CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

020604Orig1s040

Trade Name: **SEROSTIM**

Generic Name: **Somatropin [rDNA origin] for injection**

Sponsor: **EMD Serono, Inc.**

Approval Date: **July 13, 2007**

Indications: **For the revision of the CLINICAL PHARMACOLOGY, CLINICAL STUDIES, PRECAUTIONS, and ADVERSE REACTIONS sections of the package insert to include information regarding use in patients with HIV-associated adipose redistribution syndrome (HARS)**

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APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-604/S-040

EMD Serono
Attention: Paul Lammers, MD
Acting Head, Regulatory Affairs and Quality Assurance
One Technology Place
Rockland, MA 02370

Dear Ms. Mills:

Please refer to your supplemental new drug application dated June 12, 2006, received June 14, 2006, 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 September 28, 2006, and February 6 and 27, March 27, April 9 and 24, 2007.

This supplemental new drug application provides for the revision of the CLINICAL PHARMACOLOGY, CLINICAL STUDIES, PRECAUTIONS, and ADVERSE REACTIONS sections of the package insert to include information regarding use in patients with HIV-associated adipose redistribution syndrome (HARS).

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

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert).

Please submit either an electronic version or 20 paper copies of the FPL as soon as it is available (no more than 30 days after it is printed). If paper copies are submitted, individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved supplement NDA 20-604/S-040**." Approval of this submission by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for this application.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Metabolism and Endocrinology Products and two copies of both the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

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
Food and Drug Administration
5515 Security Lane
HFD-001, Suite 5100
Rockville, MD 20852

We 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 Kati Johnson, Regulatory Project Manager, at (301) 796-1234.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, MD
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: Package Insert

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

/s/

Eric Colman
7/13/2007 11:17:33 AM
Eric Colman for Mary Parks

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020604Orig1s040

LABELING

Serostim®

[somatropin (rDNA origin) for injection]

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 5 mg and 6 mg vials for single dose administration. Serostim® is also available in 4 mg and 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 with Water for Injection, USP. The pH is adjusted with sodium hydroxide or phosphoric acid to give a pH of 6.5 to 8.5 after reconstitution with Bacteriostatic Water for Injection, USP (0.9% Benzyl Alcohol).

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).

Human immunodeficiency virus (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.

HIV-associated adipose redistribution syndrome (HARS) is characterized by abnormal accumulation of trunk fat, including visceral adipose tissue (VAT), in patients infected with HIV/acquired immune deficiency disorder (AIDS), the vast majority of whom have been treated with highly active antiretroviral therapy (HAART). VAT is comprised of the deep fat in the abdomen in the omental-mesenteric and retroperitoneal compartments. HARS, a subset of HIV lipodystrophy, is more specifically defined as maldistribution of body fat characterized by central fat accumulation (lipohypertrophy) with or without lipoatrophy (subcutaneous fat depletion primarily in the face and limbs). In HARS patients, fat may additionally accumulate in the upper body subcutaneous area such as the dorsocervical area (i.e., “buffalo

hump"). These changes may be accompanied by metabolic disturbances including insulin resistance, glucose intolerance, and dyslipidemia, as well as belly image distress. Initial 12-week treatment with Serostim® resulted in decreases in VAT, trunk fat, and patient-reported belly appearance distress (see CLINICAL STUDIES). The clinical significance of these changes with respect to improved cardiovascular risk profile or compliance with HAART has not been studied.

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.

Decreases in trunk fat and total body fat, and increases in lean body mass were observed during two double-blind, placebo-controlled studies wherein Serostim® vs. placebo were administered daily for 12 weeks to patients with HARS. (see CLINICAL STUDIES).

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.

Physical Performance:

Cycle ergometry work output and treadmill performance were examined in separate 12-week, placebo-controlled trials (see 'Clinical Studies'). In both studies, work output improved significantly in the group receiving Serostim® 0.1 mg/kg/day subcutaneously vs placebo. Isometric muscle performance, as measured by grip strength dynamometry, declined, probably as a result of a transient increase in tissue turgor known to occur with Serostim® therapy.

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

HIV-Associated Wasting or Cachexia

The clinical efficacy of Serostim® [somatropin (rDNA origin) for injection] in HIV-associated wasting or cachexia 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

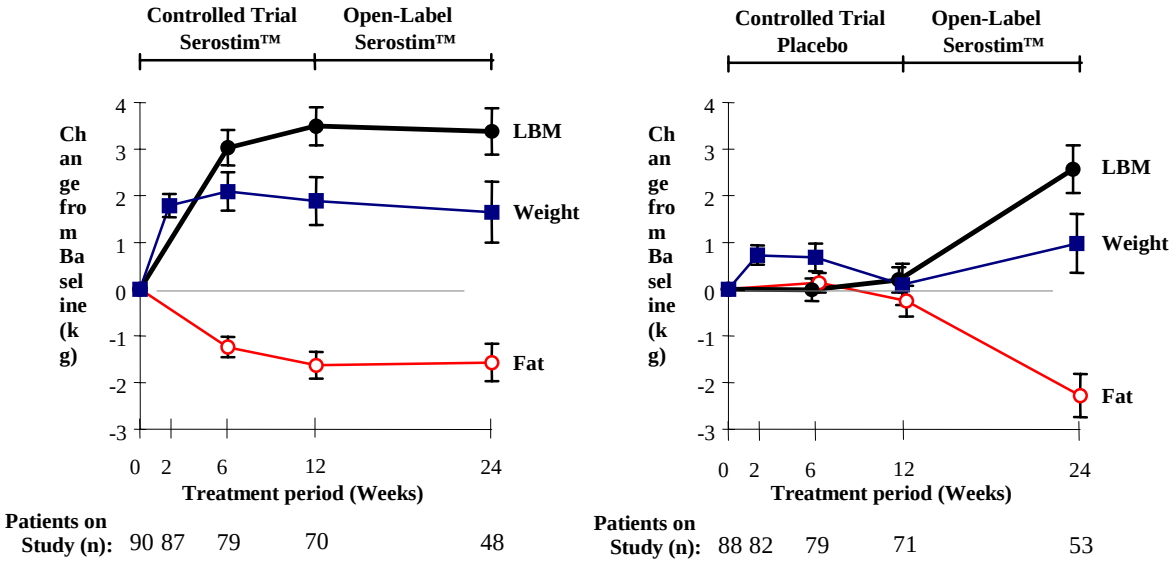
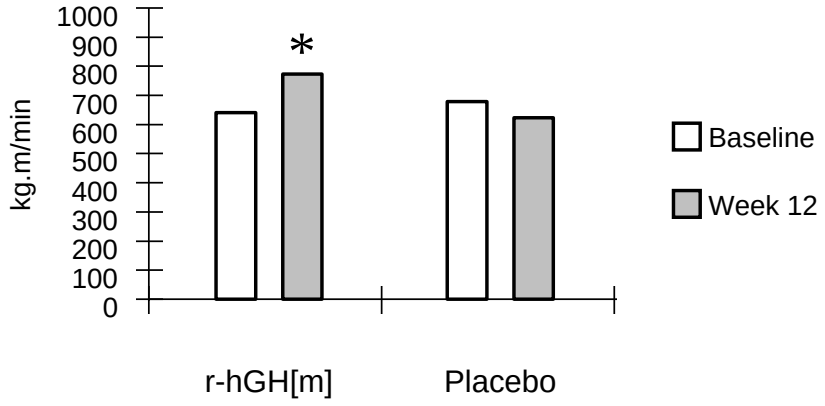


Figure 2: Median Treadmill Work Output



*p = 0.039

<u>Clinical Trial 2:</u> 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[c] (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. 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). 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.

HIV-Associated Adipose Redistribution Syndrome (HARS)

The clinical efficacy of Serostim® [somatropin (rDNA origin) for injection] for the treatment of patients with HARS was assessed in two double-blind, placebo-controlled trials. The inclusion and exclusion

criteria were essentially identical in both studies. Patients with a history of diabetes, impaired fasting glucose or impaired glucose tolerance were excluded. Approximately 20% of the patients screened were excluded from study enrollment as a result of a diagnosis of diabetes or glucose intolerance. Study subjects received concomitant antiretroviral therapy and met the generally accepted criteria for excess central adipose tissue deposition assessed by anthropometric methodology (e.g., waist circumference, waist:hip ratio).

HARS Study 1 (24 weeks)

Induction Phase (12 weeks): A double-blind, placebo-controlled, parallel group study randomized 245 patients with HARS. The co-primary efficacy endpoints were change in visceral adipose tissue (VAT) and trunk:limb fat ratio after 12 weeks of treatment. Secondary efficacy endpoints included changes from baseline to Week 12 in trunk fat, abdominal subcutaneous adipose tissue (SAT), total body fat, lean body mass, various lipid parameters and patient reported outcome (PRO) scores. Patients meeting the inclusion/exclusion criteria were treated with either placebo, Serostim® 4 mg every other day (qod) or Serostim® 4 mg daily qhs. Eighty seven percent (87%) of patients were male, 80% were Caucasian, 97% were receiving treatment with nucleoside reverse transcriptase inhibitors (NRTIs), and 30% were receiving treatment for dyslipidemia.

Maintenance Phase (12 Weeks): Patients completing the 12-week induction phase who were treated with Serostim® 4 mg daily were rerandomized to therapy with either Serostim® 4 mg qod or placebo for an additional 12 weeks. Patients completing the 12 week induction phase who were treated with Serostim® 4 mg qod received Serostim® 4 mg qod for an additional 12 weeks, while patients who were treated with placebo received Serostim® 4 mg daily for an additional 12 weeks. Two hundred and eight patients received study drug and had a maintenance phase visit. The primary and secondary efficacy endpoints were the same as described above.

HARS Study 2 (36 weeks)

Induction Phase (12 Weeks): A double-blind, placebo-controlled, parallel group study randomized 326 patients with HARS. The primary efficacy endpoint was change in VAT after 12 weeks of treatment. The secondary endpoints were similar to those in HARS Study 1. Patients meeting the inclusion/exclusion criteria were treated with either placebo or Serostim® 4 mg daily qhs. Baseline demographic characteristics were very similar to Study 1.

Maintenance Phase (24 Weeks): Patients completing the 12-week induction phase were rerandomized to treatment with either Serostim® 2 mg qod or placebo for an additional 24 weeks. Two hundred fifty six patients received study drug and had a maintenance phase visit. The primary and secondary efficacy endpoints were the same as described above.

<u>Induction Phase (Weeks 0-12) Results For Both Studies</u>

The difference in the change from baseline to Week 12 in VAT (approximately -20 cm^2) was statistically significant after treatment with Serostim® 4 mg qod vs. placebo in Study 1 (Table 3). As seen in Tables 3 and 4, the differences in the change from baseline to Week 12 in VAT (approximately -17-18 cm^2) were also statistically significant after treatment with Serostim® 4 mg daily vs. placebo in both studies. The VAT response to treatment with Serostim® 4 mg qod vs. placebo in Study 1 was very similar to the response observed after treatment with Serostim® 4 mg daily (Table 3). Patients with the largest VAT levels at baseline manifested the largest reductions in VAT in response to Serostim® treatment (data not shown).

Table 3: HARS Study 1 Induction Phase – Mean Change from Baseline to Week 12 in Visceral Adipose Tissue (cm^2)[a] by Treatment Group (Modified ITT Population with LOCF)

	Placebo n=57	Serostim® 4 mg qod n=58	Serostim® 4 mg daily n=61
Baseline (SE)[b]	133 (12)	130 (14)	138 (12)
Change from Baseline (SE)[c]	-9 (6)	-28 (7)	-27 (6)
Difference from Placebo for Change (95% CI)[c]		-20 (-38, -2) p=0.034	-18 (-35, -2) p=0.031

(a) Measured by computed tomography (CT) scan; (b) Analysis of variance model with terms for treatment group, gender, and treatment-by-gender interaction; (c) Analysis of covariance model with terms for treatment group, gender, and treatment-by-gender interaction, and baseline VAT as covariate; (d) CI = confidence interval and SE = standard error

Table 4: HARS Study 2 Induction Phase – Mean Change from Baseline to Week 12 in Visceral Adipose Tissue (cm^2)[a] by Treatment Group (Modified ITT Population with LOCF)

	Placebo n=74	Serostim® 4 mg daily n=210
Baseline (SE)[b]	110 (11)	116 (6)
Change from Baseline (SE)[c]	-12 (5)	-29 (3)
Difference from Placebo for Change (95% CI)[c]		-17 (-29, -5) p=0.005

(a) through (d) Same as Table 3

Subgroup analysis by gender revealed that women did not have a significant reduction in VAT in response to Serostim® 4 mg daily as indicated by the descriptive statistics by gender in Table 5 (only results from Study 2 are shown, but the results from Study 1 were similar).

Table 5: HARS Study 2 Induction Phase – VAT (cm^2)[a] Descriptive Statistics by Gender

	Female		Male	
Variable as Mean (SD)[b]	Placebo	Serostim® 4 mg daily	Placebo	Serostim® 4 mg daily
	n=9	n=31	n=65	n=179
Baseline	77 (50)	87 (34)	143 (54)	144 (65)
Change from Baseline	-7 (44)	-7 (19)	2 (33)	-37 (39)

(a) Measured by computed tomography (CT) scan; (b) SD = standard deviation

Improvements in some secondary body composition endpoints (trunk fat, abdominal SAT, total body fat, and lean body mass) were observed in both Serostim® dose groups regardless of gender. Although a greater response was observed with 4 mg daily dosing, this dose was associated with a higher rate of adverse events, dose reductions and study discontinuation (see PRECAUTIONS and ADVERSE REACTIONS). Improvements were not observed in other secondary endpoints including non-HDL cholesterol.

Maintenance Phase Results

In Study 2, VAT reaccumulated to the same extent in patients treated with Serostim® 2 mg qod and placebo.

The maintenance phase results from Study 1 are summarized in Table 6. In patients initially treated with Serostim® 4 mg daily during the induction phase, rerandomization to Serostim® 4 mg qod (vs. placebo) resulted in less reaccumulation of VAT, trunk fat and total body fat.

Table 6: HARS Study 1 Maintenance Phase: Descriptive Statistics for Mean Changes from Week 12 to Week 24 in Various Body Composition Endpoints in Patients Randomized to Placebo vs. Serostim® 4 mg qod After 12 Weeks of Induction Therapy with Serostim® 4 mg Daily

Variable as Mean (SD)[c]		Placebo	Serostim® 4 mg qod
Visceral Adipose Tissue[a] (cm^2)	Week 12	138.7 (46.2) (n=25)	114.1 (75.0) (n=27)
	Change	17.7 (32.3) (n=25)	5.7 (41.4) (n=27)
Trunk Fat[b] (kg)	Week 12	8.3 (3.7) (n=27)	6.6 (3.3) (n=23)
	Change	1.2 (1.5) (n=27)	0.3 (1.2) (n=23)
Total Body Fat[b] (kg)	Week 12	13.9 (7.1) (n=27)	10.7 (5.5) (n=23)
	Change	1.3 (2.2) (n=27)	0.2 (1.9) (n=23)

(a) Measured by computed tomography (CT) scan; (b) Assessed by dual energy X-Ray absorptiometry (DEXA) scan; (c) SD = standard deviation

Patient Reported Outcomes

Belly appearance distress, belly size estimation and belly profile assessment (the essential PRO secondary efficacy endpoints) were measured using a validated PRO instrument, the Body Image Impact Module (BIIM) in both studies. Only results for belly appearance distress and belly size estimation are discussed in that the belly profile assessment was used to establish responder criteria for the belly appearance distress and the belly size estimation. Both Serostim® treatment groups manifested more improvement in belly appearance distress and belly size estimation than placebo-treated patients. Although a greater response was observed with 4 mg daily dosing during the induction phase, this dose was associated with a higher rate of adverse events, dose reductions and study discontinuation (see PRECAUTIONS and ADVERSE REACTIONS). The improvements in belly appearance distress and belly size estimation were sustained during the maintenance phase of Study 1.

The clinical significance of the changes described above in the HARS subsection of the CLINICAL STUDIES section with respect to improved cardiovascular risk profile or compliance with HAART has not been studied.

INDICATIONS AND USAGE

HIV-Associated Wasting or Cachexia

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.

There are limited data in women with HARS, especially those taking estrogen. The 47 women treated with Serostim®, 6 of whom were taking estrogen, showed no difference from placebo with respect to reduction in VAT after 12 weeks of induction treatment. It is well established that GH deficient women concomitantly treated with oral estrogen replacement therapy require substantially more rhGH to obtain comparable rhGH-related treatment effects. In addition, women with HARS have lower baseline VAT levels; lower baseline VAT levels have been demonstrated by several authors to predict a lesser reduction in VAT in response to treatment with rhGH.

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. None of the Serostim®-treated HARS study participants with available test results developed detectable antibodies to rhGH during the induction or maintenance phases of treatment.

Recombinant human growth hormone (rhGH) has been associated with acute pancreatitis.

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

In HARS patients who had normal fasting glucose levels at screening, treatment with Serostim® 4 mg daily and 4 mg qod for 12 weeks (vs. placebo) was associated with approximately 7 and 6 mg/dL increases in mean fasting blood glucose concentrations, respectively. With respect to the induction phase, peak sugars on-study usually occurred early after initiation of Serostim® treatment, and, most often decreased spontaneously with continued Serostim® therapy or responded to dose reduction. Transient and occasionally sustained peak sugars between 100 and 126 mg/dL (and transient sugars in excess of 126 mg/dL) occurred in a substantial minority of patients (including patients with normal fasting blood glucose levels at baseline). Treatment with Serostim® 4 mg daily resulted in a greater number of glucose intolerance-related adverse reactions than treatment with Serostim® 4 mg qod (see ADVERSE REACTIONS). In HARS Study 2, hemoglobin A1c increased from a mean of 5.0% at baseline to 5.3% at Week 12 after treatment with Serostim® 4 mg daily, but it remained in the desirable range (less than 7.0%) in all patients. HARS patients are often insulin resistant and even glucose intolerant to some degree at baseline, and therefore are very susceptible to more overt glucose intolerance after treatment with large pharmacologic amounts of rhGH. Therefore, if HARS patients are treated with Serostim®, they should be very closely monitored for glucose intolerance.

During safety surveillance of patients with HIV-associated wasting and HARS, 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 of these patients required initiation or adjustment of antidiabetic treatment while on Serostim®.

No cases of intracranial hypertension (IH) have been observed among patients 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 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.

Published *in vitro* data indicate that growth hormone may be an inducer of cytochrome P450 3A4. In clinical trials of HIV-infected patients with wasting or HARS who were receiving antiretroviral therapy, Serostim® did not adversely alter antiretroviral effectiveness, such as mean circulating levels of CD4 counts or HIV-1 RNA (viral load). When Serostim® is administered in combination with drugs known to be metabolized by CYP P450 3A4 hepatic enzymes, such as some antiretroviral drugs, it is advisable to monitor the clinical effectiveness of these drugs.

