition, it was noted that the manner in which subjects were weighed (with an empty bladder, in a hospital gown) is not documented in the source documents; however, the protocol did not require the documentation of this information. Data from this site are acceptable.

(2) **Patrick Cadigan, MD**
South Beach Medical, PA
777 17th Street, Suite 403
Miami, Florida 33139

Inspection Dates: May 15-22, 2003

Methodology: Inspection assignments were issued to the field office.

(a) What was inspected

b(4)

The inspection confirmed that all subjects signed and dated consent forms prior to enrolling in the study. The site enrolled / subjects. Fourteen subjects' records were reviewed in-depth for data integrity, with special emphasis on cycle ergometry. Subjects' records were noted to be complete, well organized and legible. Endpoint efficacy data in source documents were compared to data in case report forms, and sponsor-provided data listings. No major deviations were noted.

(b) Limitations of inspection: None

(c) General observations/commentary

An 8-item 483 was issued. One subject was seen outside the study window for week 12. There were discrepancies in the case history for one subject pertaining to an adverse event. Two subjects did not have adverse events reported to the sponsor, and 3 subjects signed an updated version of the consent form late. Data from this site are acceptable.

(3) W. Christopher Mathews, MD
Owen Clinic
UCSD Medical Center
200 West Arbor Drive
San Diego, California 92103

Inspection Dates: May 27-June 11, 2003

Methodology: Inspection assignments were issued to the field office. b(4)

(a) What was inspected

The inspection confirmed that all subjects signed consent forms prior to enrollment in the study [redacted] subjects were enrolled. Fifteen subjects' records were reviewed for data integrity. Source documents were noted to be organized, complete and legible. Data in source documents supported data in case report forms.

(b) Limitations of Inspection: None.

(c) General observations/commentary

A 6-item 483 was issued. The site did not calibrate its scales as required by the protocol. The site did not have records to support that subjects enrolled under Amendment 1A were contacted on an annual basis to determine survival status. The site did not promptly submit Amendment 3 to the IRB, and did not promptly submit an updated Form FDA 1572 to the sponsor. Data from this site are acceptable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Both Dr. Cadigan and Dr. Mathews submitted adequate responses addressing the inspectional observations noted on the Form 483. I recommend that data from all 3 of these clinical sites can be used for the evaluation of Study Protocol #9037 submitted in support of NDA 20-604/S-027 for review by FDA.

Andrea Slavin, RN
Consumer Safety Officer
Good Clinical Practice Branch 1, HFD-46
Division of Scientific Investigations

CONCURRENCE:

Supervisory comments

Khin Maung U, MD
Branch Chief
Good Clinical Practice Branch 1, HFD-46
Division of Scientific Investigations

DISTRIBUTION:
NDA #20-604/S-027
HFD-45/Division File/Reading File
HFD-45/Program Management Staff (electronic copy)
HFD-46/U/Slavin
HFD-47/George GCPB1 Files #3994, #10929, #10948

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

/s/

Sherry George
7/16/03 03:10:58 PM
TECHNICAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

JUL - 2 2003

Patrick J. Cadigan, M.D.
South Beach Medical, P.A.
777 17th Street, Suite 403
Miami, Florida 33139

Dear Dr. Cadigan:

Between May 15 and 22, 2003, Ms. Jennifer M. Menendez, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (protocol #9037 entitled: "A Randomized, Parallel-Group, Double-Blind, Placebo Controlled, Dose-Ranging, Multicenter Study of Serostim®, Mammalian Cell-Derived Recombinant Human Growth Hormone (r-hGH[m]) in the Treatment of HIV-Associated Catabolism/Wasting") of the investigational drug Serostim® [somatropin (rDNA origin) for injection], performed for Serono, Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report, the documents submitted with that report, and your June 4, 2003 written response, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We are aware that at the conclusion of the inspection, Ms. Menendez presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

1. You did not conduct the study according to the investigational plan [21 CFR 312.60] in that subject b(6) was not seen for the week 12 visit within the visit window specified by the protocol. The week 12 visit was postponed by greater than 2 weeks.

2. You did not report adverse events to the sponsor [21 CFR 312.64(b)].

   a. For subject b(6) body aches and numbness in hands and toes were not reported.

   b. For subject b(6) hyperglycemia was not reported.

3. You did not adequately document informed consent [21 CFR 50.27(a)] in that subjects b(6) did not sign the 4/11/01 version of the consent form until 6/21/01, 6/7/01, and 6/28/01 respectively.

4. You did not maintain adequate and accurate case histories [21 CFR 312.62(b)] in that for for subject b(6) an elevated glucose level was reported in the source documents at week 12, however, hypertriglyceridemia was recorded in the CRF.

We acknowledge your commitment, as stated in your June 4, 2003, written response, to make appropriate changes in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies. Any response and all correspondence will be included as a permanent part of your file.

We appreciate the cooperation shown Investigator Menendez during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

Khin Maung U, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

b(4)

FEI: [redacted]
Field Classification: VAI
Headquarters Classification:
_____1)NAI
_____2)VAI- no response required
_____3)VAI- response requested
__X_ 4)VAI-RR (response received and accepted)
_____5)OAI

Deficiencies noted:
X_failure to obtain subject consent (02)
X_failure to adhere to protocol (05)
X_inadequate and inaccurate records (06)
X_failure to report adverse events (16)
Deficiency Codes: 2, 5, 6, 16

cc:
HFA-224
HFD-510 Doc.Rm. NDA#20-604/S-027
HFD-510 Review Div.Dir./Orloff
HFD-510 MO/Perlstein
HFD-510 PM/Johnson
HFD-46/47c/r/s/ GCP File #10929
HFD-46/47 CSO/Slavin
HFR-SE250 DIB/Gallant
HFR-SE250 Bimo Monitor/Torres
HFR-SE2575 Field Investigator/Menendez
GCF-1 Seth Ray
r/d: (AS):6/24/03
reviewed:KMU:6/27/03
f/t: sg:6/30/03; ML:7/1/03
o:**Slavin\Cadigan letter**

Reviewer Note to Rev. Div. M.O.

This was the initial inspection of Dr. Cadigan in support of the AIDS wasting indication for Serostim®. The site screened [redacted] subjects and randomized [redacted] subjects. [redacted] subjects completed the study. b(4)
Fourteen subjects' records were audited for data integrity with an emphasis on cycle ergometry at the baseline and week 12 visits. The inspection confirmed that data in case report forms accurately reflected what was reported in source documents. Subjects' records were noted to be complete, well organized and legible. At the completion of the inspection, an 8-item 483 was issued to Dr. Cadigan. Four of the items on the 483 were not cited in the letter because it was felt they pertained to deviations from Good Clinical Practice, but were not regulatory violations. Dr. Cadigan submitted an adequate written response on June 4, 2003 addressing the items in the 483 and promising corrections in research procedures at his site. Data are acceptable in support of NDA 20-604/S-027. The inspection is classified as VAI-RR, response received and accepted.

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

/s/

Khin U

7/2/03 04:56:59 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

JUL 14 2003

W. Christopher Mathews, M.D.
Owen Clinic
UCSD Medical Center
200 West Arbor Drive
San Diego, California 92103-8681

Dear Dr. Mathews:

Between May 27 and June 11, 2003, Mr. Thomas R. Beilke, representing the Food and Drug Administration (FDA), conducted an investigation to review your conduct of a clinical investigation (protocol #9037 entitled: "A Randomized, Parallel-Group, Double-Blind, Placebo-Controlled, Dose-Ranging, Multicenter Study of Serostim®, Mammalian Cell-Derived Recombinant Human Growth Hormone (r-hGH [m]) in the Treatment of HIV-Associated Catabolism/Wasting") of the investigational drug Serostim® [somatropin (r-DNA origin) for injection], performed for Serono, Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of the study have been protected.

From our review of the establishment inspection report, the documents submitted with that report, and your June 18, 2003 written response, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We are aware that at the conclusion of the inspection, Mr. Beilke presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

1. You did not adhere to the investigational plan [21 CFR 312.60] in that the scales used to weigh study subjects were not calibrated to an accuracy of ± 0.2 kg. as required by the protocol.