Somatropin inhibits 11β-hydroxysteroid dehydrogenase type 1 (11βHSD-1) in adipose/hepatic tissue and may significantly impact the metabolism of cortisol and cortisone. As a consequence, in patients treated with somatropin, previously undiagnosed primary (and secondary) hypoadrenalism may be unmasked requiring glucocorticoid replacement therapy. In addition, patients treated with glucocorticoid replacement therapy for previously diagnosed hypoadrenalism may require an increase in their maintenance or stress doses; this may be especially true for patients treated with cortisone acetate and prednisone since conversion of these drugs to their biologically active metabolites is dependent on the activity of the 11βHSD-1 enzyme.

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

HIV-Associated Wasting or Cachexia

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 7 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 7: Controlled Clinical Trial 2 Adverse Events

	Placebo	0.1 mg/kg qod Serostim®	0.1 mg/kg daily Serostim®
	Patients (n=247)	Patients (n=257)	Patients (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
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 trial participants receiving Serostim® during the first 12 weeks of Clinical Trial 2 thought to be related to Serostim® included dependent edema, periorbital edema, carpal tunnel syndrome, hyperglycemia and hypertriglyceridemia.

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.

HIV-Associated Adipose Redistribution Syndrome (HARS)

In the initial 12-week treatment periods of the two HARS, placebo-controlled clinical trials, 406 patients were treated with Serostim®. Clinical adverse events which occurred during the first 12 weeks of both studies combined in at least 5% of the patients in either of the two active treatment groups are listed by treatment group in Table 8, without regard to causality assessment. The most common adverse reactions judged to be associated with Serostim® were edema, arthralgia, pain in extremity, hypoesthesia, myalgia, and blood glucose increased, all of which were more frequently observed when Serostim® 4 mg was administered on a daily basis compared with alternate days. These symptoms were generally rated by investigators as mild to moderate in severity and often subsided with dose reduction. In addition, during the 12-week induction phase, 1) approximately 26% of patients receiving Serostim® 4 mg daily and 19% of patients receiving Serostim® 4 mg qod required dose reductions; and 2) discontinuations as a result of adverse events occurred in 13% of patients receiving Serostim® 4 mg daily and 5% of patients receiving Serostim® 4 mg qod. Once again, the most common reasons for dose reduction and/or drug discontinuation were peripheral edema, hyperglycemia (including blood glucose increased, blood glucose abnormal, and hyperglycemia), and arthralgia.

Table 8: Controlled HARS Studies 1 and 2 Combined - Adverse Events with >5% Incidence in Either Active Treatment Arm

System Organ Class Preferred Term	Placebo Patients (n=159) %	Serostim® 4 mg qod[1] Patients (n=80) %	Serostim® 4 mg daily Patients (n=326) %
Musculoskeletal and connective tissue disorders			
Arthralgia	11.9	27.8	37.1
Pain in extremity	3.8	5.0	19.3
Myalgia	3.8	2.5	12.6
Musculoskeletal stiffness	1.9	3.8	8.0
Joint stiffness	1.3	3.8	7.7
Joint swelling	0.6	5.0	6.1
General disorders and administration site conditions			
Edema peripheral	3.8	18.8	45.4
Fatigue	1.9	6.3	8.9
Nervous system disorders			
Hypoesthesia	0.6	8.8	15.0
Headache	3.1	3.8	14.1
Paraesthesia	2.5	12.5	11.0
Investigations (Laboratory Evaluations)			
Blood glucose increased[2]	2.5	3.8	13.8
Metabolism and nutrition disorders			
Hyperglycemia[2]	0.6	8.8	7.1
Fluid retention	0.6	2.5	5.2
Gastrointestinal disorders			
Nausea	2.5	1.3	6.1
Psychiatric disorders			
Insomnia	1.9	7.5	8.3
Infections and infestations			
Upper respiratory tract infection	5.0	10.0	5.2

[1] Study 22388 only
[2] similar terms were grouped together and reported below

Glucose-Related Terms: Similar glucose-related adverse event terms (including hyperglycemia, blood glucose increased, blood glucose abnormal) were grouped together which resulted in a greater than 5% incidence in Serostim®-treated patients. During the initial 12-week treatment periods of HARS Studies 1 and 2, the incidence of glucose-related adverse events was 4% for the placebo group, 13% for the 4 mg qod group and 22% for the 4 mg daily group. No patients required treatment for hyperglycemia. Of the 23 patients who discontinued due to hyperglycemia during <u>any</u> phase of these studies, 13 were being treated with induction therapy with Serostim® 4 mg daily (and 9 of these 13 during the 12 week induction phases of HARS Studies 1 and 2). One of these patients whose baseline fasting blood glucose was 95 mg/dL demonstrated substantial hyperglycemia (384 mg/dL) 12 days after treatment with Serostim® 4 mg daily was begun; however, the patient was normoglycemic 1 month after Serostim® was discontinued without treatment for hyperglycemia. A second patient in HARS Study 2 whose fasting blood glucose was 89 mg/dL at baseline manifested a fasting blood glucose of 404 mg/dl 21 days after treatment with Serostim® 4 mg daily was begun. His last known fasting blood glucose 1 week after Serostim® had been

discontinued was 224 mg/dl and then he was lost to follow-up. Whether sustained overt diabetes mellitus persisted is therefore unknown.

Breast-Related Terms: Similar breast-related adverse event terms (including nipple pain, gynecomastia, breast pain/mass/tenderness/swelling/edema/hypertrophy) were grouped together which resulted in a greater than 5% incidence in Serostim®-treated patients. The incidence of breast-related adverse event reports was 1% for the placebo group, 3% for the 4 mg qod group and 6% for the 4 mg daily group.

Adverse events that occurred in 1% to less than 5% of trial participants receiving Serostim® during the first 12 weeks of HARS Studies 1 and 2 thought to be related to Serostim® include carpal tunnel syndrome, tinel's sign and facial edema.

The adverse events reported for Serostim® 4 mg qod during the maintenance phase of HARS Study 1 (Week 12 to Week 24) were similar in frequency and quality to those observed after treatment with Serostim® 4 mg qod during the 12-week induction phase.

During safety surveillance of patients with HIV-associated wasting and HARS, 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 of these patients required 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

HIV-Associated Wasting or Cachexia

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

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

Each vial of Serostim® 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) and each vial of Serostim® 4 mg is reconstituted in 0.5 to 1 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® can be administered using (1) a standard sterile, disposable syringe and needle, (2) a compatible Serostim® needle-free injection device or (3) a compatible Serostim® needle injection device. For proper use, refer to the Instructions for Use provided with the administration device.

Serostim® [somatropin (rDNA origin) for injection] is available in the following forms:

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® vials containing 4 mg (approximately 12 IU) somatropin (mammalian-cell) with Bacteriostatic Water for Injection, USP (0.9% Benzyl Alcohol). Package of 7 vials. NDC 44087-0004-7

Serostim® vials 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: EMD Serono, Inc., Rockland, MA 02370

Rx Only BX Rated

July 2007

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020604Orig1s040

SUMMARY REVIEW

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993-002

DIVISION DIRECTOR'S MEMO

NDA	20-604/Supplement 040
Drug name	Serostim® (Recombinant human growth hormone)
Applicant	Serono
Date of Submission	June 12, 2006 (stamp date)
Reviewers	Robert Perlstein, M.D. Lee Pian, Ph.D. Todd Sahlroot, Ph.D.
Regulatory Project Manager	Kati Johnson

Introduction

On June 12, 2006, the Division received this efficacy supplement proposing the use of Serostim® (mammalian cell-derived recombinant human growth hormone, rhGH) for the treatment of Human Immunodeficiency Virus-Associated Adipose Redistribution Syndrome (HARS). The proposed dosing regimen for HARS was Serostim 4 mg QD for 12 weeks followed by Serostim 2 mg QOD for an additional 24 weeks of maintenance therapy.

The primary characteristic of HARS is an increase in the amount of visceral adipose tissue (VAT). In addition, adipose tissue may accumulate subcutaneously in the trunk or dorsocervical area (buffalo hump). Conversely, loss of subcutaneous adipose tissue or SAT (lipoatrophy) may also occur on the face, buttocks, and extremities, leading to the dysmorphic features that Dr. Perlstein has aptly described in his review as “pregnant skeleton” or “apple on a stick”. The immediate concern about such negative physical changes is that they might result in non-compliance with anti-retroviral therapies, which may significantly impact longevity in HIV-infected patients. Other accompanying metabolic perturbations of HARS include insulin resistance, glucose intolerance, dyslipidemia, and hypertension. Again, as noted by Dr. Perlstein, these are risk factors which may contribute to an increased risk for cardiovascular (CV) disease. It should therefore be reasonable to ask how any therapy targeting treatment of HARS might impact compliance with HIV therapy and/or reduce the risk of long-term CV complications.

The etiology of HARS has not been established but is likely multifactorial including use of anti-retroviral therapies, underlying HIV disease itself, and adipocyte dysfunction resulting from leptin deficient/excess states or adiponectin deficiency. GH deficiency has been implicated in the development of HARS as its reduced secretion and increased clearance has been observed in patients. In this regard, lack of the peripheral inhibitory effect of GH on llβ-hydroxysteroid dehydrogenase type 1(11βHSD1) activity resulting in increased local cortisol production has been posited as contributing to the lipodystrophy syndrome. 11βHSD1 catalyzes the conversion of inactive cortisone to the active cortisol and increased local cortisol production is thought to promote adipogenesis and increase VAT. It has been observed that VAT cells have higher levels of 11βHSD1. GH is thought to inhibit 11βHSD1 activity which might reduce local cortisol levels and stimulation of VAT production. It would therefore seem logical that

administration of rhGH, which has well established lipolytic effects, might reverse or treat some of the clinical manifestations of HARS.

Dr. Perlstein, in his reviews, and the applicant, in its submission, have summarized the regulatory history and communications between the FDA and Serono, Inc. regarding the clinical development program and endpoint measures. There is documentation that HARS was agreed to be a clinical entity for which treatment could be targeted and that the endpoints, VAT measured by cross-sectional CT scan and truncal fat measured by DEXA scan, could serve as primary and secondary efficacy measures, respectively. In addition, correlation between the changes in body fat distribution and changes in quality of life instruments would need to be assessed. With this feedback, the company conducted a clinical program which consisted of a 24-week, dose-finding study (Study 22388) and a 36-week study (Study 24380) which further evaluated doses selected based on the results from Study 22388. These studies evaluated induction and maintenance regimens for the treatment of HARS. The End-of-Phase 2 meeting minutes did emphasize the importance of demonstrating sustained efficacy and a satisfactory safety profile during the maintenance phase.

Study 22388

This study randomized eligible patients 1:1:1 to the following treatment groups for a 12-week *induction* phase:

1. 4 mg Serostim daily (QD) dosing (n=82)
2. 4 mg Serostim every other day (QOD) dosing (n=82)
3. placebo (n=81)

At the end of Week 12, patients received treatments as follows for an additional 12 weeks:

- 4 mg Serostim QD re-randomized 1:1 to → Serostim 4 mg OOD / placebo
- 4 mg Serostim QOD remained on this dosing regimen
- placebo received Serostim 4 mg QD

At the end of Week 24, patients were offered enrollment in Study 23056. This memo will not discuss the findings of that trial. Please refer to Dr. Perlstein's original review of this application for details of Study 23056.

This study was conducted in 2001-2002.

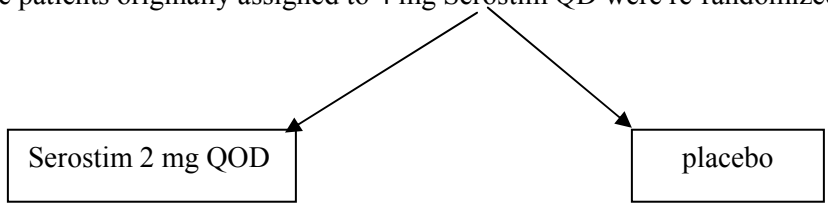
Study 24380

This study randomized eligible patients in a 3:1 ratio to the following treatment groups for 12 weeks:

1. 4 mg Serostim daily (QD) dosing (n=245)
2. placebo (n=81)

At the end of Week 12, patients entered a 24-week treatment period with the following treatment assignments:

- those patients originally assigned to 4 mg Serostim QD were re-randomized 1:1 to:



- those patients originally assigned to placebo continued to receive placebo for 12 weeks then received Serostim 4 mg QD for 12 weeks

The entire treatment periods can be summarized as follows:

1st 12 weeks (Wk 0-12)	**2nd 12 weeks (Wk 12-24)**	**3rd 12 weeks (Wk 24-36)**
Serostim 4 mg QD	Serostim 2 mg QOD	Serostim 2 mg QOD
	Placebo	Placebo
Placebo	Placebo	Serostim 4 mg QD

This study was conducted in 2004-2005.

Efficacy

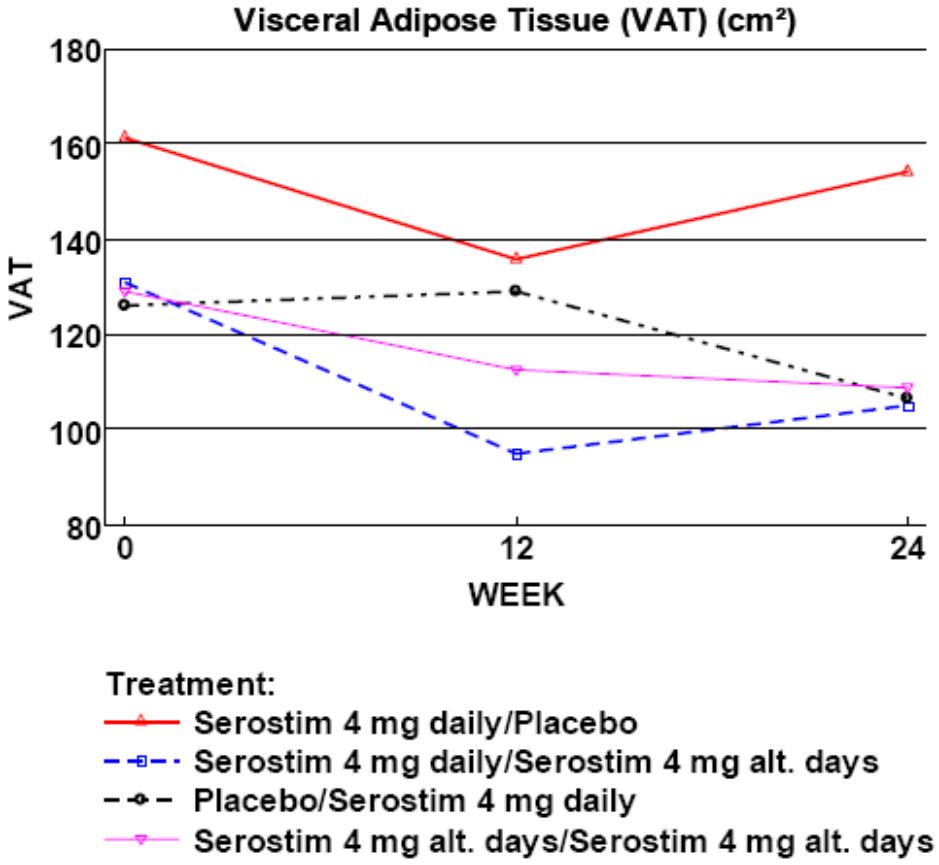
The primary efficacy variable in both trials was change from baseline at Week 12 in absolute area of VAT as measured by cross-sectional CT at the level of L4/L5. Secondary efficacy measures included change from baseline at Week 12 in DEXA-derived truncal fat and other assessments of subcutaneous fat, lean body mass, and lipid profile described under Section 6.1.3.6.1.2 of Dr. Perlstein's review.

From both studies, Serostim 4 mg QD was significantly better than placebo in reducing VAT during the 12-week induction period. From Study 22388, Serostim 4 mg QD and 4 mg QOD were similarly effective in reducing VAT during the 12-week induction period.

Maintenance of effect was evaluated differently in the 2 studies. In Study 24380, the maintenance dose of Serostim 2 mg QOD was not significantly different from placebo in maintaining the loss of VAT achieved with induction therapy. In Study 22388, Serostim 4 mg QOD was clearly better than placebo in maintaining the loss of VAT achieved with induction therapy. The Serostim 4 mg QOD regimen resulted in similar effects on VAT change during maintenance treatment regardless of prior induction treatment with either Serostim 4 mg QD or 4 mg QOD, although the 4 mg QD regimen appears to have afforded a greater reduction initially. The following figure from Dr. Pian's review summarizes the median VAT from Week 0 through 24 in the four different treatment dosing regimens/sequences of Study 22388.

Figure 11 median VAT at baseline, week 12 and week 24

22388



There was no statistically significant effect of drug therapy on VAT reduction compared to placebo in women. Differences in baseline VAT, estrogenic effects on rhGH responsiveness, or small sample size may have influenced this finding. Regardless, the efficacy of Serostim on VAT in this program was limited to men and further studies in women are warranted.

The applicant is proposing the use of Serostim for 24 weeks after a 12-week induction period. In both studies, re-randomization of Serostim therapy to placebo resulted in reaccumulation of any VAT loss during the induction phase which supports the conclusion that maintenance of efficacy requires continued, perhaps chronic, therapy.

Trunk fat was significantly reduced with both doses of Serostim compared to placebo. In Study 22388, there was evidence of a dose-response with the 4 mg QD dosing regimen resulting in greater trunk fat change than 4 mg QOD dosing.

Patient reported outcomes (PRO) evaluated the patient's perception of his/her appearance using questionnaires and scoring systems of responses. The methodology for evaluating and reporting PRO was reviewed by the Agency's Study Endpoints and Label Development (SEALD) team and detailed discussions of these secondary efficacy measures are summarized in Dr. Laurie Burke's review dated March 8, 2007. At Week 12, improvements in Belly Appearance Distress (BAD), Belly Size Evaluation

(BSE), and Belly Profile Assessment (BPA) were observed for both Serostim 4 mg QD and QOD, but was only significant with the former dosing regimen.

For efficacy based on the primary endpoint, VAT, it appears that the originally proposed dosing regimen of Serostim 4 mg QD followed by 2 mg QOD was not supported by the 36-week study; however, the 24-week dose-ranging study appeared to support either the 4 mg QD/4 mg QOD (induction/maintenance) or 4 mg QOD/4 mg QOD dosing regimen. The conclusion of efficacy is based on changes in biomarkers with a presumed clinical benefit. The reliance on an unvalidated surrogate for clinical efficacy should not be accompanied by safety findings that may counterbalance the expected clinical benefit. As stated in my opening paragraphs of this memo, any therapy targeting treatment of HARS should take into consideration its impact on compliance with HIV therapy and reducing risk of long-term CV complications. The company has conceded and I have been informed by the SEALD team that demonstration of improved drug compliance is extremely difficult and not feasible. I must therefore look for evidence that any beneficial effect of rhGH on VAT, trunk fat, or the patient's perception of body image is accompanied by improvement in other measures to support the conclusion that rhGH will either have a presumed benefit on long-term CV complications or, at a minimum, will NOT adversely impact it.