2. You did not maintain adequate and accurate case histories [21 CFR 312.62(b)] in that there were no records available to document that subjects enrolled under Amendment 1A, were contacted on an annual basis to determine survival status as required by this amendment to the protocol.

3. You did not promptly report all changes in research activity to the IRB [21 CFR 312.66] in that Amendment 3 to the protocol, dated 5/8/01, was not submitted to the IRB until 5/2/02.

4. You did not ensure that an investigation is conducted according to the signed investigator statement [21 CFR 312.60] in that an updated Form FDA 1572, listing the names of sub-investigators, was not promptly submitted to the sponsor.

We acknowledge your commitment, as stated in your June 18, 2003, written response, to make appropriate changes in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies. Any response and all correspondence will be included as a permanent part of your file.

We appreciate the cooperation shown Investigator Beilke during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

Khin Maung U, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

CFN/FEI: [redacted]
Field Classification: VAI b(4)
Headquarters Classification:
_____1)NAI
_____2)VAI- no response required
_____3)VAI- response requested
_X____4)VAI-RR (response received and accepted)
_____5)OAI

Deficiencies noted:
_X___failure to adhere to protocol (05)
_X___inadequate and inaccurate records (06)
_X___failure to list additional investigators on 1572 (12)
_X___failure to notify IRB of changes, failure to submit progress reports (15)

Deficiency Codes: 5, 6, 12, 15
cc:
HFA-224
HFD-510 Doc.Rm. NDA#20-604/S-027
HFD-510 Review Div.Dir./Orloff
HFD-510 MO/Perlstein
HFD-510 PM/Johnson
HFD-46/47c/r/s/ GCP File #10948
HFD-46/47 GCP Reviewer/Slavin
HFR-PA252 DIB/Tucker
HFR-PA2565 Bimo Monitor/Koller
HFR-PA2535 Field Investigator/Beilke
GCF-1 Seth Ray

r/d: (REVIEWER):
reviewed:KMU:7/14/03
f/t:sg:7/14/03
o:**Slavin\Mathews letter** b(4)

Reviewer Note to Rev. Div. M.O.
This was the initial inspection of Dr. Mathews pursuant to NDA 20-604 for the AIDS-wasting indication for Serostim. This site randomized [redacted] subjects. The source documents for all subjects were noted to be organized, complete and legible. Data in case report forms were supported by data in source documents. At the completion of the inspection, a 6-item Form 483 was issued to Dr. Mathews. An item that was listed on the 483, but not cited in the letter, pertained to the calibration of the exercise bicycle that was used for cycle ergometry. Because the protocol did not specify that the bicycle must be calibrated, this issue was not cited in the letter. Dr. Mathews states in his written response that "these bicycles were purchased because of their mechanical and electronic durability and accuracy." Dr. Mathews submitted a written response that adequately addressed all the issues in the 483. Data from this site are acceptable in support of

NDA 20-604/S-027. The inspection is classified as VAI-RR, response received and accepted.

FEI: [redacted] b(4)
Field Classification: Refer to Center

Headquarters Classification:
_____1)NAI
__x__2)VAI- no response required
_____3)VAI- response requested
_____4)OAI

Deficiencies noted:

__x__failure to adhere to protocol (5)

Deficiency Code: 5

cc:
HFA-224
HFD-580/Doc.Rm. NDA#21-550
HFD-580/MO/Batra
HFD-580/PM/DeGuia
HFD-46/47c/r/s/ GCP File #010937
HFD-46 Blay
HFR-SE340/DIB/Lewis
HFR-SE350/Bimo Monitor/Abel
HFR-SE3555/Field Investigator/Smith

r/d: 7.10.03
revised: rab/
reviewed: KMU:
reviewed:aeh:
f/t:sg:7/14/03

c:\data\royblay\vai letters\McMurray.doc
o:\blay\McMurray.doc

Reviewer Note to Rev. Div. M.O.

[redacted] subjects were randomized to the study and the records for all of these subjects were reviewed in detail for items including, but not limited to, adverse events, intercurrent illnesses, and concomitant medications. Data at this site appear acceptable in support of the relevant submission.

b(4)

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

/s/

Khin U
7/17/03 10:04:13 AM

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # :_____ **Supplement Type (e.g. SE5):** _____ **Supplement Number:**_____

Stamp Date:_____ **Action Date:**_____

HFD____ **Trade and generic names/dosage form:** _____

Applicant: _____ **Therapeutic Class:** _____

Indication(s) previously approved:_____

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s):_____

Indication #1: _____

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/ Grace Carmouze
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**

- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min ____	**kg____**	**mo.____**	**yr.____**	**Tanner Stage____**
Max____	**kg____**	**mo.____**	**yr.____**	**Tanner Stage____**

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min ____	**kg____**	**mo.____**	**yr.____**	**Tanner Stage____**
Max____	**kg____**	**mo.____**	**yr.____**	**Tanner Stage____**

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: NDA
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

2 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

✓ Law Enforcement Records (b7)

_____ Deliberative Process (b5)

20-604/5027

1.31.03

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

OFFICE OF NEW DRUGS-IMMEDIATE OFFICE

Memorandum

Date: July 28, 2003

To: Division of Metabolic and Endocrine Drug Products, HFD 510

Subject: Study endpoint consultation
NDA 20,604/S-027; Serostim (somatropin rDNA origin; recombinant human growth hormone, r-hGH) 0.1mg/kg subQ (full dose or half dose) for AIDS wasting; Serono

From: Laurie Burke
STUDY ENDPOINTS & LABEL DEVELOPMENT TEAM (SEALD)
Voice: 301-594-5482
Fax: 301-480-8329

This memorandum provides a review of the Bristol-Meyers anorexia/cachexia recovery instrument (BACRI) and the Multidimensional Health Status Assessment (MHSA) used as non-primary endpoints in a 12-week double-blind placebo-controlled study. Comments are not given for the 24- or 48-week open-label extension studies since these studies would not support conclusions concerning the impact of Serostim on these subjective outcomes.

BACKGROUND:
The primary effectiveness measure is mean change in bicycle ergometry work output from baseline to week 12. The secondary effectiveness measure as defined by the sponsor is mean change in lean body mass as measured by the BIS from baseline to week 12. Other effectiveness measures are body weight, six-minute walk test, the BACRI and the MHSA. The submission calls the BACRI and MHSA results "health-related quality of life parameters."

The BACRI asks the patient 8 questions on how they perceive different aspects of their health since they started treatment by making a mark on a visual analogue scale, 0-100, between 2 extreme outcomes that are different for each question. Zero denotes a poor outcome and 100 the best possible outcome. The submission states that a score of 50 represents a neutral position, however the actual instrument was not provided so we cannot tell whether the 50% position was anchored for the patient. BACRI questions are listed below:

Question 1: Since you began treatment with this test drug, do you feel that any change in weight has had a significant impact on your health? (0= "health worsened" and 100="health improved.")
Question 2: To what extent has your appearance changed since treatment was started? (0="much worse" and 100="much better")
Question 3: Based on comments from friends, co-workers, and loved ones, how do you feel your appearance has changed since the start of treatment? (0="favorably" and 100="unfavorably" scored as the number subtracted from 100 to invert the scale)

Question 4: To what extent has your appetite changed since the start of treatment? (0="much worse" and 100="much better)

Question 5: Do you enjoy eating more or less than before treatment began? (0="much less" and 100="much more")

Question 6: Since beginning this treatment, do you feel better or worse overall? (0="much worse" and 100="much better")

Question 7: Do you think this treatment has been of benefit to you? (0="not at all" and 100="very much")

Question 8: Since beginning this treatment, has your quality of life become better or worse? (0="much worse" and 100="much better")

In addition to analyzing the results of each question separately, the sponsor also presents the 7-item index that combines the results of questions 1,2,3,4,5,6 and 8. A Pubmed search produced an abstract (Qual Life Res. 1995 Jun;4(3):221-231.) by D Cella et al. that claims a psychometric evaluation of the BACRI strongly supported the use of the 7-item index of subjective recovery (BACRI-7) and a single criterion item (BACRI-1) depicting patient perception of benefit (question #7). It also reports that differentiation of treatment arms seen with the 7-item scale was consistent with dose-response improvements in weight and lean body mass changes. It also suggests that the BACRI measures added some independent benefit over objective indicators of improvement.