Safety

Many of the side effects observed in this clinical development program are known effects of rhGH that are dose-related and appear to impact tolerability and adherence to treatment. Known effects include edema, arthralgias, and glucose dysregulation. I concur with Dr. Perlstein that many of these side effects are reversible and can be managed with dose reduction or interruption. However, the effect of pharmacologic rhGH dosing on development of impaired glucose tolerance, insulin resistance or diabetes mellitus raises questions about the long-term risk of CV complications. Furthermore, the poor tolerability and high discontinuation rates would suggest that any efficacy with this product would be short-lived due to patient withdrawal from treatment. As noted above, discontinuation of rhGH results in reaccumulation of VAT and, from Dr. Perlstein's review, improvements in other secondary efficacy measures are also diminished with discontinuation of treatment.

Discontinuation rates were high in the two pivotal studies. In Study 22388, 28/239 (11.7%) of patients who received drug withdrew during the 12-week induction period, and the rate of withdrawal was highest in the Serostim 4 mg QD group (20.7%). At least half of the withdrawals in the Serostim groups were due to adverse events (AEs), whereas no placebo-treated patient withdrew as a result of an AE. The following table is from Dr. Lee Pian's review and summarizes the first 12 weeks of Study 22388.

	Placebo N=78	**Serostim 4 mg QOD N=79**	**Serostim 4 mg QD N=82**	**Total**
Withdrawals	3 (3.8%)	8 (10.1%)	17 (20.7%)	28 (11.7%)
Adverse Event	0	4 (5.1%)	9 (11.0%)	13 (5.4%)
Protocol Violation	2 (2.6%)	0	0	2 (0.8%)
Lost to F/U	1 (1.3%)	1 (1.3%)	3 (3.7%)	5 (2.1%)
Patient Decision	0	2 (2.5%)	4 (4.9%)	6 (2.5%)
Administrative	0	1 (1.3%)	0	1 (0.4%)
Other	0	0	1 (1.2%)	1 (0.4%)

The maintenance period showed a similar pattern of poor tolerability with those patients switching from placebo to Serostim 4 mg QD showing the highest rate of withdrawals due to AEs (see Table 14 from Dr. Pian's review). There were 4 withdrawals in patients treated with Serostim 4 mg QD; all were due to an AE. Four out of six withdrawals in the group remaining on Serostim 4 mg QOD were due to an AE.

Table 65 from Dr. Perlstein's review describes the 23 patients who discontinued at any time from any of the studies due to glucose intolerance. Treatment with Serostim 4 mg QD resulted in the discontinuation of 13 of these patients, whereas treatment with Serostim 4 mg QOD resulted in the discontinuation of 5 patients. Clearly, treatment with Serostim 4 mg QD or QOD was associated with the largest number of patients requiring discontinuation as a result of glucose abnormalities, and a dose-response was apparent. Five fasting plasma glucose (FPG) values available at the time of study withdrawal or dose reduction were >200 mg/dL, including two patients described in Dr. Perlstein's review who registered FPG values of 386 and 404 mg/dL. One must recall that study entry criteria prohibited the enrollment of patients with FPG ≥110 mg/dL, a 2 hr post-prandial glucose ≥140 mg/dL or established diabetes mellitus. Both of these patients had normal FPG levels at baseline.

There were criteria for dose adjustments and interruption which included glucose toxicities (see Section 6.1.3.4 of Dr. Perlstein's review). So while the overall discontinuation rate due to glucose intolerance was only 23/565 (4.1%) patients, there were additional patients who required dose modification as a result of glucose intolerance. From Table 56 of Dr. Perlstein's review, 16.6% of patients in the Serostim 4 mg QD group, and 11.3% of patients in the Serostim 4 mg QOD group, required dose adjustments for glucose abnormalities. To what extent these dose modifications (reductions/interruptions) may impact efficacy is uncertain.

Other parameters of glucose tolerance included a mean increase in hemoglobin A1c of 0.3% after just 12 weeks of therapy. This degree of increase may not be considered clinically meaningful, but it only reflects assessment after 4 months of treatment. Mean fasting and 2 hr post-prandial insulin levels were significantly increased without accompanying hyperglycemia in the majority of patients. This is not unexpected as hyperinsulinemia often adequately compensates for early insulin resistance to maintain normoglycemia. Over time, the pancreatic compensation for insulin resistance is inadequate and overt diabetes mellitus develops.

The applicant's assertion that glucose intolerance is monitorable and discontinuation of therapy will result in normalization of the findings is not entirely supported by the data. In his review of the 23 discontinuation cases, Dr. Perlstein noted that follow-up glucose values were not available in many of these patients. One might argue that impaired glucose tolerance without overt diabetes mellitus is an asymptomatic monitorable condition, but recent studies have suggested that patients with impaired glucose tolerance and impaired fasting glucose are at risk for developing overt diabetes mellitus and vascular disease.

Conclusion and Recommendations

In conclusion, the applicant has demonstrated that treatment with Serostim can reduce VAT and improve other secondary measures in patients with HARS. However, these are surrogate measures for a presumed clinical benefit. One argument for treating HARS is the concern that the disfiguring effects of abnormal fat redistribution may contribute to non-compliance with life saving anti-retroviral therapies. The PRO secondary efficacy measures were designed to demonstrate improved self-perception associated with Serostim treatment; however, no drug compliance data were obtained during Studies 22388 and 24380 and will unlikely be available from other studies. Another argument for treating HARS is to reduce the risk of CV disease associated with increased VAT, insulin resistance, glucose intolerance, and dyslipidemia. The use of rhGH was clearly associated with glucose intolerance, hyperinsulinemia, and in some cases, the development of overt diabetes mellitus which may offset any benefit of reducing VAT.

I recognize that much of the company's development program had significant input from the division under the direction of Dr. David Orloff and I am not concluding that decisions made by him were inappropriate. The data presented to me in the drug application, however, have not convinced me that the benefits of reducing VAT, trunk fat, or other surrogate measures are sufficient to allay my concerns about glucose intolerance, insulin resistance and the risk of diabetes mellitus as a result of treatment with pharmacologic amounts of rhGH in a patient population that already has an increased baseline risk for CV disease. The proposal to use Serostim (b) (4) is an inadequate solution as these studies have already demonstrated that, after discontinuation of therapy, all changes in VAT or SAT return to baseline. While the underlying cause of HARS has not been clearly established, the different etiologies proposed are not short-term insults. Consequently, I would anticipate that Serostim would need to be administered chronically, and, as a result, the risk for glucose intolerance may be further increased.

Given that the program was completed with some agreements with the agency and that I believe there is important risk-benefit information to be conveyed to physicians and patients from the results of these trials, I am recommending that the results of these trials be conveyed in labeling in the Clinical Studies section as well as the Warnings, Precautions, and Adverse Reactions sections to adequately inform them about the expected efficacy and potential risks of rhGH use for HARS.

I do not believe it is feasible or realistic to require a CV outcomes trial of rhGH products in patients with HARS given the required size and duration of such a study. I am aware of other therapies under development for HARS that may not have similar adverse effects on glucose tolerance. Hence, I am hopeful that patients with HARS will eventually have available safe and effective therapies for the treatment of this condition.

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/s/

Mary Parks
8/14/2007 09:07:18 AM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020604Orig1s040

MEDICAL REVIEW(S)

<u>ADDENDUM</u> TO CLINICAL REVIEW

Application Type	20-604
Submission Number	Supplement 040
Submission Code	SE-1
Letter Date	June 8, 2006
Stamp Date	June 12, 2006
PDUFA Goal Date	**14April07**
Extension Goal Date	**14July07**
Reviewer Name	Robert Perlstein MD, FACP, FACE
Original Review Completion Date	**26March07**
Addendum Completion Date	**1July07**
Established Name	Serostim
(Proposed) Trade Name	Serostim
Therapeutic Class	rhGH (recombinant human growth hormone)
Applicant	EDB Serono, Inc.
Priority Designation	S
Formulation	Lyophilized rhGH
Proposed Dosing Regimen	Induction: 4 mg SC QD Maintenance: 2 mg SC QOD
Indication	HARS (Human Immunodeficiency Syndrome [HIV]-Associated Adipose Redistribution Syndrome)
Intended Population	Patients with AIDS (Acquired Immunodeficiency Syndrome) who have HARS

1 AMENDMENT TO ORIGINAL EXECUTIVE SUMMARY

1.1 Amended Recommendation on Regulatory Action

Subsequent to the completion of my original review on 26Mar07, this Medical Officer had extensive discussions with the Division's Director and Statistical Reviewers (see Section 1.1.1 for details). As a result, **this Medical Officer now recommends APPROVAL of the HARS indication for Serostim in men only (rather than men and women) - including approval of Serostim 4 mg QOD as a 12 week induction dose (rather than Serostim 4 mg QD as a 12 week induction dose), and approval of Serostim 4 mg QOD as a 12 week maintenance dose (rather than Serostim 2 mg QOD as a 24 week maintenance dose). In addition, this Medical Officer also strongly recommends a Phase 4 study including much larger numbers of women, with a similar placebo-controlled design but of sufficient duration to assess meaningful changes in better surrogates predicting cardiovascular outcomes, i.e. carotid intima media thickness (IMT).**

I must hasten to add at this juncture that the Division Director has serious concerns about 1) the **absence of long-term cardiovascular outcome data**, i.e. VAT remains an unvalidated surrogate for long-term cardiovascular outcomes; 2) **the absence of data regarding better surrogates predicting long-term cardiovascular outcomes, i.e. carotid IMT**; and 3) the well established fact that the administration of **pharmacologic amounts of rhGH may worsen glucose tolerance and increase cardiovascular risk**. **As a result, the Division Director has decided NOT to grant APPROVAL of the HARS indication for any dose of Serostim**. Rather, the **current intention of the Division Director** is to **allow the sponsor to include a description of the efficacy and safety findings of the 2 pivotal studies** in the CLINICAL STUDIES and ADVERSE REACTIONS sections of the Serostim PI, respectively; (b) (4)

1.1.1 Amended Efficacy Recommendations (and Conclusions)

- **This Medical Officer now recommends approval of Serostim 4 mg QOD as a 12 week induction dose (rather than Serostim 4 mg QD as a 12 week induction dose).**
    - I originally **concluded** (see Section 1.3.2.3.A in my original review) the following: Serostim 4 mg QD and Serostim 4 mg QOD were equally efficacious in reducing VAT (and potentially reducing long-term cardiovascular risk), and the safety profile for Serostim 4 mg QD was clearly more adverse than the safety profile for Serostim 4 mg QOD suggesting, on its face, that the smaller dose should be approved for the induction phase. **However**, in that 1) there was a global dose response with regard to the differences in change from baseline to Week 12 in

multiple consequential non-PRO and PRO secondary efficacy endpoints (i.e., **trunk fat, abdominal SAT, BAD/BSE**, total fat mass and LBM); and 2) **the more adverse safety profile observed with Serostim 4 mg QD is tolerable and acceptable if it is only administered during the 12 week induction period, and certain caveats regarding the use of Serostim 4 mg QD will be clearly labeled, <u>I therefore concluded that Serostim 4 mg QD should be approved as the 12 week induction dose</u>.**

- After extensive discussions with the **Division's Director who expressed serious concerns** about 1) the **absence of long-term cardiovascular outcome data**, i.e. VAT remains an unvalidated surrogate for long-term cardiovascular outcomes; 2) **the absence of data regarding better surrogates predicting long-term cardiovascular outcomes, i.e. carotid IMT**; and 3) the well established fact that the administration of **pharmacologic amounts of rhGH may worsen glucose tolerance and increase cardiovascular risk**, **<u>I have therefore changed my mind and now conclude that Serostim 4 mg QOD (rather than Serostim 4 mg QD) should be approved as a 12 week induction dose</u>**.

- **<u>This Medical Officer now recommends approval of Serostim 4 mg QOD as a 12 week induction dose in men, but not women (rather than men *and* women)</u>.**

  - I originally **<u>concluded</u>** (see Section 1.3.2.3.B in my original review) the following: Women treated with either dose of Serostim (vs. placebo) did not demonstrate a difference in the change from baseline to Week 12 in VAT (perhaps related to estrogen-mediated resistance to rhGH and/or to the fact that the clearly lower baseline VAT levels in women compared to men predicts a lesser response and/or to the fact that the studies may have been underpowered to detect a significant treatment effect in women) suggesting, on its face, that the indication should be limited to men. **However**, in that 1) the differences in change from baseline to Week 12 in multiple consequential non-PRO and PRO secondary efficacy endpoints including trunk fat, abdominal SAT, and BAD/BSE were very similar in men and women; and 2) **the more adverse safety profile observed with Serostim 4 mg QD is tolerable and acceptable if it is only administered during the 12 week induction period, and certain caveats regarding the use of Serostim 4 mg QD will be clearly labeled, <u>I therefore concluded that Serostim 4 mg QD should be approved as a 12 week induction dose in women as well as men</u>.**
  - After extensive discussions with the **Division's Director who expressed serious concerns** about 1) the **absence of long-term cardiovascular outcome data**, i.e. VAT remains an unvalidated surrogate for long-term cardiovascular outcomes; 2) **the absence of data regarding better surrogates predicting long-term cardiovascular outcomes, i.e. carotid IMT**; and 3) the well established fact that the administration of **pharmacologic amounts of rhGH may worsen glucose tolerance and**

increase cardiovascular risk, **<u>I have therefore changed my mind and now conclude that the indication should be limited only to men</u>.**

- **Nonetheless, I <u>still recommend</u> the following:**
  - **<u>The CLINICAL STUDIES section of the PI should clearly indicate that women did not demonstrate a significant reduction in VAT after treatment with Serostim 4 mg QD or Serostim 4 mg QOD (vs. placebo), but did respond as well as men with regard to reduction in trunk fat, abdominal SAT, total body fat, and non-HDL cholesterol, increase in LBM, and improvement in BAD and BSE scores</u>. A small table containing descriptive statistics depicting the VAT response by gender should be included in the CLINICAL STUDIES section as well.**
  - [redacted] (b) (4)
  - **<u>The sponsor should be firmly requested to make a formal Phase IV commitment to conduct an adequately powered study in women as soon as feasible</u>.**

- **<u>This Medical Officer now recommends approval of Serostim 4 mg QOD as a 12 week maintenance dose (rather than Serostim 2 mg QOD as a 24 week maintenance dose)</u>.**

  - I originally **<u>concluded</u>** (see Section 1.3.2.3.C in my original review) the following: During the 24 week maintenance phase of Study 24380, VAT reaccumulated to the same extent after treatment with Serostim 2 mg QOD or placebo (by ANOVA). On the other hand, 1) the Division had previously indicated to the sponsor that if >50% of the subjects who lost VAT during the induction period regained, during the maintenance period, <50% of the VAT originally lost, that would be considered a "maintenance success". In fact, ~60% of subjects treated with Serostim 2 mg QOD met that criteria (vs. ~46% in the placebo group); and 2) there was significantly less reaccumulation of trunk fat and deterioration of LBM after treatment with Serostim 2 mg QOD (vs. placebo). **<u>I therefore concluded that Serostim 2 mg QOD should be approved as a 24 week maintenance dose</u>**
  - Subsequently, the Division's Statistical Reviewers provided this Medical Officer with additional revealing analyses of the maintenance phase results from both Studies 24380 and 22388 (see Section 1.3 ahead). These analyses revealed that Serostim 4 mg QOD for 12 weeks (Study 22388) was a much better maintenance dose than Serostim 2 mg QOD for 24 weeks (Study 24380), i.e. there was clearly less reaccumulation of VAT (vs. placebo). **<u>I have therefore changed my mind and now conclude</u>**

that Serostim 4 mg QOD for 12 weeks (rather than Serostim 2 mg QOD for 24 weeks) should be approved as a maintenance dose.

1.1.2 Safety Recommendations

- Since this Medical Officer is no longlonger recommending Serostim 4 mg QD as a 12 week induction dose (in men), the caveats regarding its usage listed in my original review (see Section 1.1.2 in my original review) are no longer applicable. **Serostim 4 mg QOD as a 12 week induction dose and a 12 week maintenance dose is tolerable and acceptable**. Nonetheless, patients should be **carefully monitored** for the well known **adverse effects** of pharmacologic (and physiologic) doses of **rhGH** (**in particular glucose intolerance** given that most patients with HARS are insulin resistant and some glucose intolerant in the untreated state). In addition, as indicated above, the **PRECAUTIONS** section of the PI should also contain language (b) (4)

1.2 Recommendation on Postmarketing Actions

See Section 1.2.2

1.2.1 Risk Management Activity

None.

1.2.2 Required Phase 4 Commitments

This Medical Officer strongly recommends a Phase 4 study including much larger numbers of women, with a similar placebo-controlled design but of sufficient duration to assess meaningful changes in better surrogates predicting cardiovascular outcomes, i.e. carotid intima media thickness (IMT).

1.2.3 Other Phase 4 Requests

None.

1.3 New Analyses of Maintenance Phase Results From Both Studies

1.3.1 Maintenance Phase Efficacy Results for Study 24380 (Week 12 to Week 36)

In Study 24380, at Week 12, patients originally treated with Serostim 4 mg QD during Weeks 0-12, were rerandomized to Serostim 2 mg QOD vs. placebo during Weeks 12-36.

There are several lines of evidence which indicate that <u>Serostim 2 mg QOD for 24 weeks is an ineffective maintenance dose</u>. The following analyses were for the most part performed by the Division's Statistical Reviewer.

1) The proportion of patients who regained, during Weeks 12-36, >50% of the VAT that was lost during Weeks 0-12 was calculated in the subset of patients who lost VAT during the induction period. The proportions of 61% (37/61) (Serostim 2 mg QOD) vs. 48% (31/65) (placebo) were not significantly different (p=0.2). In addition, the placebo group came within 2 percentage points of being a "successful maintenance therapy" as per the protocol-designated criterion - which diminishes the importance of the findings in the Serostim 2 mg QOD group.

2) Table 1 displays the change from Week 12 to Week 36 in VAT using descriptive statistics. The **mean increases** in VAT (**23.3 and 23.7 cm^2**) were **<u>very similar</u>** for the 2 rerandomized groups.

Table 1: Study 24380 -VAT Descriptive Statistics During the Maintenance Period (Weeks 12-36)

VAT in cm^2	**Serostim 4 mg QD/2 mg QOD n=75**		**Serostim 4 mg QD/Placebo n=73**	
	Mean	(SD)	Mean	(SD)
VAT at Baseline	135.6	(69.9)	134.8	(63.2)
VAT at Week 12 LOCF	96.7	(44.8)	103.2	(49.8)
VAT at Week 36 LOCF	119.9	(58.3)	126.9	(64.7)
VAT Chg LOCF 36 - LOCF 12	**23.3**	**(34.9)**	**23.7**	**(45.1)**

3) As depicted in Table 2, the difference in the change from Week 12 to Week 36 in VAT (-1.2 cm^2) was not significant (p=0.898) (by ANCOVA).