No discussion of the minimum difference in means on the BACRI 7-item total between treatment groups that would be considered clinically meaningful is presented. The sponsor reports that statistically significant improvements relative to placebo and dose dependent improvements were observed for each of the questions individually and for the composite score. The mean results by treatment group reported for Question 7 at Week 12 was 51.6, 65.4 and 72.3 for the placebo, half-dose and full-dose groups, respectively. Similar results for the composite score (max. possible score=700) were 399.7, 440.9, and 464.0, respectively.

The wording used to describe BACRI results in the sponsor's proposed PI claims [redacted] and describes the BACRI as [redacted] b(4)

The sponsor also incorporated the Multidimensional Health Status Assessment (MHSA) in the 12-week trial. The "short version" of the MHSA was administered as 2 modules, A and B, at baseline and at Weeks 4, 8, and 12. No additional information was provided regarding the development of validation of the MHSA or this abbreviated version of the instrument. Module A Questions 1 and 2 and Module B Questions 7D, 7E and 7H (in bold below) demonstrated very small differences in group mean change from baseline at 12 weeks. None of the other questions, including Module B Question 5, demonstrated such a difference.

Module A; Question 1: In general, would you say your health is: 1=Excellent, 2=Very Good, 3=Good, 4=Fair or 5=Poor.

Module A; Question 2: During the past 4 weeks, how much bodily pain have you had? 1=None, 2=Very Mild, 3=Mild, 4=Moderate, 5=Severe, 6=Very Severe

Module A; Question 2A: On the line, 0 is death and 100 is perfect health, how would you rate your current state of health?

Module B; Question 1: During the past 4 weeks, has your health kept you from working at a job, doing work around the house, or going to school? 1=Yes, for all of the time; 2=Yes, for some of the time; 3=No

Module B: Question 2: [Same as Module A; Question 2]

Module B; Question 3: During the past 4 weeks, how much has your physical health or emotional problems interfered with your normal social activities? 1=Not at all, 2=A little bit, 3=Moderately, 4=Quite a bit, 5=Extremely

Module B; Question 4: During the past 4 weeks, have you been unable to do certain kinds or amounts of work, housework, or schoolwork because of your health?

Module B; Question 5: During the past 4 weeks, how much did pain interfere with your normal work (including housework)? 1=Not at all, 2=A little bit, 3=Moderately, 4=Quite a bit, 5=Extremely

Module B; Question 6: How much, if at all, does your health now limit you in the following activities?

A: Vigorous activities like lifting heavy objects, running or participating in strenuous sports.
B: Moderate activities like moving a table or carrying groceries.
C: Walking uphill or climbing a few flights of stairs
D: Eating, dressing, bathing, or using the toilet

Module B; Question 7: How much of the time during the past 4 weeks...

A: ...has your health limited your social activities, like visiting with family and friends?
B: ...did you have trouble keeping your attention on any activity for long?
C: ...did you have difficulty reasoning and solving problems?
D: ...have you felt calm and peaceful?
E: ...have you felt down-hearted and blue?
F: ...did you feel tired?
G: ...did you have enough energy to do the things you wanted to do?
H: ...have you been a happy person?
I: ...have you had trouble remembering things?

Module B; Question 8A: My health is excellent
B: I have been feeling bad lately

b(4)

REVIEW COMMENTS:

1. Documentation of the development and validation of either the BACRI or the MHSA was not included in the submission. The publication referenced above supports the use of the 7-item index as a measure of subjective recovery from anorexia/cachexia symptoms. In this study, each of the 7 items demonstrated a fairly remarkable improvement for the full dose group. All items approach or exceed 0.5 SD improvement in the mean for the full dose group compared to the placebo group. The changes in the half dose group were not as remarkable. Since documentation of the development of this instrument was not available for review, we cannot determine conclusively that an b(4) achieved since we cannot be sure that ALL concepts that patients would consider importan b(4) Furthermore, since the measure does not capture any adverse impact of treatment, allowing a claim of b(4) unbalanced since we know the treatment has adverse effects that are not captured by this measure.
2. Using a single-item global of patient-reported benefit can be used to interpret other patient-reported findings, but does not provide support for claims b(4) the determinants of that perception cannot be ascertained. In the case of the BACRI, the global treatment benefit item (Question 7) might be useful for looking at each responder to determine what is important to that patient in terms of the other items impacted. It also gives us confidence that the 7-item index discussed above is a meaningful endpoint since the global item showed the same type of result, but it is misleading to use such a question b(4)
3. The MHSA, on the other hand, demonstrated very small differences in mean changes from baseline between treatment groups. The only item that approached 0.5 SD was Question 2 concerning pain, representing an adverse effect of treatment. b(4)

4 [redacted] b(4)

5. Because the BACRI and MHSA are not pre-specified in an integrated analysis plan for all study endpoints, [redacted] justified. [redacted] b(4)

6. According to developing standards in patient-reported outcomes measurement, the BACRI [redacted] The BACRI does not capture the negative impacts of treatment. The MHSA does capture pain, but does not capture patient-reported symptoms associated with fluid retention, tumors, or abnormal fasting blood glucose levels, other AEs reported in the submission [redacted]

7. [redacted] b(4)

8. If BACRI results are used in labeling, we suggest omitting [redacted] . BACRI should be referenced by name.. The only result that should be given is for that of [redacted] patients' perceptions of the impact of treatment on their symptoms." [redacted] b(4) b(4)

Please feel free to contact me for clarification or other questions concerning the subjective outcomes in this submission.

Drafted: LBurke 7/28/03
Comments: JScott 7/29/03
Finalized: LBurke 7/29/03

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

/s/

Laurie Burke
7/29/03 02:41:49 PM
INTERDISCIPLINARY

Sandy--The Division has requested that all DFS entries for this NDA be completed by August 1. Thanks!

Sandra L. Kweder
7/31/03 11:39:11 AM
MEDICAL OFFICER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research

Memorandum of Consultation

DATE: July 11, 2003

TO: Robert Peristein, M.D. Medical Officer, Division of Endocrinology (HFD-510)
Monika Johnson, Pharm.D. (HFD-510)

FROM: Teresa C. Wu, M.D., Ph.D. Medical Officer, Division of Antiviral Drug Products (HFD-530)

Through: Katie Laessig, M.D., Team Leader (HFD-530)
Debra Birnkrant, M.D., Division Director (HFD-530)

SUBJECT: **NDA 20-604/S-027, Serostim (somatropin, r-hGH), for the treatment of HIV-infected patients with wasting or cachexia**

This consult refers to the Dr. Monika Johnson's request, dated 1/17/03, requesting this division's input regarding:

- The effect of Serostim therapy on HIV related secondary endpoints
- The proposed package insert

Background

The marketing approval of Serostim® was granted on 08/23/96 under accelerated approval regulation. The approval was based on clinical data obtained from two pivotal studies: Studies 5341 and 7033, both were placebo-controlled and double-blind in design. Since the approval, the sponsor designed and conducted a confirmatory study, GF 9037, as part of phase 4 commitments. In October, 2002, the sponsor submitted S-027 which contains the results of GF 9037, and intended to use these data to support the traditional approval of Serostim.

Summary of Study Design

Study GF 9037 was entitled as: **A randomized, parallel group, double-blind, placebo-controlled, dose-ranging, multicenter study of recombinant human growth hormone (Serostim®) in the treatment of HIV-associated catabolism/wasting**

This study was designed as a 12-week randomized, double-blind, placebo-controlled study phase followed by an open-label Serostim treatment phase for a total of up to 48 weeks. The study was designed to confirm in a large patient cohort the effects of Serostim that were documented in the two previous phase III studies, Study 5341 and 7033. While the study endpoints (primary and secondary) were not the same between Study GF 9037 and two previous studies, all HIV-associated measurements (immunology, virology, OIs) were not considered as study endpoints, rather they were treated as part of safety evaluation for all three studies. Of significance is that Study GF 9037 differed from Studies 5341 and 7033 in two aspects:

1. Studies 5341 and 7033 were conducted in 1992 and 1994, respectively. Whereas GF 9037, conducted in 2000, places Serostim in today's treatment of AIDS with a majority of the patients receiving HAART.
2. While HIV RNA viral load levels were measured only at baseline in Studies 5341 and 7033, these data were available for both baseline and week 12 in Study GF 9037, albeit in a subset of patients.