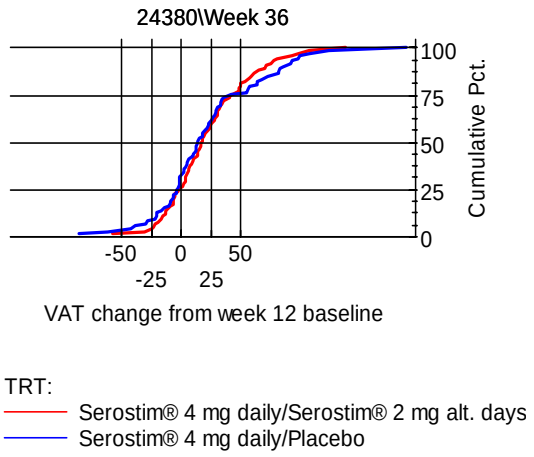
Table 2 (Table 46 in Original Review): Study 24380 - Change & Percent Change from Week 12 to Week 36 in VAT (cm^2) by Treatment Group (Modified ITT Population w/ LOCF)

	Serostim 4 mg QD/ Placebo n=73	**Serostim 4 mg QD/ Serostim 2 mg QOD n=75**
Baseline (SD)	134.8 (63.2)	135.6 (69.9)
Baseline (SE)[a]	113.3 (11.1)	116.7 (10.6)
Week 12 (SD)	103.2 (49.8)	96.7 (44.8)
Week 12 (SE)[a]	93.3 (8.7)	87.6 (8.3)
Week 36 (SD)	126.9 (64.7)	119.9 (58.3)
Week 36 (SE)[a]	110.1 (9.9)	103.2 (9.5)
Change from Week 12 to Week 36 (SD)	**23.7 (45.1)**	**23.3 (34.9)**
Change from Week 12 to Week 36 (SE)[b]	**16.8 (7.0)**	**15.5 (6.7)**
Raw Mean Difference from Placebo for Change (CI)	**---**	**-0.4 (-15.6, 14.8)**
Difference from Placebo for Change (CI)[b]	**---**	**-1.2 (-20.3, 17.8) p=0.898**
% Change from Week 12 to Week 36 (SD)	**40.2 (127.9)**	**44.0 (152.5)**
% Change from Week 12 to Week 36 (SE)[b]	**28.0 (21.6)**	**29.7 (20.6)**
Raw Mean Difference from Placebo for % Change (CI)	**---**	**3.8 (-43.3, 51.0)**
Difference from Placebo for % Change (CI)[b]	**---**	**1.8 (-57.1, 60.7) p=0.953**

(a) Ordinary LSM from ANOVA model including effects for gender, treatment and their interaction
(b) Ordinary LSM from ANCOVA model including effects for gender, treatment and their interaction with baseline VAT as covariate

4) As seen in Figure 1, the CDF curves for change from Week 12 to Week 36 in VAT were **almost identical** in the groups rerandomized to Serostim 2 mg QOD vs. placebo at Week 12.

Figure 1: Study 24380 - Cumulative Distribution of Change from Week 12 to Week 36 in VAT



5) Figure 2 displays **median changes** from baseline to Week 12, and median changes from Week 12 to Week 36, in VAT, and Figure 3 displays **median VAT levels** at baseline, Week 12 and Week 36 **for completers** in Study 24380. In the 2 groups rerandomized to Serostim 2 mg QOD vs. placebo at Week 12 (red [placebo] and blue dashed [Serostim 2 mg QOD] lines in Figure 2), median VAT decreased during both Serostim 4 mg QD induction periods (Weeks 0-12), but increased after treatment with placebo and Serostim 2 mg QOD for 24 weeks (Weeks 12-36). The Serostim 4 mg QD/Serostim 2 mg QOD group and the Serostim 4 mg QD/placebo group manifested **very similar median increases in VAT** between Week 12 and Week 36, i.e. **17 and 14 cm^2**, respectively. These findings are also reflected in Figure 3 which displays the median values of VAT at various timepoints in Study 24380.

Figure 2: Study 24380 - Median Change in VAT at Various Timepoints in Completers

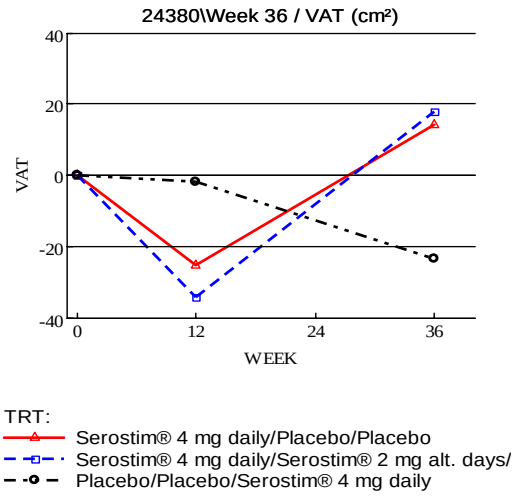
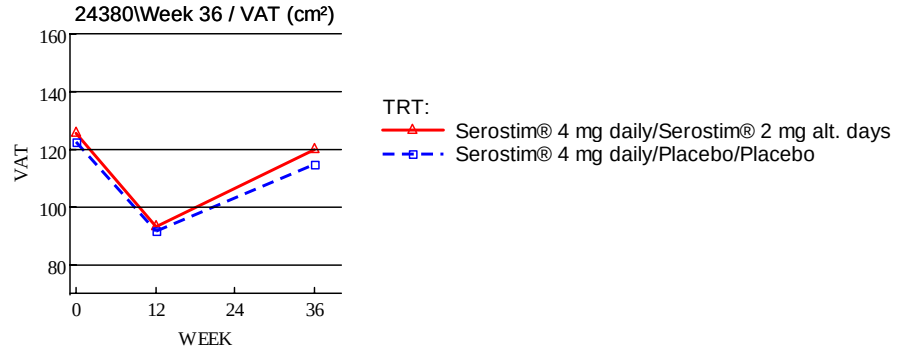


Figure 3: Study 24380 - Median Levels of VAT at Various Timepoints in Completers



6) Table 3 displays the change from Week 12 to Week 36 in trunk fat using descriptive statistics. The **mean increases** in trunk fat (**1.5 and 2.1 kg**) were **very similar** for the 2 rerandomized groups.

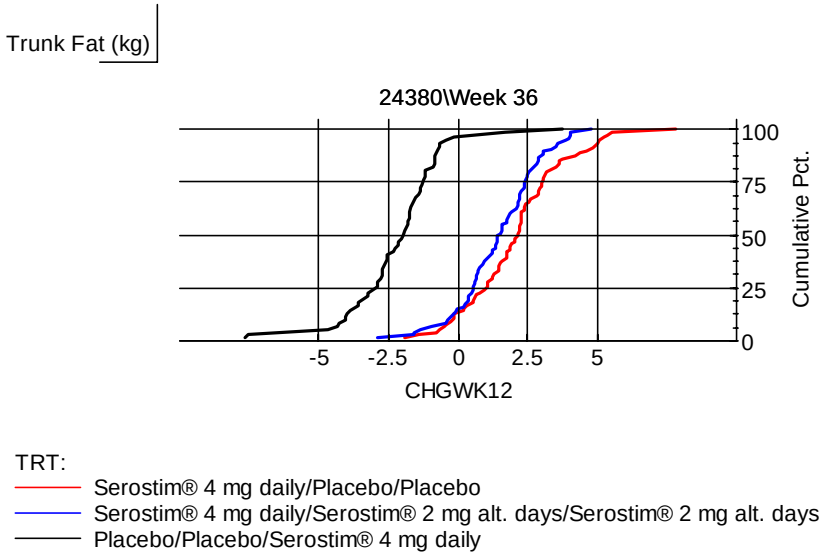
Table 3: Study 24380 – Trunk Fat Descriptive Statistics During the Maintenance Period (Weeks 12-36)

	Serostim 4 mg QD/2 mg QOD			Serostim 4 mg QD/Placebo		
	n	Mean	(SD)	n	Mean	(SD)
Trunk Fat at Baseline	75	10.7	(4.2)	79	11.6	(5.2)
Trunk Fat at Week 12 LOCF	75	8.4	(4.1)	79	9.5	(5.2)
Trunk Fat at Week 36 LOCF	75	9.8	(4.3)	79	11.6	(5.5)
Trunk Fat Change LOCF 36 - LOCF 12	**75**	**1.5**	**(1.5)**	**79**	**2.1**	**(1.8)**

7) The difference in the change from Week 12 to Week 36 in trunk fat (-1.2 kg) was marginally significant (p=0.045) (by ANOVA; see Table 47 on page 97 of my original review).

8) As seen in Figure 4, the CDF curves for change from Week 12 to Week 36 in trunk fat were **very similar** in the groups rerandomized to Serostim 2 mg QOD vs. placebo at Week 12.

Figure 4: Study 24380 - Cumulative Distribution of Change from Week 12 to Week 36 in Trunk Fat



9) The differences in the change from Week 12 to Week 36 in LBM was marginally significant (p=0.039; see Table 48 on page 98 of my original review), in non-HDL cholesterol non-significant (see Table 49 on page 99 of my original review) and in BAD non-significant (see Table 50 on page 100 of my original review).

1.3.1.1 Revised Conclusions Regarding Maintenance Phase Efficacy Results for Study 24380 (Week 12 to Week 36)

- The multiple analyses presented above in items 1 through 5 clearly indicate that the administration of Serostim 2 mg QOD for 24 weeks was not superior to placebo in preventing the reaccumulation of VAT.
- The analyses presented above in items 6 and 7 indicate that the administration of Serostim 2 mg QOD for 24 weeks was minimally superior to placebo in preventing the reaccumulation of trunk fat.
- The analyses referred to in item 9 indicate that the administration of Serostim 2 mg QOD for 24 weeks was minimally superior to placebo in preventing loss of LBM, and not superior to placebo in preventing reaccumulation of non-HDL cholesterol and decline in the BAD point score.
- **Therefore, it is concluded that Serostim 2 mg QOD for 24 weeks is an ineffective maintenance dose**.

1.3.2 Maintenance Phase Efficacy Results for Study 22388 (Week 12 to Week 24)

In Study 22388, at Week 12, patients originally treated with Serostim 4 mg QD during Weeks 0-12, were rerandomized to Serostim 4 mg QOD vs. placebo during Weeks 12-24. Patients originally treated with Serostim 4 mg QOD during Weeks 0-12 were continued on Serostim 4 mg QOD during Weeks 12-24, and patients originally treated with placebo during Weeks 0-12 received Serostim 4 mg QD during Weeks 12-24.

There are several lines of evidence which indicate that Serostim 4 mg QOD for 12 weeks is an effective maintenance dose. All of the following analyses (based on additional datasets submitted by the sponsor on 9April07) were exploratory in nature/descriptive in that the maintenance phase was not powered to show treatment differences (and for the most part were performed by the Division's Statistical Reviewer).

1.3.2.1 VAT

As seen in Table 4 (row 1), after induction with Serostim 4 mg QD, the group rerandomized to Serostim 4 mg QOD reaccumulated less VAT than the group rerandomized to placebo (**4.16 vs. 15.5 cm^2, respectively**). In the group initially "induced" with Serostim 4 mg QOD and then "maintained" with Serostim 4 mg QOD, the extent of VAT reaccumulation was **very similar** to that seen in the group "induced" with Serostim 4 mg QD and then rerandomized to Serostim 4 mg QOD (**4.92 vs. 4.16 cm^2, respectively**) .

As seen in Table 5 (row 1), the LSM difference in the change from Week 12 to Week 24 in VAT (Serostim 4 mg QD/Serostim 4 mg QOD vs./minus Serostim 4 mg QD/placebo) **was significant** (**-19.86 cm^2; p=0.03**). This exploratory analysis (as well as all of the between-group analyses of the changes in secondary endpoints in subsequent sections performed by the Division's Statistical Reviewer) was accomplished utilizing an ANCOVA model with treatment as a fixed effect and Week 12 baseline as covariate.

The sponsor analyzed these same data (as well as the changes in secondary endpoints in subsequent sections) with an ANOVA model including effects for treatment, gender and their interaction (to minimize the likelihood of Type 1 error compared with the ANCOVA model). The treatment difference was not significant (data not shown).

The ANCOVA results by gender for VAT revealed a significant treatment effect in men which was similar to the response observed in the entire population (**-25.26 cm^2**), and no significant treatment difference in women (**+2.34 cm^2**).

Table 4: Study 22388 - Descriptive Statistics for VAT, Trunk Fat, Total Body Fat, BAD, Abdominal SAT, LBM and Non-HDL Cholesterol at Week 12 and Change from Week 12 to Week 24

Variable Name	PB/SS QD			SS QOD/SS QOD			**SS QD/PB***			**SS QD/SS QOD***		
Mean (SD)	n	Wk 12	Chg	n	Wk 12	Chg	**n**	**Wk 12**	**Chg**	**n**	**Wk 12**	**Chg**
VAT (cm²)	54	136.16 (55.04)	-20.98 (35.46)	54	115.72 (50.28)	**4.92 (33.42)**	**27**	**139.4 (46.28)**	**15.5 (34.92)**	**29**	**112.76 (72.82)**	**4.16 (40.76)**
Trunk Fat (kg)	56	10.68 (4.58)	-1.74 (1.18)	51	8.84 (3.72)	**0.04** (1.26)	**27**	**8.28 (3.7)**	**1.16 (1.46)**	**26**	**6.94 (3.68)**	**0.34 (1.2)**
Total Body Fat (kg)	56	16.86 (7.26)	-2.26 (1.82)	51	14.9 (7.02)	**0.02** (2)	**27**	**13.88 (7.06)**	**1.32 (2.18)**	**26**	**11.58 (6.58)**	**0.34 (1.8)**
BAD (points)	68	27.38 (22.36)	14.88 (23.38)	65	32.3 (23.26)	**9.04** (22.38)	**30**	**45.42 (30.18)**	**-15.84 (27.64)**	**33**	**35.22 (23.48)**	**6.82 (25.6)**
Abdominal SAT (cm²)	54	177.64 (105.92)	-0.7 (32.24)	54	171.24 (110.1)	3.3 (25.66)	**27**	**131.72 (50.16)**	**14.46 (29.06)**	**29**	**125.04 (82.32)**	**6.42 (24.24)**
LBM (kg)	56	62.88 (12.66)	3.18 (2.92)	51	65.44 (8.18)	-0.12 (1.98)	**27**	**66.7 (10.48)**	**-2.6 (2.6)**	**26**	**64.22 (9.66)**	**-1.74 (2.02)**
Non-HDL Cholesterol (mg/dL)	66	178.28 (39.38)	-13.08 (31.76)	61	169.62 (44.32)	2.5 (32.62)	**30**	**164.94 (29.04)**	**6.86 (24.4)**	**33**	**151.54 (50.62)**	**2.24 (41)**

*rerandomized groups
SS QD=Serostim 4 mg QD
SS QOD=Serostim 4 mg QOD

Table 5: Study 22388 - Differences in Change from Week 12 to Week 24 in VAT, Trunk Fat, Total Body Fat, BAD, Abdominal SAT, LBM and Non-HDL Cholesterol (Serostim 4 mg QD/Serostim 4 mg QOD vs./minus Serostim 4 mg QD/Placebo) in Modified ITT Population w/LOCF

Variable name	LSM*	SE	Lower CI	Upper CI	p
VAT (cm²)	**-19.86**	(9.00)	[-37.92	-1.80]	**0.0317**
Trunk Fat (kg)	**-0.94**	(0.36)	[-1.67	-0.20]	**0.0134**
Total Body Fat (kg)	**-1.15**	(0.55)	[-2.25	-0.05]	**0.0411**
BAD (points)	**17.06**	(5.73)	[5.59	28.53]	**0.0042**
Abdominal SAT (cm²)	-8.81	(6.88)	[-22.61	4.99]	0.2060
Lean Body Mass (kg)	0.76	(0.64)	[-0.54	2.05]	0.2453
Non-HDL Cholesterol (mg/dL	-7.48	(8.49)	[-24.47	9.51]	0.3819

*ANCOVA model with treatment as fixed effect and Week 12 baseline as covariate

As seen in Figure 5, the CDF curves for change from Week 12 to Week 24 in VAT demonstrate a **clear separation** between the group rerandomized to Serostim 4 mg QOD at Week 12 after induction with Serostim 4 mg QD (blue) (as well as the group that continued treatment with Serostim 4 mg QOD after induction with Serostim 4 mg QOD [black]) vs. the group rerandomized to placebo at Week 12 after induction with Serostim 4 mg QD (red).

Figure 5: Study 22388 - Cumulative Distribution of Change from Week 12 to Week 24 in VAT

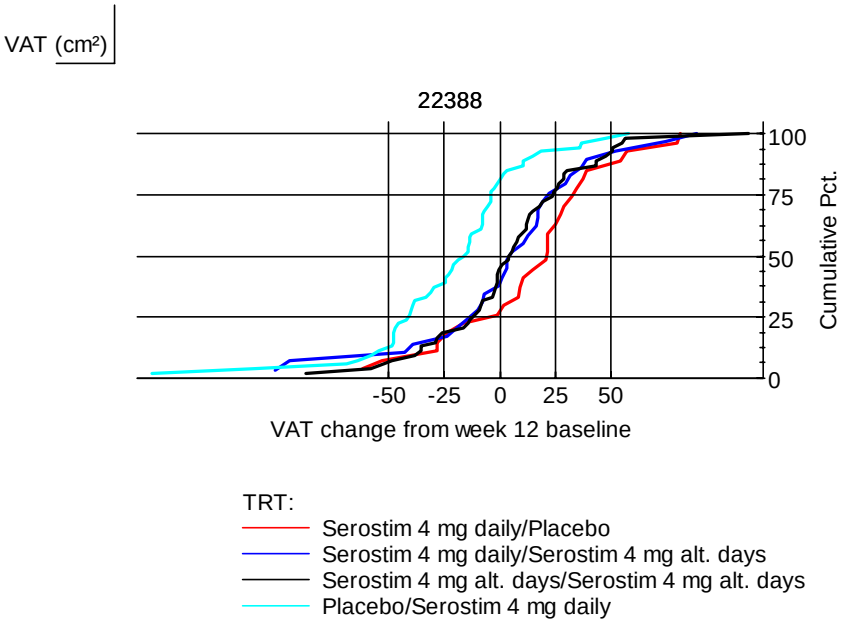


Figure 6 displays **median changes** from baseline to Week 12, and median changes from Week 12 to Week 24 in VAT for completers in Study 22388. In the 2 groups rerandomized to Serostim 4 mg QOD vs. placebo at Week 12 (red [placebo] and blue dashed [Serostim 4 mg QOD] lines in Figure 6), median VAT decreased during both Serostim 4 mg QD induction periods (Weeks 0-12), but increased after treatment with placebo and Serostim 4 mg QOD for 12 weeks (Weeks 12-24). **The amount of VAT reaccumulation was clearly less in the Serostim 4 mg QD/Serostim 4 mg QOD group (blue dashed line in Figure 6) compared with the Serostim 4 mg QD/placebo group (red line in Figure 6) during the maintenance period**. The median change in VAT from Week 12 to Week 24 was **22 cm^2** in the Serostim 4 mg QD/placebo group compared to **5 cm^2** in the Serostim 4 mg QD/Serostim 4 mg QOD group. In the Serostim 4 mg QOD/Serostim 4 mg QOD group (pink in Figure 6), the median VAT decrease during Weeks 0-12 and increase during Weeks 12-24 were very similar to the changes observed after treatment with Serostim 4 mg QD/Serostim 4 mg QOD. In the placebo/Serostim 4 mg QD group (black dotted line in Figure 6), median VAT did not change during the placebo treatment period (Weeks 0-12), but did decrease as expected after 12 weeks of treatment with Serostim 4 mg QD (Weeks 12-24). These findings are also reflected in Figure 7 which displays the **mean values** of VAT at various timepoints in Study 22388.

Figure 6: Study 22388 - Median Change in VAT at Various Timepoints

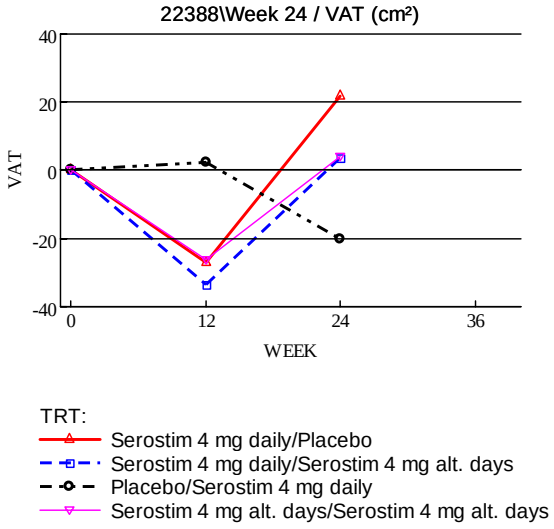


Figure 7: Study 22388 – Mean VAT Levels at Various Timepoints

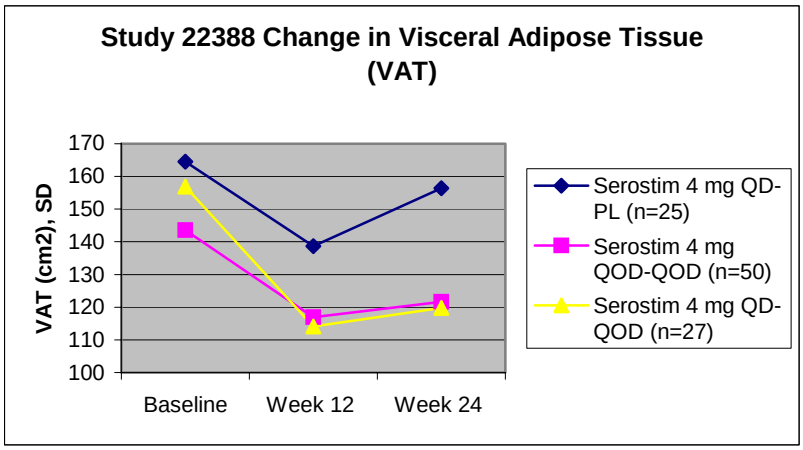
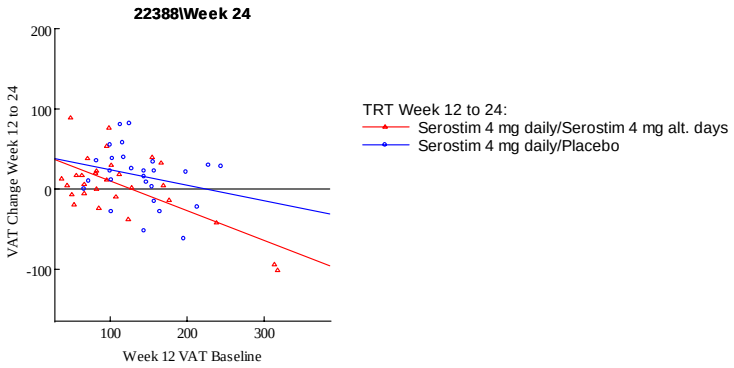


Figure 8 displays the linear regression lines for the Serostim 4 mg QD/Serostim 4 mg QOD (red line) and the Serostim 4 mg QD/placebo (blue line) treatment groups during Weeks 12-24 in Study 22388 (change in VAT vs. Week 12 VAT). **As Week 12 VAT decreased, the reduction in VAT from Week 12 to Week 24 decreased in both groups**. **The difference in VAT reduction** from Week 12 to Week 24 between the Serostim 4 mg QD/Serostim 4 mg QOD group and the Serostim 4 mg QD/placebo group **increased as the baseline VAT increased**. A similar relationship was observed between baseline VAT and reduction in VAT after treatment with Serostim 4 mg QD vs. placebo during the induction phase in Study 24380 (see Figure 7 on page 54 of my original review).

Figure 8: Study 22388 - Change in VAT from Week 12 to Week 24 by Baseline VAT



1.3.2.2 Trunk Fat

As seen in Table 4 (row 2), after induction with Serostim 4 mg QD, the group rerandomized to Serostim 4 mg QOD reaccumulated less trunk fat than the group rerandomized to placebo (**0.34 vs. 1.16 kg, respectively**). In the group initially "induced" with Serostim 4 mg QOD and then "maintained" with Serostim 4 mg QOD, the extent of VAT reaccumulation was **similar** to that seen in the group "induced" with Serostim 4 mg QD and then rerandomized to Serostim 4 mg QOD (**0.04 vs. 0.34 kg, respectively**).

As seen in Table 5 (row 2), the LSM difference in the change from Week 12 to Week 24 in trunk fat (Serostim 4 mg QD/Serostim 4 mg QOD vs./minus Serostim 4 mg QD/placebo) **was significant** (**-0.94 kg; p=0.01)** (ANCOVA; Division's Statistical Reviewer). The treatment difference was not significant in the sponsor's ANOVA (data not shown).

As seen in Figure 9, the CDF curves for change from Week 12 to Week 24 in trunk fat demonstrate a **clear separation** between the group rerandomized to Serostim 4 mg QOD at Week 12 after induction with Serostim 4 mg QD (dark blue) (as well as the group that continued treatment with Serostim 4 mg QOD after induction with Serostim 4 mg QOD [black]) vs. the group rerandomized to placebo at Week 12 after induction with Serostim 4 mg QD (red).

Figure 9: Study 22388 - Cumulative Distribution of Change from Week 12 to Week 24 in Trunk Fat

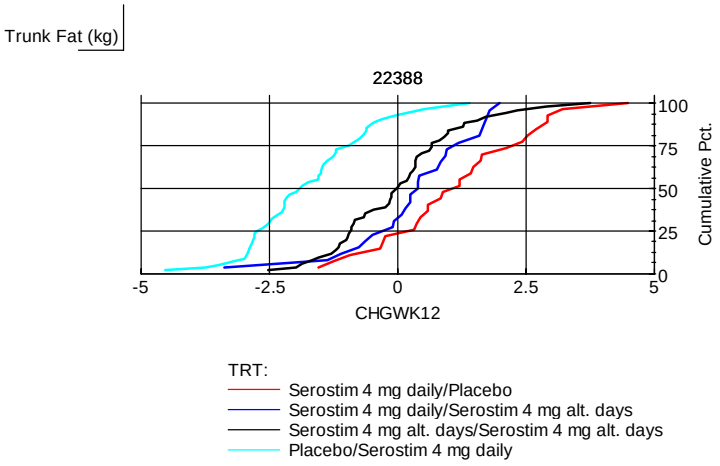
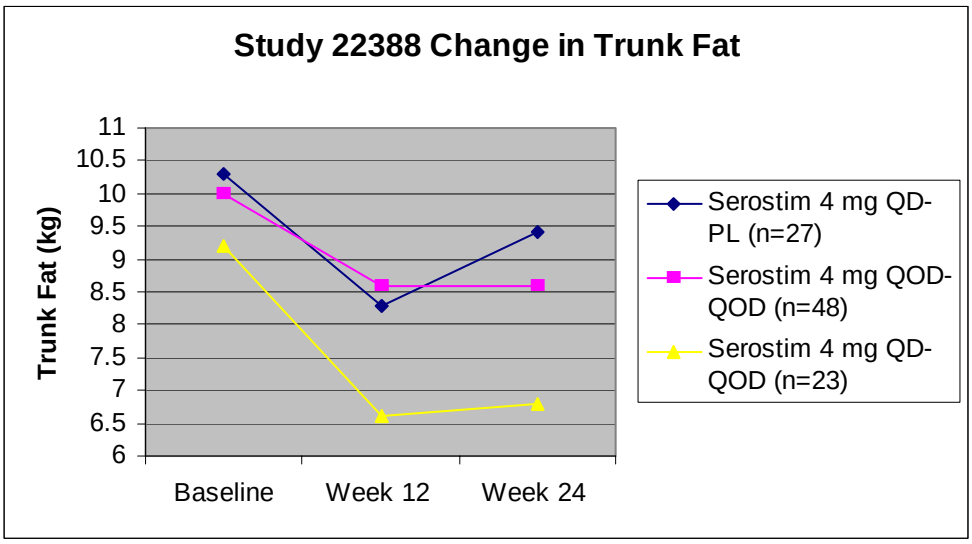


Figure 10 displays the **mean values** of trunk fat at various timepoints for completers in Study 22388. In the 2 groups rerandomized to Serostim 4 mg QOD vs. placebo at Week 12 (blue [placebo] and yellow [Serostim 4 mg QOD] lines in Figure 10), mean trunk fat decreased during both Serostim 4 mg QD induction periods (Weeks 0-12), but increased after treatment with placebo and Serostim 4 mg QOD for 12 weeks (Weeks 12-24). **The amount of trunk fat reaccumulation was clearly less in the Serostim 4 mg QD/Serostim 4 mg QOD group (yellow line in Figure 6) compared with the Serostim 4 mg QD/placebo group (blue line in Figure 6) during the maintenance period**. In the Serostim 4 mg QOD/Serostim 4 mg QOD group (pink in Figure 6), the mean trunk fat decrease during Weeks 0-12 and plateau during Weeks 12-24 were similar to the changes observed after treatment with Serostim 4 mg QD/Serostim 4 mg QOD.

Figure 10: Study 22388 - Mean Trunk Fat Levels at Various Timepoints



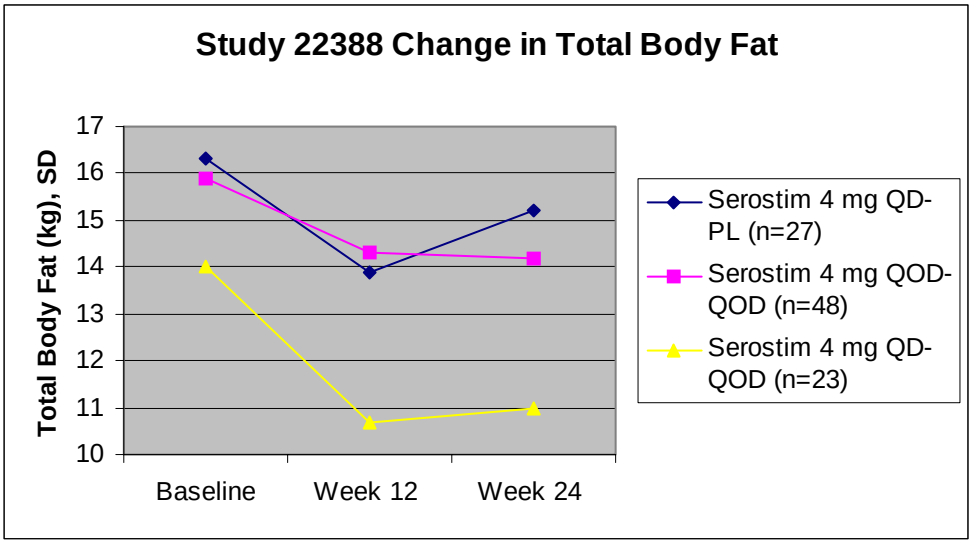
1.3.2.3 Total Body Fat

As seen in Table 4 (row 3), after induction with Serostim 4 mg QD, the group rerandomized to Serostim 4 mg QOD reaccumulated less total body fat than the group rerandomized to placebo (**0.34 vs. 1.32 kg, respectively**). In the group initially "induced" with Serostim 4 mg QOD and then "maintained" with Serostim 4 mg QOD, the extent of VAT reaccumulation was **similar** to that seen in the group "induced" with Serostim 4 mg QD and then rerandomized to Serostim 4 mg QOD (**0.02 vs. 0.34 kg, respectively**).

As seen in Table 5 (row 3), the LSM difference in the change from Week 12 to Week 24 in total body fat (Serostim 4 mg QD/Serostim 4 mg QOD vs./minus Serostim 4 mg QD/placebo) **was significant** (**-1.15 kg; p=0.04**) (ANCOVA; Division's Statistical Reviewer). The treatment difference was not significant in the sponsor's ANOVA (data not shown).

Figure 11 displays the **mean values** of total body fat at various timepoints for completers in Study 22388. In the 2 groups rerandomized to Serostim 4 mg QOD vs. placebo at Week 12 (blue [placebo] and yellow [Serostim 4 mg QOD] lines in Figure 10), mean total body fat decreased during both Serostim 4 mg QD induction periods (Weeks 0-12), but increased after treatment with placebo and Serostim 4 mg QOD for 12 weeks (Weeks 12-24). **The amount of total body fat reaccumulation was clearly less in the Serostim 4 mg QD/Serostim 4 mg QOD group (yellow line in Figure 6) compared with the Serostim 4 mg QD/placebo group (blue line in Figure 6) during the maintenance period**. In the Serostim 4 mg QOD/Serostim 4 mg QOD group (pink in Figure 6), the mean total body fat decrease during Weeks 0-12 and plateau during Weeks 12-24 were similar to the changes observed after treatment with Serostim 4 mg QD/Serostim 4 mg QOD.

Figure 11: Study 22388 - Mean Total Body Fat Levels at Various Timepoints



1.3.2.4 BAD

As seen in Table 4 (row 4), after induction with Serostim 4 mg QD, the group rerandomized to Serostim 4 mg QOD manifested a more stable BAD than the group rerandomized to placebo (+**6.82 vs. -15.84 points, respectively**). In the group initially "induced" with Serostim 4 mg QOD and then "maintained" with Serostim 4 mg QOD, the change in BAD was **similar** to that seen in the group "induced" with Serostim 4 mg QD and then rerandomized to Serostim 4 mg QOD (+**9.04 vs. +6.82 points, respectively**).

As seen in Table 5 (row 4), the LSM difference in the change from Week 12 to Week 24 in BAD (Serostim 4 mg QD/Serostim 4 mg QOD vs./minus Serostim 4 mg QD/placebo) **was significant** (**+17.06; p=0.004**) (ANCOVA; Division's Statistical Reviewer). The treatment difference **was also significant** in the sponsor's ANOVA (**+20.8; p=0.01**).

As seen in Figure 12, the CDF curves for change from Week 12 to Week 24 in BAD demonstrate a **clear separation** between the group rerandomized to Serostim 4 mg QOD at Week 12 after induction with Serostim 4 mg QD (dark blue) (as well as the group that continued treatment with Serostim 4 mg QOD after induction with Serostim 4 mg QOD [black]) vs. the group rerandomized to placebo at Week 12 after induction with Serostim 4 mg QD (red).

Figure 12: Study 22388 - Cumulative Distribution of Change from Week 12 to Week 24 in Belly Appearance Distress Score

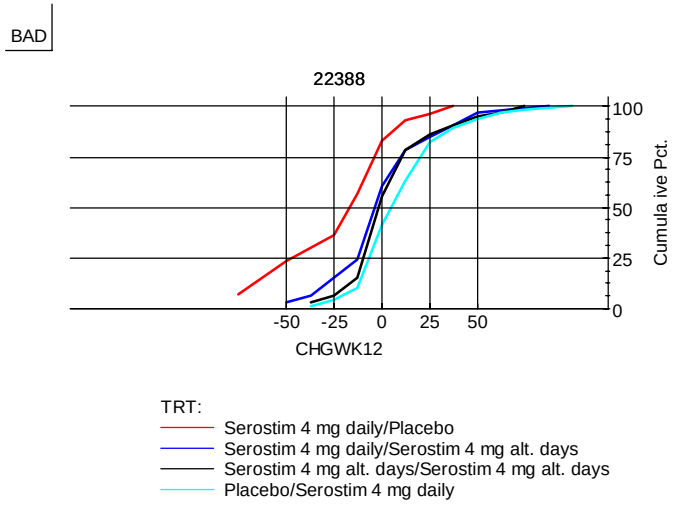
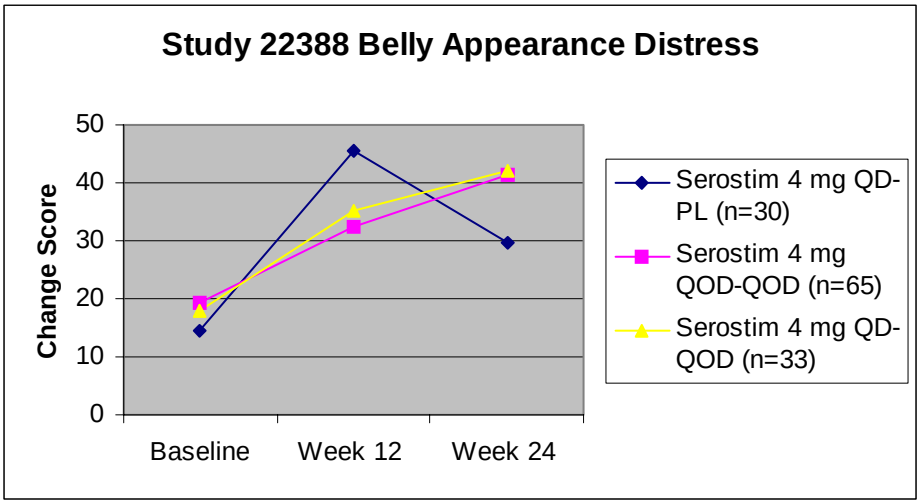


Figure 13 displays the **mean values** of BAD at various timepoints for completers in Study 22388. In the 2 groups rerandomized to Serostim 4 mg QOD vs. placebo at Week 12 (blue [placebo] and yellow [Serostim 4 mg QOD] lines in Figure 13), mean BAD increased during both Serostim 4 mg QD induction periods (Weeks 0-12); however, after treatment with placebo and Serostim 4 mg QOD for 12 weeks (Weeks 12-24), BAD decreased and further increased, respectively. **Clearly, BAD further improved in the Serostim 4 mg QD/Serostim 4 mg QOD group (yellow line in Figure 6) and deteriorated in the Serostim 4 mg QD/placebo group (dark blue line in Figure 13) during the maintenance period**. In the Serostim 4 mg QOD/Serostim 4 mg QOD group (pink in Figure 13), the mean BAD increase during Weeks 0-12 and further increase during Weeks 12-24 were similar to the changes observed after treatment with Serostim 4 mg QD/Serostim 4 mg QOD.