Study GF 9037 enrolled a total of 770 patients who had documented HIV infection (positive in one of the following tests: Western blot, HIV culture, PCR, bDNA, p24), evidence of AIDS wasting defined as unintentional weight loss of 10% or weight less than 90% of IBW, had been on stable antiretroviral therapy for at least 8 weeks prior to study day 1 and had agreed not to change the regimen during the 12 weeks of study, no evidence of active AIDS-defining opportunistic infection, no active malignancy, and no chronic diarrhea.

Patients were randomized equally to 3 treatment arms:

- Full dose arm: during the 12-week double-blind phase, r-hGH was to be given subcutaneously at 0.1 mg/kg/day up to 6 mg/day, according to body weight

- Half-dose arm: during the 12-week double-blind phase r-hGH 6 mg daily was to be alternately administered subcutaneously with placebo

- Placebo arm

At the end of the 12-week double-blind, placebo-controlled study phase, all patients received open-label r-hGH at 0.1 mg/kg/day for additional 36 weeks in the extension study phase.

Summary of HIV-relevant Results

- At baseline, the most prevalent HIV risk factors were homosexual contact with HIV-infected person (78%), heterosexual contact with HIV-infected person (8.6%) and intravenous drug abuse (6.5%).

- Nearly all patients received NRTIs as part of antiretroviral treatment. Most of the patients (87.6%) received HAART. Among them, about 57% of patients received PI-containing HAART. The pattern of antiretroviral use at baseline was comparable among treatment groups.

- The three treatment groups were well balanced with respect to baseline CD4 counts and HIV-RNA levels. The mean CD4+ counts ranged from 380-426 /mm3. The median HIV-RNA levels ranged from 668-1056 copies/ml (bDNA assay). Of note, HIV RNA measurement was added based on a protocol amendment. As such, HIV RNA data were only available for a subset of patients (n=395) enrolled after that amendment.

- The results of the measurements of CD4 counts, CD8, CD4/CD8 ratio at baseline and at week 12 showed no significant changes occurred in any of the Serostim treatment groups versus placebo.

- The results of the measurements of viral load at baseline and at week 12 showed no significant changes occurred in any of the Serostim treatment groups versus placebo.

- Abnormal fasting blood glucose levels (>140, $\leq$ 259 mg/dl) were observed during the first 12 weeks in 3.1% of the patients treated with half-dose and in 2.4% of the patients treated with full-dose compared with 1.8% in the placebo group. These slight increases generally occurred early during treatment.

- A subset of 24 patients receiving Serostim 0.1 mg/kg daily with disproportionally high baseline trunk fat ($\geq$ 5.91 kg, measured by DEXA) showed significantly greater improvement in loss of trunk fat than the Serostim-treated group with baseline trunk fat < 5.91 kg.

Comments:

1. All SAEs and death cases were reviewed. Most opportunistic infections occurred during the extension study phase. Because the extension phase was 'open-label' without a placebo control, the causal relationship to Serostim treatment was difficult to assess.

2. We wish to retract the previous request to the sponsor asking for additional analysis comparing changes in HIV RNA levels between patients who received antiretroviral treatment during the 12-week study period and those who did not, since data provided in Table 14-159 indicate that over 98% of patients received at least one NRTI.

3. We could not find in the report the analysis that supports the following sentence in the labeling:

Under Clinical Trial #2, last sentence "

b(4)

Appears This Way
On Original

MEMORANDUM OF TELECON

DATE: July 12, 2002

TIME: 11:00 am to 12:00 noon (EST)

LOCATION: Parklawn Building Room 14B45 (Conference Room)

APPLICATION NUMBER: IND 38,087, Serostim (Somatropin rDNA origin for injection)

BETWEEN:

Robert Kirsch, Directior, Regulatory Affairs
Pam Williamson, Vice President, Regulatory Affairs
Laurie Ridener, Manager, Regulatory Affairs
Joseph Gertner, Vice President, Serostim Clinical Development Unit
Susan Kenley, Worldwide Director, Biostatistics and StatisticalProgramming
Fanny O'Brien, Manager, Biostatistics
Reed George, Manager, Statistical Programming

Phone: 781-681-2272
Representing: Serono, Inc.

AND

David Orloff, Division Director
Enid Galliers, Chief, Project Management Staff
Monika Johnson, PharmD, Regulatory Project Manager
Robert Perlstein, MD, Medical Reviewer
Bruce Stadel, MD, Medical Reviewer (Consultant)
Division of Metabolic and Endocrine Drug Products, HFD-510

SUBJECT: Discuss and agree on the format, content and analysis of the confirmatory study report (Protocol GF 9307).

Serostim (somatropin [rDNA origin] injection) was approved under 21CFR 314.510 (accelerated) August 23, 1996, for the treatment of AIDS wasting or cachexia. This indication is based on analysis of surrogate endpoints in studies of up to 12 weeks in duration. 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.

Protocol GF 9307 entitled "A randomized, parallel group, double-blind, placebo controlled, dose-ranging, multicenter study of recombinant human growth hormone (Serostim) in the treatment of HIV-associated catabolism/wasting" was submitted May 17, 2000 and conducted pursuant to the Subpart H regulations.

Italicized comments provided to Serono represent discussion (agreements) that took place during the teleconference.

1. Does the Agency agree that the content regarding safety and efficacy analyses planned for inclusion in the final study report for protocol GF 9037 is adequate?

FDA comment: The content regarding safety and efficacy analyses appears to be adequate. However, the Division has the following questions, comments and/or request.

Safety:

- Present the safety data for all treated patients (covering the 12 week double blind, placebo controlled portion, the extension to 48 weeks prior to Amendment 1A, and the extension to 24 weeks after Amendment 1A) by dose and also by duration of exposure.
- Focus on the incidence of hyperglycemia, tumorigenesis, Insulin Growth Factor-Standard Deviation Scores (IGF-1 SDS) responses, and edema/arthralgia/other established adverse effects associated with recombinant human growth hormone (rhGH) therapy. Detailed narratives should be provided when appropriate, and glucose/IGF-1 SDS data should be presented in a comprehensive fashion (i.e., shift tables, distribution plots).

Serono agreed with these requests.

Efficacy:

- The efficacy results in the submission for the primary endpoint [redacted] b(4)
  The primary analysis population should be the Intent to Treat (ITT) population consisting of ALL patients who have baseline data and at least 1 post treatment assessment. The ITT population should also include those patients with inconsistent data. Patients without a 12-week assessment should have their last on-study measurement used in the analysis (last observation carried forward [LOCF]). Other analyses may be performed to assess the impact of dropouts and data inconsistencies.

- Please indicate to the Division how you plan to present the efficacy data for patients who continued in the study after completing the 12-week, double blind, placebo controlled portion. More specifically: will the efficacy data for patients enrolled before Amendment 1A who continued to receive 2 doses of rhGH in a blinded fashion after week 12 (for as long as 36 additional weeks) be presented separately from the efficacy data for patients enrolled after Amendment 1A (who received full doses of rhGH in an open label fashion for 12 additional weeks after week 12)?
- In addition, are you planning to present combined 24 week efficacy data for ALL patients (i.e., patients enrolled before or after Amendment 1A)?

Serono agreed to provide post-12 week efficacy data for patients enrolled before and after Amendment 1A separately and combined.

- Furthermore, in this regard, how were patients already enrolled in the study and at different cutpoints for rhGH therapy (i.e., <12 weeks, 12-24 weeks, >24 weeks) dealt with after Amendment 1A was instituted?

Serono indicated that all patients enrolled before Amendment 1A were followed as per the original unamended protocol.