Figure 13: Study 22388 – Mean Belly Appearance Distress Scores at Various Timepoints



1.3.2.5 Abdominal SAT, LBM and Non-HDL Cholesterol

As seen in Table 5 (rows 5-7), the LSM differences in the change from Week 12 to Week 24 in abdominal SAT, LBM and non-HDL cholesterol (Serostim 4 mg QD/Serostim 4 mg QOD vs./minus Serostim 4 mg QD/placebo) **were not significant** (ANCOVA; Division's Statistical Reviewer). The treatment differences **were also not significant** in the sponsor's ANOVA.

1.3.2.6 Conclusions Regarding Maintenance Phase Efficacy Results for Study 22388 (Week 12 to Week 24)

1.3.2.6.1 VAT

- ANCOVA analysis (even though the maintenance phase was not powered to demonstrate a treatment effect), descriptive statistics, CDF curves and plots of mean VAT levels and changes in median VAT levels **all indicate that maintenance treatment with Serostim 4 mg QOD during Weeks 12-24 in Study 22388 preserved a clearly larger amount of the decrease in VAT observed after induction treatment than did placebo**.
- **Irrespective of whether (similar) reduction in VAT was induced with Serostim 4 mg QD or Serostim 4 mg QOD, the administration of Serostim 4 mg QOD during the maintenance phase resulted in similar preservation of the initial decrease in VAT** (see similar descriptive statistics, identical CDF curves and identical plots of mean VAT levels as well as changes in median VAT levels during Weeks 12-24 for Serostim 4 mg QOD [regardless of whether it follows induction with Serostim 4 mg QD or Serostim 4 mg QOD]).
- In spite of reaccumulation of VAT to some extent after maintenance treatment with Serostim 4 mg QOD during Weeks 12-24, a larger baseline VAT predicted a greater reduction in VAT. **The difference in VAT reduction** from Week 12 to Week 24 between the Serostim 4 mg QD/Serostim 4 mg QOD group and the Serostim 4 mg QD/placebo group **increased as the baseline VAT increased** (similar to the relationship observed between baseline VAT and reduction in VAT after treatment with Serostim 4 mg QD vs. placebo during the induction phase in Study 24380).

1.3.2.6.2 Trunk Fat

- ANCOVA analysis (even though the maintenance phase was not powered to demonstrate a treatment effect), descriptive statistics, CDF curves and plots of mean trunk fat levels **all indicate that maintenance treatment with Serostim 4 mg QOD during Weeks 12-24 in Study 22388 preserved a clearly larger amount of the decrease in trunk fat observed after induction treatment than did placebo**.
- **Irrespective of whether reduction in trunk fat was induced with Serostim 4 mg QD or Serostim 4 mg QOD, the administration of Serostim 4 mg QOD during the maintenance phase resulted in similar preservation of the initial decrease in trunk fat** (see similar descriptive statistics, CDF curves and plots of mean trunk fat levels during Weeks 12-24 for Serostim 4 mg QOD [regardless of whether it follows induction with Serostim 4 mg QD or Serostim 4 mg QOD]).

1.3.2.6.3 Total Body Fat

- ANCOVA analysis (even though the maintenance phase was not powered to demonstrate a treatment effect), descriptive statistics, and plots of mean total body fat levels **all indicate that maintenance treatment with Serostim 4 mg QOD during Weeks 12-24 in Study 22388 preserved a clearly larger amount of the decrease in total body fat observed after induction treatment than did placebo**.
- **Irrespective of whether reduction in total body fat was induced with Serostim 4 mg QD or Serostim 4 mg QOD, the administration of Serostim 4 mg QOD during the maintenance phase resulted in similar preservation of the initial decrease in total body fat** (see similar descriptive statistics and plots of mean total body fat levels during Weeks 12-24 for Serostim 4 mg QOD [regardless of whether it follows induction with Serostim 4 mg QD or Serostim 4 mg QOD]).

1.3.2.6.4 Belly Appearance Distress (BAD)

- ANCOVA analysis (even though the maintenance phase was not powered to demonstrate a treatment effect), descriptive statistics, CDF curves and plots of mean BAD levels **all indicate that maintenance treatment with Serostim 4 mg QOD during Weeks 12-24 in Study 22388 preserved a clearly larger amount of the increase in BAD observed after induction treatment than did placebo**.
- **Irrespective of whether increase in BAD was induced with Serostim 4 mg QD or Serostim 4 mg QOD, the administration of Serostim 4 mg QOD during the maintenance phase resulted in similar preservation of the initial increase in BAD** (see similar descriptive statistics, identical CDF curves and identical plots of mean BAD levels during Weeks 12-24 for Serostim 4 mg QOD [regardless of whether it follows induction with Serostim 4 mg QD or Serostim 4 mg QOD]).

1.3.2.6.5 Abdominal SAT, Lean Body Mass (LBM) and Non-HDL Cholesterol

- ANCOVA analyses and plots of mean abdominal SAT, LBM and non-HDL cholesterol levels indicate that maintenance treatment with Serostim 4 mg QOD during Weeks 12-24 in Study 22388 did not preserve the improvements in these variables observed after induction treatment any better than placebo.

1.3.2.6.6 Overall Conclusions

- **Maintenance treatment with Serostim 4 mg QOD during Weeks 12-24 in Study 22388 preserved a clearly larger amount of the decreases in VAT, trunk fat and total body fat, and the increase in BAD, observed after induction treatment (Weeks 0-12) than did placebo, i.e. maintenance treatment with Serostim 4 mg QOD resulted in durability of effect/sustained efficacy.**

- **Maintenance treatment with Serostim 4 mg QOD during Weeks 12-24 in Study 22388 resulted in identical or similar changes in VAT, trunk fat, total body fat and BAD irrespective of whether the induction dose was Serostim 4 mg QD or Serostim 4 mg QOD during Weeks 0-12.**
- **Therefore, it is concluded that Serostim 4 mg QOD for 12 weeks is an effective maintenance dose**.

1.3.3 Maintenance Phase Safety Results for Study 22388 (Week 12 to Week 24) and Studies 22388-23056 Combined (Week 36 to Week 60 [equivalent to Week 12 to Week 36 of Study 23056])

1.3.3.1 Maintenance Phase Safety Results for Study 22388 (Week 12 to Week 24)

Table 6 compares the incidence of common rhGH-related grouped adverse events (i.e., arthralgia-like, edema, dysglycemia, nerve compression sequelae) after treatment with Serostim 4 mg QOD vs. placebo during Weeks 12-24 in Study 22388. **Clearly, and not surprisingly, there was a much greater incidence of common rhGH-related adverse events in patients treated with Serostim 4 mg QOD compared with placebo-treated patients**. However, depending on the adverse event group, rhGH-related adverse events were 1/8 (i.e., nerve compression sequelae) to 1/4 (i.e., edema) to 1/3 - 2/5 (i.e., arthralgia-like) to 3/5 (i.e., dysglycemia) as frequent after treatment with Serostim 4 mg QOD than they were after treatment with Serostim 4 mg QD. In general, the incidence of common rhGH-related adverse events **was similar** in patients treated with Serostim 4 mg QOD during the Week 12-24 maintenance phase **irrespective** of whether they were treated with Serostim 4 mg QD or Serostim 4 mg QOD during the Week 0-12 induction phase.

1.3.3.2 Maintenance Phase Safety Results for Studies 22388-23056 Combined (Week 36 to Week 60 [equivalent to Week 12 to Week 36 in Study 23056])

Table 7 compares the incidence of common rhGH-related grouped adverse events after treatment with Serostim 1 mg QD (~2 mg QOD) vs. **Serostim 2 mg QD (~4 mg QOD)** during Weeks 36-60 in Studies 22388-23056 combined (equivalent to Weeks 12-36 in Study 23056). The incidence of arthralgia-like adverse events was comparable after treatment with Serostim 2 mg QD and Serostim 1 mg QD; however, the incidences of **edema, dysglycemia and nerve compression-related adverse events were more common after treatment with Serostim 1 mg QD compared with Serostim 2 mg QD**. The incidence of rhGH-related adverse events after treatment with **Serostim 2 mg QD (~4 mg QOD) for 24 weeks** (Weeks 36-60) in Studies 22388-23056 combined **was less than** the incidence of the same adverse events after treatment with **Serostim 4 mg QOD for 12 weeks** (Weeks 12-24) in Study 22388 (see Section 1.3.3.1 above).

Table 6: Study 22388 - Patient and Event Counts for Grouped Adverse Events by Treatment Group During Weeks 12-24 (Modified ITT Population)

Weeks 0-12/ Weeks 12-24	Placebo/ Serostim 4 mg QD (n=74)		Serostim 4 mg QOD/ Serostim 4 mg QOD (n=69)		Serostim 4 mg QD/ Placebo (n=32)		Serostim 4 mg QD/ Serostim 4 mg QOD (n=33)	
System Organ Class Preferred Term	Patients n (%)	Events n (%)	Patients n (%)	Events n (%)	Patients n (%)	Events n (%)	Patients n (%)	Events n (%)
Patients With Events and Total Events	71 (95.9)	318 (100.0)	55 (79.7)	159 (100.0)	20 (62.5)	53 (100.0)	27 (81.8)	63 (100.0)
ARTHRALGIA-LIKE	**36 (48.6)**	**56 (17.6)**	**12 (17.4)**	**17 (10.7)**	**1 (3.1)**	**1 (1.9)**	**7 (21.2)**	**7 (11.1)**
ARTHRALGIA	**22 (29.7)**	**28 (8.8)**	**3 (4.3)**	**5 (3.1)**	**0**	**0**	**3 (9.1)**	**3 (4.8)**
PAIN IN LIMB	8 (10.8)	9 (2.8)	6 (8.7)	6 (3.8)	0	0	1 (3.0)	1 (1.6)
POLYARTHRALGIA	6 (8.1)	6 (1.9)	2 (2.9)	2 (1.3)	0	0	1 (3.0)	1 (1.6)
JOINT STIFFNESS	1 (1.4)	1 (0.3)	2 (2.9)	2 (1.3)	0	0	1 (3.0)	1 (1.6)
MUSCULOSKELETAL STIFFNESS	3 (4.1)	3 (0.9)	0	0	1 (3.1)	1 (1.9)	0	0
BACK PAIN	1 (1.4)	1 (0.3)	1 (1.4)	1 (0.6)	0	0	1 (3.0)	1 (1.6)
TEMPOROMANDIBULAR JOINT DISORDER	3 (4.1)	3 (0.9)	0	0	0	0	0	0
EARLY MORNING JOINT STIFFNESS	2 (2.7)	2 (0.6)	0	0	0	0	0	0
BONE PAIN	1 (1.4)	1 (0.3)	0	0	0	0	0	0
JOINT RANGE OF MOTION DECREASED	1 (1.4)	1 (0.3)	0	0	0	0	0	0
NECK PAIN	0	0	1 (1.4)	1 (0.6)	0	0	0	0
TRIGGER FINGER	1 (1.4)	1 (0.3)	0	0	0	0	0	0
EDEMA	**37 (50.0)**	**61 (19.2)**	**9 (13.0)**	**15 (9.4)**	**0**	**0**	**4 (12.1)**	**4 (6.3)**
PERIPHERAL SWELLING	**18 (24.3)**	**27 (8.5)**	**6 (8.7)**	**10 (6.3)**	**0**	**0**	**1 (3.0)**	**1 (1.6)**
OEDEMA PERIPHERAL	10 (13.5)	12 (3.8)	1 (1.4)	1 (0.6)	0	0	1 (3.0)	1 (1.6)
JOINT SWELLING	6 (8.1)	7 (2.2)	1 (1.4)	1 (0.6)	0	0	0	0
FLUID RETENTION	5 (6.8)	5 (1.6)	1 (1.4)	1 (0.6)	0	0	1 (3.0)	1 (1.6)
OEDEMA LOWER LIMB	2 (2.7)	3 (0.9)	1 (1.4)	1 (0.6)	0	0	0	0
FACE OEDEMA	3 (4.1)	3 (0.9)	0	0	0	0	0	0
PITTING OEDEMA	2 (2.7)	2 (0.6)	0	0	0	0	0	0
SKIN TIGHTNESS	1 (1.4)	1 (0.3)	1 (1.4)	1 (0.6)	0	0	0	0
OEDEMA UPPER LIMB	1 (1.4)	1 (0.3)	0	0	0	0	0	0
SWELLING NOS	0	0	0	0	0	0	1 (3.0)	1 (1.6)
DYSGLYCEMIA	**15 (20.3)**	**16 (5.0)**	**13 (18.8)**	**13 (8.2)**	**2 (6.3)**	**2 (3.8)**	**4 (12.1)**	**5 (7.9)**
HYPERGLYCAEMIA	**7 (9.5)**	**7 (2.2)**	**9 (13.0)**	**9 (5.7)**	**1 (3.1)**	**1 (1.9)**	**4 (12.1)**	**5 (7.9)**
BLOOD GLUCOSE INCREASED	8 (10.8)	9 (2.8)	3 (4.3)	3 (1.9)	1 (3.1)	1 (1.9)	0	0
GLUCOSE INTOLERANCE	0	0	1 (1.4)	1 (0.6)	0	0	0	0
NERVE COMPRESSION SEQUELAE	**19 (25.7)**	**28 (8.8)**	**4 (5.8)**	**5 (3.1)**	**1 (3.1)**	**1 (1.9)**	**1 (3.0)**	**1 (1.6)**
HYPOAESTHESIA	**10 (13.5)**	**11 (3.5)**	**1 (1.4)**	**1 (0.6)**	**0**	**0**	**1 (3.0)**	**1 (1.6)**
PARAESTHESIA	7 (9.5)	7 (2.2)	1 (1.4)	1 (0.6)	1 (3.1)	1 (1.9)	0	0
CARPAL TUNNEL SYNDROME	3 (4.1)	3 (0.9)	1 (1.4)	1 (0.6)	0	0	0	0
PERIPHERAL NEUROPATHY	2 (2.7)	2 (0.6)	1 (1.4)	1 (0.6)	0	0	0	0
HYPERAESTHESIA	2 (2.7)	2 (0.6)	0	0	0	0	0	0
BURNING SENSATION NOS	1 (1.4)	1 (0.3)	0	0	0	0	0	0
NEURITIS NOS	1 (1.4)	1 (0.3)	0	0	0	0	0	0
SCIATICA	1 (1.4)	1 (0.3)	0	0	0	0	0	0
SENSORY LOSS	0	0	1 (1.4)	1 (0.6)	0	0	0	0
MYALGIA-LIKE	**8 (10.8)**	**9 (2.8)**	**5 (7.2)**	**5 (3.1)**	**2 (6.3)**	**3 (5.7)**	**0**	**0**
MYALGIA	**8 (10.8)**	**9 (2.8)**	**5 (7.2)**	**5 (3.1)**	**0**	**0**	**0**	**0**
MUSCLE SPASMS	0	0	0	0	2 (6.3)	2 (3.8)	0	0
MUSCLE CRAMPS	0	0	0	0	1 (3.1)	1 (1.9)	0	0

Table 7: Studies 22388-23056 Combined: Patient and Event Counts for Grouped Adverse Events by Treatment Group During Weeks 36-60 (Equivalent to Weeks 12-36 in Study 23056) (Modified ITT Population)

	Serostim 1 mg QD (n=87)		Serostim 2 mg QD (n=32)	
System Organ Class Preferred Term	**Patients n (%)**	**Events n (%)**	**Patients n (%)**	**Events n (%)**
Patients With Events and Total Events	69 (79.3)	181	23 (71.9)	46
Arthralgia-Like	**14 (16.1)**	**16 (8.8)**	**4 (12.5)**	**6 (13.0)**
Arthralgia	**5 (5.7)**	**5 (2 8)**	**4 (12.5)**	**5 (10.9)**
Back pain	3 (3.4)	3 (1.7)	0	0
Pain in limb	2 (2.3)	2 (1.1)	1 (3.1)	1 (2.2)
Polyarthralgia	3 (3.4)	3 (1.7)	0	0
Joint stiffness	1 (1.1)	1 (0.6)	0	0
Neuropathy NOS	1 (1.1)	1 (0.6)	0	0
Temporomandibular joint disorder	1 (1.1)	1 (0.6)	0	0
Edema	**5 (5.7)**	**7 (3 9)**	**0**	**0**
Oedema peripheral	**2 (2.3)**	**3 (1.7)**	**0**	**0**
Peripheral swelling	2 (2.3)	2 (1.1)	0	0
Angioneurotic oedema	1 (1.1)	1 (0.6)	0	0
Swelling face	1 (1.1)	1 (0.6)	0	0
Dysglycemia	**9 (10.3)**	**10 (5.5)**	**2 (6.3)**	**2 (4.3)**
Hyperglycaemia NOS	**7 (8.0)**	**8 (4.4)**	**2 (6.3)**	**2 (4.3)**
Blood glucose increased	1 (1.1)	1 (0.6)	0	0
Glucose tolerance increased	1 (1.1)	1 (0.6)	0	0
Nerve Compression Sequelae	**6 (6.9)**	**6 (3 3)**	**1 (3.1)**	**1 (2.2)**
Paraesthesia	**5 (5.7)**	**5 (2 8)**	**0**	**0**
Hypoaesthesia	1 (1.1)	1 (0.6)	1 (3.1)	1 (2.2)
Myalgia–Like	**0**	**0**	**1 (3.1)**	**1 (2.2)**
Tendonitis	0	0	1 (3.1)	1 (2.2)

1.3.3.3 Conclusions Regarding Maintenance Phase Safety Results for Study 22388 (Week 12 to Week 24) - Specifically Conclusions Regarding the Relative Safety of Serostim 4 mg QOD as a Maintenance Dose

- As expected, treatment with **Serostim 4 mg QOD** during Weeks 12-24 in Study 22388 (i.e., 12 weeks) **resulted in much more frequent rhGH-related adverse events compared to placebo, but substantially less rhGH-related adverse events compared to Serostim 4 mg QD**.
- The incidence of rhGH-related adverse events after treatment with **Serostim 2 mg QD (~4 mg QOD)** during Weeks 36-60 in Studies 22388-23056 combined (i.e., 24 weeks) **was comparable to** (and with regard to certain adverse events **less than**) the incidence of rhGH-related adverse events after treatment with **Serostim 1 mg QD (~2 mg QOD)** during the same timeframe in the same study.

- The incidence of rhGH-related adverse events after treatment with **Serostim 2 mg QD (~4 mg QOD) for 24 weeks** (Weeks 36-60) in Studies 22388-23056 combined **was less than** the incidence of the same adverse events after treatment with **Serostim 4 mg QOD for 12 weeks** (Weeks 12-24) in Study 22388. Cross-study comparisons must be **interpreted with caution**; **however, perhaps these observations are related to the fact that longer exposure to Serostim 4 mg QOD resulted in a degree of "adaptation/tolerance"**.
- **The safety profile of Serostim 4 mg QOD as a maintenance dose for 12 weeks is not ideal but, in the opinion of this Medical Officer, is considered to be acceptable**.