Efficacy AND Safety:

Given the substantial efficacy of highly active antiretroviral therapy (HAART) therapy during the last ~5 years in patients with AIDS, the Division is concerned about the current prevalence of patients with global AIDS wasting in the United States who would benefit from rhGH therapy (as opposed to the increasing incidence of Human Immunodeficiency Virus-associated Adipose Redistribution Syndrome (HARS) [characterized by central adiposity +/- subcutaneous fat atrophy] in HAART-treated AIDS patients). Please address and reference this issue in detail in your submission. Please provide appropriate subgroup group analyses in both the efficacy and safety analyses (i.e., patients treated with HAART [including a protease inhibitor] vs. patients not treated with HAART [including a protease inhibitor], patients with central adiposity vs. patients without central adiposity).

Serono agreed to provide literature supporting the continued need for rhGH therapy in an important subset of AIDS patients with global wasting. Serono agreed to provide efficacy and safety subgroup analyses for 1) patients treated with HAART (with or without a protease inhibitor) vs. patients not treated with HAART (with or without a protease inhibitor), patients with central adiposity vs. patients without central adiposity (in the subset where DEXA scans were performed and such information is available), and, in addition, in patients with varying BMIs at study entry.

2. Does the Agency agree that a final clinical report submitted in the International Conference on Harmonisation (ICH) E3 format would be adequate to fulfill the Subpart H requirement for NDA 20-604?

FDA response: A clinical report submitted in the ICH E3 format would be adequate. However, the proposed detailed study report Table of Contents (see Appendix 2 of Serono's submission) for the Efficacy Evaluation does not have all the required ICH E3 format subsections, specifically, Handling of Dropouts or Missing Data and Examination of Subgroups.

Serono agreed to include all relevant ICH E3 subsections.

3. Does the Agency have any additional requests that should be considered in preparation of the GF 9037 special supplement?

FDA response: See response to Questions 1 and 2.

FDA comments:

Concerning the proposed electronic data submission in the sponsor's Appendix 3, Electronic Components to be provided with Protocol GF 9037 Final Report, please refer to the FDA Guidance for Industry Providing Regulatory Submissions in Electronic Format: New Drug Applications

Specifically refer to Item 11, the Case Report Tabulations (CRTs) sections 3 and 6. Section 3, Documentation of the datasets, includes the annotated case report forms (blankcrf.pdf) as well as the define.pdf. Section 6 discusses variables to include in each dataset, such as unique patient ID, treatment assignment, baseline value, ...etc, to save the reviewer's time.

Monika Johnson, PharmD
Regulatory Project Manager

Supervisory concurrence

Kati Johnson, RPh
Chief, Project Management Staff

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

/s/

Monika Johnson
7/22/02 04:26:44 PM

510 King (2)

Meeting Minutes

IND # and Drug Name:	38,087 Serostim (somatropin [rDNA origin] for injection)
Meeting Date:	December 16, 1999
Time:	2:00 pm
Location:	Parklawn Potomac Conference Room
Indication:	AID wasting and cachexia
Sponsor:	Serono
Type of Meeting:	Phase 4 study
Sponsor Contact:	Pamela Williamson Joyce @ 781-681-2298
Regulatory Project Manager:	Crystal King @ 301-827-6423
FDA Participants:	Robert Temple, M.D., Associate Director for Medical Policy
	John Jenkins, M.D., Office Director
	Sol Sobel, M.D., Division Director
	Saul Malozowski, M..D., Ph.D., Medical Team Leader
	Heidi Jolson, M.D., Director, Division of Anti-Viral Drug Products
	Robert Perlstein, M.D., Medical Reviewer
	Crystal King, P.D., M.G.A., Regulatory Project Manager
Sponsor Participants:	Thomas Lang, Senior Vice president, Strategic Product Development
	Hal Landy, M.D., Medical Director
	Norma Muurahainen, M.D., Ph.D., Medical Director
	Ellen Frank, Ph.D., President
	Joseph Gertner, M.B., M.R.C.P., Medical Director, Growth & Metabolism CDU
	Pamela Williamson Joyce, Executive Director, Regulatory Affairs

Meeting Objective:

To discuss the status of and proposed changes to the Phase 4 commitment study 9037.

Background:

Serostim was approved on August 23, 1996, with Phase 4 commitments under subpart H. At this time, approximately 250 patients out of the 732 required are enrolled. Serono has proposed to improve enrollment by changing the original study protocol.

Presentation:

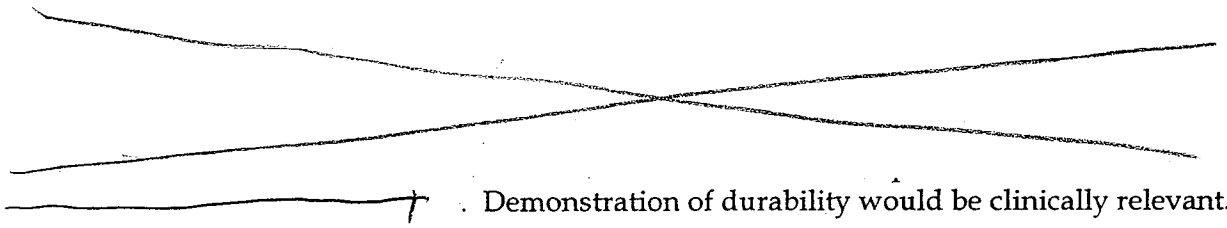
J. Gertner presented material to explain how they have complied with the regulations, as well as the difficulties encountered in enrolling patients in the study. Factors include: (1) the increase in the number of available therapies for AIDS patients and the decrease in the prevalence of wasting; (2) the availability of growth hormone in the market; and, (3) earlier, more aggressive interventions to prevent severe weight loss.

Attachment A provides a copy of the slides used in the presentation.

Agreements:

FDA accepted the sponsor's rationale for increasing the flexibility of the inclusion criteria.

Given the changing environment, as well as changing treatment modalities, FDA agreed to consider broader inclusion criteria: (1) greater than 5% unintentional weight loss instead of greater than 10% [but noted that this might make it more difficult to show a benefit] and (2) removing the exclusion of patients with a history of concurrent or recent opportunistic infections). FDA also agreed to consider a study time duration of 12 weeks instead of 48 weeks for the primary endpoint.



b(4)

. Demonstration of durability would be clinically relevant.

Unresolved Issues:

No decision was reached regarding the proposed timeline for study completion.

Action Items:

Within four weeks, Serono will forward a new proposal incorporating the changes to the Division.

Although FDA minutes are the official documentation of the meeting, we note that Sponsor minutes have not been provided at this time, therefore no discrepancies are noted.

Prepared by: _____ 1/11/00, Regulatory Project Manager
Crystal King, P.D., M.G.A. date

Approval: _____ 1/4/00, Meeting Facilitator
Saul Malozowski, M.D., Ph.D date

Concurrence:	Robert Temple, M.D., Associate Director for Medical Policy		12/29/99
	John Jenkins, M.D., Office Director	ncr by	01/11/00
	Solomon Sobel, M.D., Division Director	ncr by	01/11/00
	~~Heidi Jolson~~, M.D., Director, Division of Anti-Viral Drug Products		01/03/00
	Robert Perlstein, M.D., Medical Reviewer		12/29/99

Attachments:
A. Serono slides from December 16, 1999

cc: IND 38,087
Division File
HFD-510: S.Sobel/S.Malozowski/R.Perlstein/C.King
HFD-40: R.Temple
HFD-102: J.Jenkins
HFD-530: H.Jolson

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

7.22.02
faxed to firm

IND 38,087

Serono, Inc.
Attention: Pamela Williamson Joyce
Vice President, Regulatory Affairs
One Technology Place
Rockland, MA 02370

Dear Mr. Joyce:

Please refer to the meeting between representatives of your firm and FDA on July 12, 2002. The purpose of the teleconference was to discuss and agree on the format, content and analysis of the confirmatory study report (Protocol GF 9307) for the approved indication of treatment of AIDS wasting or cachexia.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at 301-827-6370.

Sincerely,

{See appended electronic signature page}

Monika Johnson
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:

July 12, 2002 Teleconference minutes

20. OTHER

A. ENVIRONMENTAL RISK ASSESSMENT

Pursuant to 21 CFR 25.31(a), Serono, Inc. claims categorical exclusion from the preparation and submission of an Environmental Assessment since the approval of this application will not significantly increase the use of the active moiety, somatropin.

B. ANALYSIS OF PATIENTS WITH CENTRAL ADIPOSITY

Please see the table entitled "Change from Baseline to Week 12 in Trunk Fat (kgs) (DEXA) (Population: ITT Patients)" attached herewith.

C. AGENCY REQUEST FOR PUBLICATIONS ON AIDS PATIENTS WITH GLOBAL WASTING

Reference is made to the following request made by the Agency during a July 12, 2002 pre-NDA meeting (teleconference) held to discuss the format and content of a Serostim® Subpart H supplemental application:

Please provide literature supporting the continued need for rhGH in an important subset of AIDS patients with global wasting.

Accordingly, please see selected publications attached herewith provided in response to the Agency request cited above.

Change from Baseline to Week 12 in Trunk Fat (kgs) (DEXA)
(Population: ITT Patients)

Baseline Trunk Fat	Statistics	Placebo	Half-Dose Serostim®	Full-Dose Serostim®	p-value for Placebo vs. Half-Dose	p-value for Placebo vs. Full-Dose
Greater Than or Equal to 5.91 kgs	n	20	29	24	0.0001	0.0001
	Mean (SD)	0.1 (1.1)	-1.3 (1.1)	-2.2 (1.3)		
	Median	-0.4	-1.4	-2.2		
	Range	(-1.4, 2.4)	(-3.8, 1.3)	(-4.9, 0.0)		
Less Than 5.91 kgs	n	72	71	57	0.0001	0.0001
	Mean (SD)	0.04 (1.5)	-0.6 (0.9)	-0.7 (1.0)		
	Median	-0.1	-0.6	-0.6		
	Range	(-3.9, 7.0)	(-2.4, 2.4)	(-3.3, 2.3)		
p-values for comparison within treatment group:		0.9896	0.002	0.0001		

p-values from ANOVA on ranked data with effects for treatment, pooled center, baseline trunk fat category, and the treatment by trunk fat interaction.

HARS study had Baseline Trunk Fat of 5.91 kgs for the lower 10%.
Thus, HARS like patients have Baseline Trunk Fat > = 5.91 kgs.

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S-027-SL

serono

NDA SUPPL AMENDMENT

ORIGINAL

Serono, Inc.
One Technology Place
Rockland, MA 02370
Tel: 781-982-9000
Fax: 781-681-2924
www.seronousa.com

S-027-SL

June 10, 2003

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852

NDA 20-604/S-027 Serostim® [somatropin (rDNA origin) for injection]
Response to Request for Additional Information

Dear Central Document Room:

Reference is made to Serostim® NDA 20-604 approved on August 23, 1996 according to 21 CFR 314.510, Subpart H. Further reference is made to supplemental application S-027 submitted on October 31, 2002 and to a June 3, 2003 teleconference with the Agency during which additional information was requested.

Specifically, Dr. Robert Perlstein (HFD-510) requested that the proposed package insert contained in S-027 be submitted with red-lining to indicate changes from the currently approved package insert. Accordingly, please find enclosed a CD-ROM that contains the proposed package insert. Please be advised that minor editorial changes have been made to titles and headings in Figure 4 for clarity in response to Medical Officer (HFD-510) comments made during the teleconference cited above.

All electronic files have been scanned and checked for viruses using Norton AntiVirus Version 7.00. The files are free of all viruses as tested by that software.

Please note that Serono, Inc. considers this submission and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any questions concerning this submission, please contact Robert M. Kirsch, Director, Regulatory Affairs, at (781) 681-2272 or the undersigned at (781) 681-2298.

Sincerely,

Pamela Williamson Joyce, RAC
President, Regulatory Affairs & Quality Assurance – U.S.

Cc: David Orloff, M.D. (HFD-510)

Enclosures

CONFIDENTIAL

Serono, Inc.
One Technology Place
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Fax: 781-681-2924
www.seronousa.com

April 3, 2003

Andrea Slavin, RN
Center for Drug Evaluation and Research
Food and Drug Administration
Division of Scientific Investigations (HFD-46)
Good Clinical Practice Branch 1, Room 125
7520 Standish Place
Rockville, MD 20855

NDA 20-604/S-027 Serostim® [somatropin (rDNA origin) for injection]
Response to a Request for Additional Information

Dear Ms Slavin:

Reference is made to Serostim® NDA 20-604 approved on August 23, 1996 according to 21 CFR 314.510, Subpart H. Further reference is made to supplemental application S-027 submitted on October 31, 2002 and to a February 5, 2002 Agency facsimile that requested specific information on three clinical sites (sites 001, 020 and 499).

Accordingly, please find the requested information enclosed herewith, in a separate volume for each clinical site, as follows:

1. Address and phone number of the site – Attachment 1
2. Investigator's Form FDA 1572 – Attachment 2
3. A copy of the protocol (protocol #9037) and any amendments – Attachment 3
4. One completed case report form – Attachment 4
5. Randomization list for the site – Attachment 5
6. Total number of subjects entered into each study arm – Attachment 6
7. The number of drop-outs/discontinued subjects, identified by the subjects' study numbers – Attachment 7
8. List by subjects' study number of all evaluable/inevaluable subjects – Attachment 8
9. List by subjects' study number of all reportable AEs, SAEs and deaths, with a narrative for all SAEs and deaths – Attachment 9
10. List of protocol violations and deviations for the site – Attachment 10
11. Data listings of the efficacy endpoint (primary endpoint) data for each subject – Attachment 11
12. Names of monitors and monitoring logs – Attachment 12

Please note that Serono, Inc. considers this submission and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any questions concerning this submission, please contact Robert M. Kirsch, Director, Regulatory Affairs, at (781) 681-2272 or the undersigned at (781) 681-2298.

Sincerely,

Pamela Williamson Joyce, RAC
Vice President, Regulatory Affairs & Quality Assurance – North America

Cc: David Orloff, M.D. (HFD-510)

Enclosures

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Serono, Inc.
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February 7, 2003

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852

NDA 20-604/S-027 Serostim® [somatropin (rDNA origin) for injection]
Request for Additional Information

Dear Central Document Room:

Reference is made to Serostim® NDA 20-604 approved on August 23, 1996 according to 21 CFR 314.510, Subpart H. Further reference is made to supplemental application S-027 submitted on October 31, 2002 and to a December 13, 2002 teleconference with the Agency (HFD-510) during which additional information was requested.

Specifically, the Division (HFD-510) requested that a WORD version of the proposed package insert, in revision mode, be submitted to supplement S-027 and that it be sent on CD-ROM directly to the Central Document Room. Accordingly, please find enclosed a CD-ROM that contains the requested proposed package insert.

All electronic files have been scanned and checked for viruses using Symantec Norton Antivirus Corporate Edition (version 7.0 and virus data file version 40626t dated June 26, 2002) produced and sold by Symantec, Inc. The files are free of viruses as tested by that software.

Please note that Serono, Inc. considers this submission and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any questions concerning this submission, please contact Robert M. Kirsch, Director, Regulatory Affairs, at (781) 681-2272 or the undersigned at (781) 681-2298.

Sincerely,

Pamela Williamson Joyce
Vice President, Regulatory Affairs – North America

Enclosures

Cc: David Orloff, M.D. (HFD-510)

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JAN 3 0 2003

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Serono, Inc.
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Fax: 781-681-2924
www.seronousa.com

January 29, 2003

David Orloff, M.D.
Director, Division of Metabolism and Endocrine
Drug Products, HFD-510
Center for Drug Evaluation and Research
Attn: Fishers Document Room
Parklawn Building, Room 8B-45
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

SE7027 (AP)

NDA SUPPL AMENDMENT

NDA 20-604/S-027 Serostim® [somatropin (rDNA origin) for injection]
Request for Additional Information

Dear Dr. Orloff:

Reference is made to Serostim® NDA 20-604 approved on August 23, 1996 according to 21 CFR 314.510, Subpart H. Further reference is made to supplemental application S-027 submitted on October 31, 2002 and to a December 13, 2002 teleconference with the Agency during which additional information was requested.