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/s/

Robert Perlstein
7/12/2007 11:32:13 AM
MEDICAL OFFICER

Mary Parks
7/12/2007 06:34:56 PM
MEDICAL OFFICER
see Director's memo

CLINICAL REVIEW*

*Also see Addendum dated 30June07

Application Type	20-604
Submission Number	Supplement 040
Submission Code	SE-1
Letter Date	8June06
Stamp Date	12June06
PDUFA Goal Date	**14April07**
Reviewer Name	Robert S. Perlstein MD, FACP, FACE
Review Completion Date	**26March07**
Established Name	Serostim
(Proposed) Trade Name	Serostim
Therapeutic Class	rhGH (recombinant human growth hormone)
Applicant	EDB Serono, Inc.
Priority Designation	S
Formulation	Lyophilized rhGH
Proposed Dosing Regimen	Induction: 4 mg SC QD Maintenance: 2 mg SC QOD
Indication	HARS (Human Immunodeficiency Syndrome [HIV]-Associated Adipose Redistribution Syndrome)
Intended Population	Patients with AIDS (Acquired Immunodeficiency Syndrome) who have HARS

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This Medical Officer recommends APPROVAL of the human immunodeficiency virus (HIV)-associated adipose redistribution syndrome **(HARS) indication for Serostim - including approval of Serostim 4 mg QD as a 12 week induction dose, approval for women as well as men, and approval of Serostim 2 mg QOD as a 24 week maintenance dose (all of which were requested by the sponsor).**

1.1.1 Efficacy Recommendations

- **This Medical Officer recommends approval of Serostim 4 mg QD as a 12 week induction dose (as requested by the sponsor). The detailed rationale behind this decision can be found in the Efficacy Conclusions section. The more adverse safety profile observed with Serostim 4 mg QD is tolerable and acceptable if it is only administered during the 12 week induction period, and certain caveats regarding the use of Serostim 4 mg QD are added/labeled, i.e. cut back to Serostim 4 mg QOD if significant rhGH-related adverse events should occur, start with Serostim 4 mg QOD in patients considered to be at special risk for rhGH-related adverse effects (see Safety Conclusions and Recommendations ahead).**

- **This Medical Officer recommends approval of Serostim 4 mg QD as a 12 week induction dose for women as well as men (as requested by the sponsor). Again, the detailed rationale behind this decision can be found in the Efficacy Conclusions section. This recommendation comes with certain caveats/conditions as well:**

  - **The CLINICAL STUDIES section of the PI should clearly indicate that women did not demonstrate a significant reduction in visceral adipose tissue (VAT) after treatment with Serostim 4 mg QD (vs. placebo), but did respond as well as men with regard to reduction in trunk fat, abdominal subcutaneous adipose tissue (SAT), total body fat, and non-high density lipoprotein (HDL) cholesterol, increase in lean body mass (LBM), and improvement in belly appearance distress (BAD) and belly size estimation (BSE) scores. A small table containing descriptive statistics depicting the VAT response by gender should be included in the CLINICAL STUDIES section as well.**
  - (b) (4)
  - **The sponsor should be firmly requested to make a formal Phase IV commitment to conduct an adequately powered similar study in women as soon as feasible.**

- **This Medical Officer recommends approval of Serostim 2 mg QOD as a 24 week maintenance dose (as requested by the sponsor). The detailed rationale behind this decision can be found in the Efficacy Conclusions section.**

1.1.2 Safety Recommendations

- **The more adverse safety profile observed with Serostim 4 mg QD is tolerable and acceptable if it is only administered during the 12 week induction period, and certain caveats regarding the use of Serostim 4 mg QD are added/labeled, i.e. cut back to Serostim 4 mg QOD if significant rhGH-related adverse events should occur, start with Serostim 4 mg QOD in patients considered to be at special risk for rhGH-related adverse effects, especially if they are predisposed to glucose intolerance**

1.2 Recommendation on Postmarketing Actions

See Section 1.2.2

1.2.1 Risk Management Activity

None.

1.2.2 Required Phase 4 Commitments

The sponsor should be firmly requested to make a formal Phase IV commitment to conduct an adequately powered similar study in women as soon as feasible.

1.2.3 Other Phase 4 Requests

None.

1.3 Summary of Clinical Findings

1.3.1 Background Information, Rationale for the Development of Serostim for the Treatment of Patients with HARS, and Brief Overview of Clinical Program

HARS is a disorder that developed after the advent of highly active antiretroviral therapy (HAART) for the treatment of patients with the acquired immunodeficiency syndrome (AIDS) in the mid-1990s in the United States and elsewhere. On HAART, many patients with HIV/AIDS display dramatic reductions in viral load and, as a consequence, marked decreases in the frequency of life-threatening AIDS-defining complications, including opportunistic infections, neoplasms, and wasting or cachexia. However, advances in antiretroviral therapy have been accompanied by (and may at least in part have directly caused) the emergence of disturbing morphologic and metabolic complications, frequently referred to as HIV lipodystrophy syndrome. Some of these complications (i.e., excess accumulation of VAT and trunk fat) have

been referred to as HARS. **HARS is characterized by the abnormal accumulation of trunk fat including VAT (lipohypertrophy) with (~2/3 of patients) or without (~1/3 of patients) lipoatrophy (SAT depletion primarily in the face and limbs, but also the buttocks and the abdomen).** Some HARS patients also present with an enlarged dorsocervical fat pad and/or excess accumulation of chest or breast fat. **HARS, in fact, is a subtype of the HIV lipodystrophy syndrome.** A survey of studies reporting on patients with the HIV lipodystrophy syndrome (through 2003) revealed that the prevalence of HARS was less than 200,000 patients - which qualified this NDA supplement submission for the treatment of HARS with Serostim for an orphan drug designation by the Agency in 2004.

The pathogenesis for the abnormal central fat accumulation in HARS remains uncertain. HARS develops primarily in HIV-infected individuals who have been receiving HAART, and, more than likely, both antiretroviral drug-related and non-drug/host factors (in the patient being treated with HAART) contribute to the etiology of the syndrome. Initially, it was hypothesized that HIV protease inhibitors (PIs) were the sole agents responsible for the development of HARS and the HIV lipodystrophy syndrome. However, it is now believed that the HIV lipodystrophy syndromes can develop in HIV patients treated with any class of antiretroviral therapy, and that the nucleoside reverse transcriptase inhibitors (NRTIs), may accelerate the development of the HIV lipodystrophy syndrome in patients receiving PIs. Furthermore, HARS and the HIV lipodystrophy syndrome have occasionally been reported in HIV patients who have never been treated with PIs, or any other antiretroviral therapy. Secondary functional growth hormone deficiency (GHD) has also been postulated as a possible etiologic factor for increased VAT in these patients.

HARS patients have a number of cardiovascular risk factors, including: insulin resistance (occasionally leading to the development of impaired glucose tolerance/impaired fasting glucose and even overt non-insulin dependent diabetes mellitus), lipid abnormalities (e.g., elevated total, low density lipoprotein (LDL), or non-HDL cholesterol, reduced HDL cholesterol, and elevated triglycerides), and hypertension. **All of these abnormalities are cardiovascular risk factors and potentially related, at least in part, to the abnormal accumulation of VAT described above. As a consequence of these risk factors, HARS patients as a group appear to have a greater than average risk of developing cardiovascular disease. This has been confirmed in preliminary observational studies**.

A 1999 publication summarized the first 65 post-marketing adverse event reports describing abnormal fat distribution in association with antiretroviral therapy that were voluntarily reported to the Agency. Case reports used terms such as "disabling" and "devastating", and described appearances like "a pregnant skeleton," an "apple on a stick," and "having an inner tube-like abdominal distension with butt and legs that were bird-like skinny." **HIV patients with fat distribution abnormalities may be readily identified by others and therefore experience shame and stigmatization in the workplace and in private life**. **In that the deforming manifestations of HARS have been attributed, at least in part, to antiretroviral medications, caretakers have become very concerned that HIV patients who have HARS, or who fear developing it, might abandon otherwise effective, lifesaving antiretroviral therapy. In 1 study published in 2000, it was reported that 30% of patients in a HARS**

cohort had changed drug regimens and 7% had stopped therapy, while more than 50% had thought about changing or stopping therapy, and the remainder claimed they planned to stop or switch therapies if their alterations became worse.

At the present time, **physicians have no approved medical therapies to treat patients with HARS** and surgery is not considered a safe or effective option. **In the last few years, newer generation antiretroviral medications have been reported not to result in as much VAT accumulation or dyslipidemia as the HAART regimens administered earlier. This is further evidenced by the significantly smaller baseline levels of VAT and various lipids in the subjects enrolled in 2004 for the sponsor's second pivotal study (Study 24380) compared with the baseline values observed in the subjects enrolled in 2001 for the sponsor's first pivotal study (Study 22388)**.

GH has been known to be lipolytic since the earliest days of research into its metabolic effects. Since rhGH first became commercially available in 1985, numerous clinical trials in adult GHD patients have consistently shown that it reduces total body fat, trunk fat, **VAT** and various lipid parameters, as well as increasing LBM. To date, there have been 5 preliminary published trials evaluating the efficacy (and safety) of Serostim for the treatment of patients with HARS. Engelson et al published the most significant of these trials in 2002 and demonstrated that treatment with **Serostim 6 mg QD** (the dose approved for HIV-associated wasting/cachexia) **significantly decreased VAT**, but also **resulted in an unacceptable amount of rhGH-related adverse events (AEs)**. **This study influenced the sponsor to evaluate the efficacy and safety of a lesser amount of Serostim for the treatment of HARS.**

Following an End-of-Phase II meeting with DMEP on 5/22/02 (after completion of Study 22388 - the sponsor's first pivotal [and dose-finding] study), it was mutually agreed that HARS was a clinical entity worth treating, and that the HARS patient population defined in the Phase III clinical development plan was adequately representative of HIV patients with excessive, pathological accumulation of central fat. Therefore, the efficacy and safety of 12 week induction (4 mg QD) and 24 week maintenance (2 mg QOD) doses of Serostim were further evaluated in this group of patients in Study 24380. With respect to the induction phase in particular, it was mutually agreed that change in VAT would be the primary efficacy endpoint, but that validated patient-reported outcome (PRO) data (reflecting the patient's perception of belly size and distress related to belly size) would be essential supporting information. A pre-sNDA meeting was conducted on 2/18/06 during which the Division and the sponsor fundamentally agreed on the content of the NDA submission. **The sponsor has therefore submitted 2 large pivotal studies for review by the Division in an attempt to gain an indication for Serostim for the treatment of patients with HARS**.

1.3.2 Efficacy

1.3.2.1 Description of Clinical Designs of the 2 Pivotal Studies (Studies 22388/23056 and 24380) (including rationale for dosing)

Study 22388 was a 24 week, randomized, double blind, placebo controlled, parallel group, **dose finding** study. During Weeks 0-12 (induction phase), patients were randomized to 3 arms: Serostim 4 mg SC QD (DD) vs. Serostim 4 mg SC QOD vs. placebo. During Weeks 12-24, patients initially treated with DD were rerandomized to 2 arms (DD to PL and DD to AD). **The primary focus of this Medical Officer's review of Study 22388 will be on the results from the induction period, Weeks 0-12**. Study 23056 was 36 week, open label, partially randomized, parallel group, dose finding study in **patients who completed Study 22388**. During Weeks 0-12 (equivalent to Weeks 24-36 of Studies 22388-23056 combined), patients were randomized to 2 arms: Serostim 4 mg SC QD or Serostim 2 mg SC QD. **During Weeks 12-36 (equivalent to Weeks 36-60 of Studies 22388-23056 combined), patients were rerandomized to Serostim 2 mg SC QD or Serostim 1 mg SC QD**. **The objective of Study 23056 was to determine the best 6 month maintenance dose of Serostim following treatment with a larger dose of Serostim during the induction period**. **This Medical Officer will therefore briefly describe the results of Weeks 12-36 (which led to the selection of the maintenance dose used in the second pivotal study, Study 24380) in this review**

Study 24380 was a 36 week, double blind, randomized, placebo controlled, parallel group study. During Weeks 0-12 (induction phase), patients were randomized to 2 arms: Serostim 4 mg SC QD vs. placebo). **Serostim 4 mg SC QD (rather than Serostim 4 mg SC QOD) was chosen as the preferred dose for induction based on the results observed during Study 22388**. **With respect to most efficacy parameters (except reduction in VAT), Serostim 4 mg SC QD appeared to be more efficacious than Serostim 4 mg SC QOD in Study 22388. The safety profile of Serostim 4 mg SC QOD was (not unexpectedly) clearly more "benign" than that of Serostim 4 mg SC QD; however, the safety profile of Serostim 4 mg SC QD was felt to be tolerable and acceptable for a 12 week induction period, given the better overall efficacy observed with Serostim 4 mg SC QD**. **The efficacy and safety results comparing Serostim 4 mg SC QD and Serostim 4 mg SC QOD during the 12 week induction period in Study 22388 (which led to the sponsor's decision to use Serostim 4 mg SC QD as the induction dose in Study 24380) will be presented in detail in this Medical Officer's review**.

During Weeks 12-36, patients initially treated with Serostim 4 mg SC QD were rerandomized to 2 arms: Serostim 2 mg SC QOD or PL QOD (in effect, a blinded randomized withdrawal). **Serostim 2 mg SC QOD was chosen as the 6 month maintenance dose in Study 24380 because the efficacy results observed during Weeks 12-36 in Study 23056 showed no difference between Serostim 1 mg SC QD and Serostim 2 mg SC QD. The results from the 6 month maintenance period (Weeks 12-36) in Study 24380 will be summarized in this review**.

The primary efficacy endpoint for both pivotal studies (Studies 22388 and 24380) **was change in the cross-sectional area of VAT (cm^2)** (measured by computed tomographic [CT] scan at the L4-5 level). Other consequential secondary efficacy endpoints (common to both pivotal studies) included additional measures of body composition (changes in abdominal SAT by CT scan, **trunk fat** by dual energy X-ray absorptiometry [DEXA] scan, total body fat by DEXA, dorsocervical fat pad and LBM), and changes in various lipid parameters.

As discussed in Section 2.6, patients with HARS are thought to be at greater risk for cardiovascular disease because of increased amounts of VAT, adverse lipid profiles and insulin resistance; **however, long-term outcome data correlating a reduction in VAT with decreased cardiovascular risk are not currently available**. In addition, as noted in Section 2.6 ahead, **the body dysmorphia and attendant psychological distress/stigmatization associated with the accumulation of VAT and central obesity per se has been reported to result in non-compliance with life-sustaining HAART**. Therefore, **for both of these reasons**, **the Division and the sponsor mutually agreed that improvement in endpoints obtained with a validated PRO instrument reflecting the patient's perception of changes in his/her body image would be extremely important to support an indication for HARS**. Toward this end, the sponsor subcontracted (b) (4) to assess the impact of HARS-associated body dysmorphia (e.g., big belly +/- dorsocervical fat pad +/- thin extremities, face, & buttocks) on the patient's psyche/emotional well being (and perhaps compliance with HAART) at baseline and after treatment with Serostim vs. placebo. (b) (4) The sponsor submitted preliminary validation data for the BIIM prior to launching the second Phase III pivotal study (Study 24380). These data were extensively reviewed by the Agency's Study Endpoints and Labeling Development (SEALD) team at that time at the request of this Medical Officer. It was mutually agreed at that time and also at the pre-NDA meeting that **changes in BAD, BSE and belly profile assessment (BPA) were the most validated and consequential components of the BIIM. This Medical Officer will therefore focus almost exclusively on these particular PRO results in this review The SEALD team was again consulted and actively assisted this Medical Officer with 1) the review of the additional validation data included by the sponsor in this NDA supplement submission; and 2) how to best label these findings**.

The dominant statistical models utilized by the Division's Statistical Reviewer and the sponsor to determine treatment differences vs. placebo for the primary and secondary efficacy variables were **equally weighted** analyses of covariance (ANCOVAs) and analyses of variance (ANOVAs) in the modified intent-to-treat (ITT) populations (**n=322** for the induction phase in Study 24380 and **n=239** for the induction in Study 22388). **The sponsor originally submitted proportionally weighted ANCOVAs and ANOVAs by gender, but the Division's Statistical Reviewer and Team Leader disagreed with that approach**. Further, in keeping the Agency's latest thinking, cumulative distribution functions (CDFs) were constructed for the primary efficacy endpoint and for the PRO secondary efficacy endpoints.

The primary safety endpoints for both pivotal studies were **measures of glucose tolerance**, serum insulin-like growth factor I (IGF I) and, even more importantly, IGF I standard deviation score (SDS) levels, the well known rhGH-related AEs related to fluid retention (i.e., edema, arthralgia, myalgia, carpal tunnel syndrome, etc), and measures reflecting the activity of preexisting HIV infection, i.e. viral load (HIV-1 RNA) and CD4 T-helper lymphocyte count.

1.3.2.2 Efficacy Summary of Results/Selective Discussion

1.3.2.2.1 Induction Phase: Weeks 0-12 of Studies 24380 and 22388

1.3.2.2.1.1 Primary Efficacy Endpoint: Change in VAT

- **The mean <u>differences</u> in the change and percent change from baseline to Week 12 in VAT between the Serostim 4 mg QD group and the placebo group were significant** in Study 24380 (**-17.0 cm^2; p=0.005**; **-17.2%; p=0.0005**), Study 22388 (**-18.2 cm^2; p=0.031**; **-14.0%; p=0.022**), and in the integrated analysis (**-18.1 cm^2; p<0.001**; **-15.0%; p<0.001**).
- CDF curves show a clear separation of the subjects in the Serostim 4 mg QD and placebo groups. With respect to change and percent change from baseline to Week 12 in VAT, the cumulative percentages of patients who were **non-responders** (defined as a response >0) **were ~50% for the placebo group vs. ~10-25% for the Serostim 4 mg QD groups** in Studies 24380 and 22388. Furthermore, if one selects a within-group change of **-25 cm^2** (a number more negative than the mean between-group differences of -17-18 cm^2) **as a cutpoint**, the cumulative percentages of patients **with changes more negative than -25 cm^2 were ~60% for the Serostim 4 mg QD groups vs. ~25-30% for the placebo groups** in Studies 24380 and 22388. Finally, if one selects a within-group percent change of **-15%** (a number approximating the robust, mean between-group differences noted in the preceding bullet - **and which clearly exceeds the -5-10% change thought to be the minimally significant difference prior to the pivotal studies) as a cutpoint**, the cumulative percentages of patients **with changes more negative than -15% were ~60-70% for the Serostim 4 mg QD groups vs. ~25% for the placebo groups** in Studies 24380 and 22388.
- **The mean <u>differences</u> in the change and percent change from baseline to Week 12 in VAT between the Serostim 4 mg QOD group and the placebo group (-19.7 cm^2 and -16.7%) were very similar to those observed between the Serostim 4 mg QD group and the placebo group (-18.2 cm^2 and -14.0%)**. This is **confirmed by the CDF curves** for Study 22388 wherein the **"plots"** for the Serostim 4 mg QD group and the Serostim 4 mg QOD group **were identical** and overlap each other. **<u>In other words, there was no dose response observed with respect to change from baseline to Week 12 in VAT</u>**.
- **The treatment by baseline VAT interaction was quantitatively significant (p=0.0002) for change from baseline to Week 12 in VAT in Study 24380. As baseline VAT decreased, the reduction from baseline to Week 12 in VAT decreased in the Serostim 4 mg QD group**, and **the difference in VAT reduction** from baseline to Week 12 between the Serostim 4 mg QD treatment group and the placebo group **significantly increased as the baseline VAT increased**. **In other words, a lower baseline VAT predicts a smaller treatment effect (Serostim 4 mg QD vs. placebo)**. This has previously been reported in patients with HARS and the non-HIV infected population.
- **The treatment by gender interactions were highly significant (p=0.0006)** and minimally significant (p=0.1) in Studies 24380 and 22388, respectively, **for the Serostim 4 mg QD treatment group vs. the placebo group in the analyses of the entire**

population. **Mean VAT levels at baseline in female treatment groups (105 cm^2 and 85 cm^2 in Studies 22388 and 24380, respectively) were clearly smaller than in the male treatment groups (156 cm^2 and 143 cm^2 in Studies 22388 and 24380, respectively)**. This has previously reported by several authors in patients with HARS as well as the obese (and non-obese) HIV-negative population. In this regard, Kotler et al reported mean VAT levels of **~56 cm^2 and ~73 cm^2** in non-HIV infected women and men, respectively, whose BMIs were roughly comparable to the BMIs of patients enrolled in Studies 22388 and 24380.