Accordingly, please find the requested information attached herewith as follows (the Agency request is presented in **bold type** first, followed by the location of the information):

- **For each clinical site included in the GF 9037 clinical study report, please provide a listing that contains the following information: the site address, the site principal investigator, the number of patients enrolled and the number of patients completed.**

  The requested information is presented in Attachment 1 in a table entitled "Serostim® Study GF 9037 Clinical Site Information".

- **Please submit Patent Information and Certification with an authorized company signature.**

  The requested signed patent information and certification is presented in Attachment 2.

- **Please submit an Environmental Risk Assessment statement with an authorized company signature.**

  The requested signed Environmental Risk Assessment statement is presented in Attachment 3.

- **Please submit a Field Copy Certification with an authorized company signature.**

  The requested signed Field Copy Certification is presented in Attachment 4.

- **Please submit an electronic version of the proposed package insert showing deletions (strikeouts) and insertions (underlining) directly to the Central Document Room.**

  An electronic version of the proposed package insert showing deletions and insertions has been sent on CD-ROM directly to the Central Document Room.

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Please note that Serono, Inc. considers this submission and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any questions concerning this submission, please contact Robert M. Kirsch, Director, Regulatory Affairs, at (781) 681-2272 or the undersigned at (781) 681-2298.

Sincerely,

Pamela Williamson Joyce
Vice President, Regulatory Affairs

Enclosures

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SC7-027-C

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SUPPL NEW CORRESP

JAN 3 0 2003

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JAN 3 1 2003

FOR CDER

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SUPPL NEW CORRESP

January 29, 2003

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852

NDA 20-604/S-027 Serostim® [somatropin (rDNA origin) for injection]
Request for Additional Information

Dear Central Document Room:

Reference is made to Serostim® NDA 20-604 approved on August 23, 1996 according to 21 CFR 314.510, Subpart H. Further reference is made to supplemental application S-027 submitted on October 31, 2002 and to a December 16, 2002 teleconference with the Agency during which additional information was requested.

Specifically, Dr. Lee Ping Pian (HFD-715) requested that Serono conduct an additional analysis for the Intent-to-Treat population with baseline data and any post follow-up data up to week 12 including inconsistent bicycle readings. The post follow-up data should include early termination visits that happened any time before the end of the 12 week period. Further, Dr. Pian requested that the analysis, and the SAS transport file of the data that went into the analysis, be submitted in electronic form to the Central Document Room. Accordingly, a CD-ROM is enclosed herewith that contains the requested analysis and SAS transport file.

Please note that Serono, Inc. considers this submission and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any questions concerning this submission, please contact Robert M. Kirsch, Director, Regulatory Affairs, at (781) 681-2272 or the undersigned at (781) 681-2298.

Sincerely,

noted
2pp 2/5/03

Pamela Williamson Joyce
Vice President, Regulatory Affairs – North America

Cc: David Orloff, M.D. (HFD-510)

Enclosures

CONFIDENTIAL

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October 31, 2002

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NDA NO. 20604 REF NO. 02
NDA SUPPL FOR SE7

David Orloff, M.D.
Director, Division of Metabolism and Endocrine
Drug Products, HFD-510
Center for Drug Evaluation and Research
Attn: Fishers Document Room
Parklawn Building, Room 8B-45
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA 20-604 Serostim® [somatropin (rDNA origin) for injection]
Special Supplemental New Drug Application – Subpart H Confirmatory Study

Dear Dr. Orloff:

to IND 37,037

Reference is made to Serostim® NDA 20-604 approved on August 23, 1996 according to 21 CFR 314.510, Subpart H. Further reference is made to the requirement that a confirmatory Phase 4 study (study GF 9037) be conducted and submitted to the Agency as a condition of approval granted under Subpart H. Finally, reference is made to a July 12, 2002 pre-NDA meeting (teleconference) held between the Agency and Serono, Inc. during which the format and content of the Subpart H supplemental application was discussed and the Agency requested that specific information and analyses be provided.

Accordingly, for ease of review, please note that the specific information and analyses requested by the Agency may be located in this supplemental application as follows (the Agency request is presented in **bold type** first, followed by where the information may be located).

- **Present the safety data for all treated patients (covering the 12 week double blind, placebo controlled portion, the extension to 48 weeks prior to Amendment 1A, and the extension to 24 weeks after Amendment 1A) by dose and also by duration of exposure.**

  Adverse events reported by more than 5%of the patients in any treatment group up to week 12 are shown in Table 12.5 and events reported by more than 5% of the patients in any treatment group during the entire study are shown in Table 12.6 of the GF 9037 study report. Complete listings of all adverse events during the first 12 weeks and during the entire study are shown in Table 12.7 and Table 12.8.

- **Focus on the incidence of hyperglycemia, tumorigenesis, Insulin Growth Factor-Standard Deviation Scores (IGF-1 SDS) responses, and edema/arthralgia/other established adverse effects associated with recombinant human growth hormone (rhGH) therapy. Detailed narratives should be provided when appropriate, and glucose/IGF-1 SDS data should be presented in a comprehensive fashion (i.e., shift tables, distribution plots).**

  Information on hyperglycemia and Insulin Growth Factor – Standard Deviation Scores is presented in Table 12.22 and in Appendix 14, Tables 14-96 and 14-97 of the GF 9037 study report; information on edema/arthralgia/other established adverse effects associated with rhGH therapy is presented in Appendix 14, Tables 14-161 to 14-184.

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- **The primary analysis population should be the Intent to Treat (ITT) population consisting of ALL patients who have baseline data and at least 1 post treatment assessment. The ITT population should also include those patients with inconsistent data. Patients without a 12-week assessment should have their last on-study measurement used in the analysis (last observation carried forward [LOCF]). Other analyses may be performed to assess the impact of dropouts and data inconsistencies.**

  Section 11.1 of the GF 9037 study report confirms that the ITT population consists of all patients who received at least one injection of double-blind treatment with an assessment at baseline and at least one post-baseline assessment.

- **Please indicate to the Division how you plan to present the efficacy data for patients who continued in the study after completing the 12-week, double blind, placebo-controlled portion. More specifically: will the efficacy data for patients enrolled before Amendment 1A who continued to receive 2 doses of rhGH in a blinded fashion after week 12 (for as long as 36 additional weeks) be presented separately form efficacy data for patients enrolled after Amendment 1A (who received full doses of rhGH in an open label fashion for 12 additional weeks after week 12)? In addition, are you planning to present combined 24 week efficacy data for ALL patients (i.e., patients enrolled before or after Amendment 1A)?**

  Please refer to Section 16.1.19, Documentation of Statistical Methods, of the GF 9037 study report for information on how efficacy data are presented for the various groups treated during the study.

- **Furthermore, in this regard, how were patients already enrolled before and at different cutpoints for rhGH therapy (i.e., <12 weeks, 12-24weeks, >24 weeks) dealt with after Amendment 1A was instituted?**

  Please refer to Section 16.1.19, Documentation of Statistical Methods, of the GF 9037 study report for information on how efficacy data are presented for the various groups treated during the study.

- **Please provide appropriate subgroup analyses in both the efficacy and safety analyses (i.e., patients treated with HAART [including a protease inhibitor] vs. patients not treated with HAART [including a protease inhibitor], patients with central adiposity vs. patients without central adiposity).**

  Please refer to Table 14-13 and Table 14-19 for efficacy analyses including HAART therapy. Regarding safety analyses, HAART vs. non-HAART analyses were not conducted because nearly 90% of study patients were on HAART therapy during the study. Regarding central adiposity analyses, because the GF 9037 study protocol did not require collection of these data, there were very limited data available. This fact notwithstanding, an analysis of central adiposity is provided in Section 20 of this application.

- **Please provide literature supporting the continued need for rhGH in an important subset of AIDS patients with global wasting.**

  Please refer to Section 20 of this application for selected publications that support the continued need for rhGH in an important subset of AIDS patients with global wasting.

serono

- **Please refer to the FDA Guidance for Industry for Providing Regulatory Submissions in Electronic Format: New Drug Applications for preparation of the Subpart H SNDA.**

  Please be advised that all electronic components of this Subpart H SNDA were prepared in accordance with the Guidance cited above, the compact discs containing the electronic components are labeled ELECTRONIC REGULATORY SUBMISSION FOR ARCHIVE as specified in the January 1999 Guidance for Industry "Providing Regulatory Submissions in Electronic Format – General Considerations" and are being submitted to the following addresss:

  Central Document Room
  Center for Drug Evaluation and Research
  Food and Drug Administration
  12229 Wilkins Avenue
  Rockville, MD 20852

  The electronic files, which are approximately 600 MB in size, are provided on 1 CD organized according to the guidance cited above. All electronic files have been scanned and checked for viruses using Symantec Norton Antivirus Coporate Edition (version 7.0 and virus data file version 40626t dated June 26, 2002) produced and sold by Symantec, Inc. The files are free of viruses as tested by that software.

  Section 12 of this application, Case Record Forms for patients that died or dropped out of the study due to an adverse event, are being submitted to the Division in paper format.

Please note that Serono, Inc. considers this submission and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any questions concerning this submission, please contact Robert M. Kirsch, Director, Regulatory Affairs, at (781) 681-2272 or the undersigned at (781) 681-2298.

Sincerely,

Pamela Williamson Joyce
Vice President, Regulatory Affairs

Enclosures

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-604/S-027

FILING ISSUES IDENTIFIED

Serono, Inc.
Attention: Pamela Williamson Joyce
One Technology Place
Rockland, MA 02370

12/20/02

Dear Ms. Joyce:

Please refer to your October 31, 2002, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Serostim (somatropin [rDNA origin] for injection).

AIDS + CACEXIA

We have completed our filing review of your application and have identified the following issues:

> We note that during our July12, 2002, teleconference with you regarding the safety and efficacy analysis of this study, we requested that the primary analysis population be the intent to treat (ITT) population-consisting of ALL patients who have baseline data and at least one post-treatment assessment.

As agreed during your December 16, 2002, phone conversation with Dr. Lee Pian, you will submit the ITT analysis as originally requested and a corresponding electronic dataset to the NDA by January 2003.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

If you have any questions, call Monika Johnson, PharmD, Regulatory Project Manager, at (301) 827-6370.

Sincerely,

{See appended electronic signature page}

Enid Galliers
Chief, Regulatory Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Enid Galliers
12/20/02 03:01:23 PM

NDA SUPPLEMENT REGULATORY FILING REVIEW

NDA 20-604/S-027, Serostim (Somatropin [rDNA origin] for injection) 4 mg, 5 mg, 6 mg, and 8.8 mg

Applicant: Serono, Inc.

Date of Application: October 31, 2002

Date of Receipt: November 1, 2002

Date of Filing Meeting: December 11, 2002

Filing Date: December 30, 2002

Indication(s) requested: for the treatment of HIV patients with wasting or cachexia. Serostim restores lean body mass and subsequently body weight, decreases fat mass, and improves physical endurance and general well-being. Concomitant antiretroviral therapy in necessary.

Type of Application: Full NDA _____ Supplement ___X____
(b)(1) ____X_ (b)(2) _____

Therapeutic Classifications: S__X__ P_____
Resubmission after a withdrawal or refuse to file _N/A___
Chemical Classification: (1,2,3 etc.)__SE7_
Other (orphan, OTC, etc.)_N/A___

User Fee Status: Paid _____Waived (e.g., small business, public health) _____
Exempt (orphan, government) __X Confirmatory Study for Subpart H/Orphan Exclusion

Form 3397 (User Fee Cover Sheet) submitted: YES
User Fee ID#_____N/A_____
Clinical data? YES __X
Date clock started after UN ____N/A___

User Fee Goal date: ____September 1, 2003___

Note: If an electronic NDA: all certifications require a signature and must be in paper.

- Does the submission contain an accurate comprehensive index? YES

- Form 356h included with authorized signature? YES
  If foreign applicant, the U.S. Agent must countersign or submit a separate certification.

- Submission complete as required under 21 CFR 314.50? YES
  If no, explain:

- If electronic NDA, does it follow the Guidance? YES

- Patent information included with authorized signature? YES, refer to NDA 20-604

- Exclusivity requested? NO

Note: An applicant can receive exclusivity without requesting it, therefore, requesting exclusivity is not a requirement.

- Correctly worded Debarment Certification included with authorized signature? YES
  If foreign applicant, the U.S. Agent must countersign or submit a separate certification.

  Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with the studies listed in Appendix ____." Applicant may not use wording such as, " To the best of my knowledge, …."

- Financial Disclosure included with authorized signature? YES
  (Forms 3454 and/or 3455)
  If foreign applicant, the U.S. Agent must countersign or submit a separate certification.

- Pediatric Rule appears to be addressed for all indications? N/A

- Pediatric assessment of all ages? N/A
  (If multiple indications, answer for each indication.)
  If NO, for what ages was a waiver requested? _____
  For what ages was a deferral requested? _____

- Field Copy Certification (that it is a true copy of the CMC technical section)? N/A

Refer to 21 CFR 314.101(d) for Filing Requirements

PDUFA and Action Goal dates correct in COMIS? YES

List referenced IND numbers: 38,087

End-of-Phase 2 Meeting? NO
If yes, distribute minutes before filing meeting.

Pre-NDA Meeting(s)? July 12, 2002_____

Project Management

Copy of the labeling (PI) sent to DDMAC? YES

Trade name and labeling (PI) sent to ODS? N/A

DSI consult NO, done in 1996 with original application.

Advisory Committee Meeting needed? NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES_____ NO _X___

Chemistry

- Did sponsor request categorical exclusion for environmental assessment? YES

- EA consulted to Nancy Sager (HFD-357)? N/A
- Establishment Evaluation Request (EER) package submitted? NO
- Parenteral Applications Consulted to Sterile Products (HFD-805)? NO

505(b)(2) N/A_X_

FILING MEETING MINUTES

DATE: December 11, 2002

BACKGROUND:

Serono, Incorporated submitted an NDA for Serostim September 11, 1995, for accelerated approval (Subpart H) under 21 CFR 314.510. The application was approved August 23, 1996, with a requirement that a confirmatory study (GF 9037) be conducted and submitted to the Agency. This division held a pre-NDA teleconference on July 12, 2002, during which the format and content of the confirmatory study was discussed. The confirmatory study was submitted on October 31, 2002 and received November 1, 2002.

ATTENDEES: Robert Perlstein, David Orloff, Lee Pian, Todd Sahlroot, Enid Galliers, Monika Johnson

ASSIGNED REVIEWERS:

Discipline	Reviewer
Medical:	Robert Perlstein, MD
Secondary Medical:	David Orloff, MD
Statistical:	Lee Pian, PhD
Pharmacology:	
Statistical Pharmacology:	
Chemist:	Janice Brown, MS
Environmental Assessment (if needed):	Janice Brown, MS

Biopharmaceutcal:
Microbiology, sterility:
Microbiology, clinical (for antimicrobial products only):
DSI:
Project Manager: Monika Johnson, PharmD
Other Consults: Div of Anti-Infective Drugs/HFD-520
LAURIE BURKE - HEALTH OUTCOMES/HFD-02

Is the application affected by the application integrity policy (AIP) NO

Per reviewers, all parts in English, or English translation? YES

CLINICAL – File __X__ Refuse to file _____

- Clinical site inspection needed: YES__X____ NO__ __

MICROBIOLOGY CLINICAL – File___N/A__ Refuse to file_____

STATISTICAL – File ___X__ Refuse to file _____

BIOPHARMACEUTICS – File ___N/A___Refuse to file _____

PHARMACOLOGY – File __N/A___ Refuse to file _____

CHEMISTRY –

- Establishment ready for inspection? N/A ____X_____

REGULATORY CONCLUSIONS/DEFICIENCIES:

__X__The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

_____ The application is unsuitable for filing. Explain why:

__Monika Johnson, PharmD___
Project Manager, HFD-510