---The treatment effects (Serostim 4 mg QD vs. placebo) for the change and percent change from baseline to Week 12 in VAT in males were significant in both studies, and very similar to the treatment effects derived from the analyses of all patients. This is not surprising in that **~85% of the patients** in the modified ITT population treated with Serostim 4 mg QD vs. placebo in each study **were male**.

---On the other hand, the treatment effects (Serostim 4 mg QD vs. placebo) for the change and percent change from baseline to Week 12 in VAT in females were not significant, i.e. the responses of women treated with Serostim 4 mg QD and placebo were similar in both studies.

---The CDF curves for change from baseline to Week 12 in VAT by gender **support the ANCOVA findings described above**. In both studies, ~10% of men treated with Serostim 4 mg QD vs. ~50% of men treated with placebo were non-responders, which mirrors the non-responder rates for the entire population. **In contrast, ~50% of the women treated with Serostim 4 mg QD or placebo in Study 24380, and ~40% of the women treated with Serostim 4 mg QD or placebo in Study 22388 were non-responders**. The response curves for women treated with Serostim 4 mg QD and placebo were essentially identical in both studies.

---In summary, the treatment of women with Serostim 4 mg QD (or 4 mg QOD) vs. placebo during the induction phases of Studies 24380 and 22388 did not result in significant treatment effects/differences. The lack of response in women may partially be explained by the fact that **estrogen** (especially orally administered hormone replacement therapy, but also endogenous estrogen in a menstruating women) diminishes the response to rhGH (i.e., generation of IGF I). This has been demonstrated in numerous publications reporting the treatment of adult GHD (see reference 45 - a Clinical Practice Guideline issued by the Endocrine Society in 2006). However, in that ~5 times as much rhGH was administered to the women with HARS in these pivotal studies as is typically administered to adult GHD women (~50 µg/kg in an 80 kg woman with HARS receiving Serostim 4 mg QD vs. ~10 µg/kg in a typical adult GHD woman), this Medical Officer has doubts about the role of estrogen, i.e. the effect of very large, pharmacologic amounts of rhGH should have "trumped" any estrogen-mediated resistance to rhGH. Another possible explanation relates to the fact that the **lower baseline VAT levels in women compared with men** (see first paragraph of this bullet) **predicts a lesser VAT reduction in response to Serostim/rhGH** (see last bullet on

previous page). **Finally, only ~15% of the subjects enrolled in each of the pivotal studies were women, and the studies may have been underpowered to detect a significant treatment effect**.

1.3.2.2.1.2 Change in Non-PRO Consequential Secondary Efficacy Endpoints

- The mean **differences** in the change from baseline to Week 12 in **trunk fat**, **abdominal SAT**, total body fat, LBM, non-HDL cholesterol (Study 24380 only), dorsocervical fat pad (integrated analysis only) between the Serostim 4 mg QD group and the placebo group **were all significant** (by ANOVA with baseline score as covariate).
- **In contrast to the VAT results, a dose response was evident** when the differences in the change from baseline to Week 12 in **trunk fat**, **abdominal SAT**, **total body fat and LBM after treatment with Serostim 4 mg QOD vs. placebo were compared with the differences observed after treatment with Serostim 4 mg QD vs. placebo**, i.e. in the case of trunk fat and LBM, the same high degree of significance ($p<0.001$) for both doses of Serostim vs. placebo, but a smaller treatment difference; in the case of abdominal SAT, a smaller, non-significant treatment difference after Serostim 4 mg QOD vs. placebo; in the case of total fat mass, a smaller, less significant treatment difference after Serostim 4 mg QOD. **The importance of these observations will be expanded upon in this Medical Officer's Efficacy Conclusions**.
- **In contrast to the VAT results**, in the case of every one of these variables, **the treatment by gender interactions were not significant** in Studies 24380 and 22388 for the Serostim 4 mg QD treatment group vs. the placebo group in the analyses of the entire population. **The importance of these observations will also be expanded upon in this Medical Officer's Efficacy Conclusions**.

1.3.2.2.1.3 Change in Most Consequential PRO Secondary Efficacy Endpoints

- The mean **differences** in the change from baseline to Week 12 in **BAD and BSE** between the Serostim 4 mg QD group and the placebo group **were all significant** (by ANCOVA with baseline score as covariate).
- **Once again, in contrast to the VAT results, and concordant with the abdominal SAT/trunk fat results, a dose response was evident** when the differences in the change from baseline to Week 12 in **BAD and BSE after treatment with Serostim 4 mg QOD vs. placebo were compared with the significant differences observed after treatment with Serostim 4 mg QD vs. placebo**, i.e. there are smaller, non-significant treatment differences after treatment with Serostim 4 mg QOD vs. placebo. **The importance of these observations will also be expanded upon in this Medical Officer's Efficacy Conclusions**.
- **Once again, in contrast to the VAT results, and concordant with the abdominal SAT/trunk fat results, in the case of each of these variables, the treatment by gender interactions were not significant** in Studies 24380 and 22388 for the Serostim 4 mg QD treatment group vs. the placebo group in the analyses of the entire population. **The**

importance of these observations will also be expanded upon in this Medical Officer's Efficacy Conclusions.

- The sponsor demonstrated **significant correlations** between changes from baseline to Week 12 in **BAD (as well as BSE)** with changes from baseline to Week 12 in VAT and **trunk fat** after treatment with Serostim 4 mg QD in Study 24380.
- The **responder analyses** performed by the sponsor are **supportive of the findings of the ANCOVAs**. The differences in the proportion of subjects who were designated as responders for BAD and BSE after treatment with Serostim 4 mg QD vs. placebo for 12 weeks in Studies 23388 and 24380 were highly significant. With regard to BAD and BSE, ~30-45% and ~40% of the subjects treated with Serostim 4 mg QD, respectively, compared with ~12-18% and ~23% of the subjects treated with placebo, respectively, were designated as responders across the 2 studies. **Once again, a dose response was apparent in that none of the differences in the proportion of subjects who were designated as responders for BAD and BSE after treatment with Serostim 4 mg QOD vs. placebo in Study 22388 for 12 weeks were significant**.
- The CDF curves reflecting the change from baseline to Week 12 in BAD after treatment with Serostim 4 mg QD vs. placebo demonstrate non-responder rates of **~25% and ~50%** for the Serostim 4 mg QD and placebo groups, respectively, in both studies. The cumulative percentages of patients with a BAD change score **>25 (equal to 2 scale units)** were **~30-40% and ~10-20%** in the Serostim 4 mg QD and placebo groups, respectively, across the 2 studies. The CDF curves reflecting the change from baseline to Week 12 in BSE after treatment with Serostim 4 mg QD vs. placebo demonstrate non-responder rates of **~12% and ~25%** for the Serostim 4 mg QD and placebo groups, respectively, in Study 24380. The cumulative percentages of patients with a BSE change score **<-50 (equal to 2 scale units)** were **~40-45% and ~25%** in the Serostim 4 mg QD and placebo groups, respectively, across the 2 studies (**which were amazingly concordant with the percentages displayed in the responder analysis table** !)

1.3.2.2.2 Maintenance Phase: Weeks 12-36 of Study 24380

1.3.2.2.2.1 Background Information

Study 22388: Weeks 12-24

During Study 22388, the reduction in VAT that had occurred from baseline to Week 12 after treatment with Serostim 4 mg QD was not sustained in subjects rerandomized to placebo during Weeks 12-24 **and, in fact, VAT reaccumulated, with a mean increase of 17.7 cm^2 between Weeks 12 and 24**. In contrast, a sustained decrease in VAT was observed in the subjects rerandomized to Serostim 4 mg QOD. **These findings indicated that Serostim maintenance therapy warranted further study.**

Studies 22388-23056 Combined: Weeks 36-60 (Equivalent to Weeks 12-36 of Study 23056)

During the 24 week maintenance period of Study 23056, subjects were assigned to treatment with Serostim 1 mg QD vs. 2 mg QD after being treated with varying doses of Serostim for the

previous 36 weeks. During the maintenance period, the expected reaccumulation of trunk fat after treatment with Serostim 1 mg QD vs. Serostim 2 mg QD was very similar, and subjects sustained a substantial amount of the trunk fat loss that they had achieved during the prior 36 week period. Given the fact that Serostim 1 mg QD had essentially the same efficacy (and safety) profile as Serostim 2 mg QD during the 24 week maintenance period, Serostim 1 mg QD was chosen for further evaluation during the maintenance period in Study 24380.

1.3.2.2.2.2 Study 24380: Weeks 12-36 – Pivotal Placebo Controlled Maintenance Phase

Study 24380 further evaluated the efficacy of Serostim 2 mg QOD (roughly equivalent to the 1 mg QD maintenance dosage chosen after completion of Study 23056 as described above). Subjects treated with Serostim 4 mg QD during the induction phase of Study 24380 (Weeks 0-12) were rerandomized to Serostim 2 mg QOD vs. placebo during a 24 week maintenance phase (Weeks 12-36). During Weeks 12-36, ~54% of subjects treated with placebo were "maintenance treatment failures", compared to ~40% of subjects treated with Serostim 2 mg QOD (maintenance failure had been defined per protocol as regaining, during the maintenance period, >50% of the VAT lost during the 12 week induction period). On the other hand, a comparison of the change from Week 12 to Week 36 in VAT revealed that the amount of expected VAT reaccumulation in both groups was very similar (~23 cm^2 for each group). Furthermore, a comparison of the change from Week 12 to Week 36 revealed less reaccumulation of trunk fat (p=0.045) and non-HDL cholesterol, and less deterioration in LBM (p=0.039) and BAD point score after treatment with Serostim 2 mg QOD (vs. placebo).

1.3.2.2.3 Other Miscellaneous Results of Interest

- Mean baseline VAT levels in Study 24380 (85 cm^2 in females and 143 cm^2 in males) (**enrolled in 2004**) were clearly smaller than the mean baseline VAT levels in Study 22388 (105 cm^2 in females and 156 cm^2 in males) (**enrolled in 2001**). The **explanation** for the baseline differences in **VAT** across the studies probably relates to the fact that the patients enrolled in Study 24380 **were being treated more often with newer generation antiretroviral medications** which have been reported to result in less VAT accumulation. The **explanation** for the baseline differences in **lipid levels** across the studies also probably relates to the fact that the patients enrolled in Study 24380 **were being treated more often with newer generation, more "lipid-friendly" antiretroviral medications**. Nonetheless, despite treatment with newer generation antiretroviral agents, HARS remains associated with a number of clinically significant metabolic abnormalities and an increased risk of atherosclerosis and myocardial infarction. Furthermore, the **greater mean baseline VAT level** in Study 22388 (which many believe contributes significantly to the dyslipidemia seen in HARS patients) in and of itself **may partially explain the greater mean baseline lipid levels** in Study 22388. **None of these differences in baseline parameters across the 2 studies were considered significant enough to preclude the performance of integrated analyses**. **However, since there were differences in important baseline parameters by study, all statistical models used by the sponsor in the efficacy analyses of the pooled/integrated data included an effect parameter for study**.

- The sponsor presented subgroup analyses for subjects in Study 22388 receiving or not receiving concomitant LLA treatment which suggest that Serostim (rhGH) and LLAs may act synergistically in lowering levels of non-HDL cholesterol in patients with HARS, i.e. a significant treatment effect for Serostim 4 mg QOD (vs. placebo) was only observed in patients receiving concomitant therapy with LLAs.

1.3.2.3 Efficacy Conclusions

A. Regarding the approval of Serostim 4 mg QD (as proposed by the sponsor) vs. Serostim 4 mg QOD as a 12 week induction dose:

On the one hand, Serostim 4 mg QD and Serostim 4 mg QOD were equally efficacious in reducing VAT (and potentially reducing long-term cardiovascular risk), and the safety profile for Serostim 4 mg QD was clearly more adverse than the safety profile for Serostim 4 mg QOD (see Safety Conclusions/Recommendations). On its face, this suggests that the smaller dose should be approved for the induction phase.

However, there was a global dose response with regard to the differences in change from baseline to Week 12 in multiple consequential non-PRO and PRO secondary efficacy endpoints (i.e., **trunk fat, abdominal SAT, BAD/BSE**, total fat mass and LBM). **The dose response for trunk fat/abdominal SAT and BAD/BSE are especially important** because it is reasonable to presume that **they are linked** both intuitively and with respect to the fact that the sponsor was able to demonstrate a **statistically significant correlation between improvements in BAD scores (as well as BSE scores) and decreases in trunk fat** (as well as VAT). In other words, **the more substantial decreases in trunk fat and abdominal SAT after treatment with Serostim 4 mg QD (compared with Serostim 4 mg QOD) may have resulted in the more substantial improvements in BAD/BSE when the same comparison is made**, i.e. the greater reductions in trunk fat/abdominal SAT (even absent a greater reduction in VAT) after treatment with the larger dose would appear to be at least part of the reason why the patient's perception of his/her belly size and his/her distress associated with belly size improved to a greater extent. **This may have major clinical implications in that patients with greater improvements in BAD/BSE may be even less inclined to discontinue or be non-compliant with lifesaving antiretroviral therapy** (please refer back to the earlier references indicating that, currently, many patients with HARS do in fact discontinue or are non-compliant with their HAART regimens because of the emotional distress/stigmatization associated with their body/belly dysmorphia)

Furthermore, the more adverse safety profile observed with the full dose is tolerable and acceptable if it is only administered during the 12 week induction period, **and** certain caveats regarding the use of Serostim 4 mg QD are added, i.e. cut back to Serostim 4 mg QOD if significant rhGH-related adverse events should occur, start with Serostim 4 mg QOD in patients considered to be at special risk for rhGH-related adverse effects (see Safety Conclusions and Recommendations).

B. Regarding the approval of Serostim 4 mg QD for men and women (as proposed by the sponsor) vs. approval for men alone:

One the one hand, as summarized in detail in this Medical Officer's Summary of Results, women treated with either dose of Serostim (vs. placebo) did not demonstrate a difference in the change from baseline to Week 12 in VAT. As discussed previously, this may relate to estrogen-mediated resistance to rhGH and/or to the fact that the clearly lower baseline VAT levels in women compared to men predicts a lesser response. On its face, this suggests that the indication should be limited to men.

However, globally speaking, the differences in change from baseline to Week 12 in multiple consequential non-PRO and PRO secondary efficacy endpoints including trunk fat, abdominal SAT, and BAD/BSE were very similar in men and women. Therefore, precisely the same argument can be made for approving Serostim 4 mg QD for women - as was made above with reference to approving Serostim 4 mg QD as the induction dose. Furthermore, **only ~15% of the subjects enrolled in each of the pivotal studies were women, and the studies may have been underpowered to detect a significant treatment effect.**

C. Regarding the approval of Serostim 2 mg QOD as a 24 week maintenance dose (as proposed by the sponsor):

On the one hand, as summarized in this Medical Officer's Summary of Results, during the 24 week maintenance phase of Study 24380, VAT reaccumulated to the same extent after treatment with Serostim 2 mg QOD or placebo (by ANOVA). On the other hand, 1) the Division had previously indicated to the sponsor that if >50% of the subjects who lost VAT during the induction period regained, during the maintenance period, <50% of the VAT originally lost, that would be considered a "maintenance success". In fact, ~60% of subjects treated with Serostim 2 mg QOD met that criteria (vs. 46% in the placebo group); and 2) there was significantly less reaccumulation of trunk fat and deterioration of LBM after treatment with Serostim 2 mg QOD (vs. placebo). The lesser amounts of 1) non-HDL cholesterol reaccumulation and 2) deterioration of the BAD point score after treatment with Serostim 2 mg QOD (vs. placebo) were not statistically significant.

1.3.3 Safety Results/Conclusions

- The AEs that occurred during these trials were the longstanding well known AEs associated with rhGH treatment (especially with large doses) - glucose intolerance and fluid retention-related AEs such as edema, arthralgia, myalgia, carpal tunnel syndrome/hypoesthesia/paresthesias.
- The safety profile of Serostim 4 mg QD was clearly and emphatically different from and more "adverse" than the safety profile of Serostim 4 mg QOD. This safety-related dose response manifested itself over and over including the following:
  --when the data from Studies 22388 and 24380 are integrated, the proportions of subjects who discontinued due to an AE were 1.3%, 5%, and 13.2% in the placebo, Serostim 4 mg QOD and Serostim 4 mg QD groups, respectively

---Amongst the 94 subjects discontinued during the entire drug development program due to an AE, 69% were being treated with Serostim 4 mg QD and ~14% were being treated with Serostim 4 mg QOD
---when the data from Studies 22388 and 24380 are integrated, and AEs with a >5% incidence in any active treatment arm are tabulated, there is a clearcut dose response with respect to each and every rhGH-related AE, i.e. the incidence of edema was 3.8%, 18.8% and 45.4% in subjects treated with placebo, Serostim 4 mg QOD and Serostim 4 mg QD, respectively
---when the data from Studies 22388 and 24380 are integrated, 1.3%, 18.8% and 25.5% of subjects treated with placebo, Serostim 4 mg QOD and Serostim 4 mg QD, respectively, required some type of dose modification due to an AE

- With regard to glucose intolerance-related issues specifically which are clearly expected given that very large amounts of rhGH are being administered to a cohort of HARS patients who already are insulin resistant and possibly glucose intolerant at baseline:
---23 patients were discontinued during drug development en toto because of hyperglycemia (and 13/23 were being treated with Serostim 4 mg QD)
---one of these 23 patients may well have developed overt diabetes mellitus;
---none of these patients were allegedly hospitalized or treated with antihyperglycemic medications and post-study FBG levels were documented as normal in some of them off Serostim, but follow-up data is not available for all of them
---peak FBGs on-study were typically between 100-126 mg/dL, usually transient, but occasionally sustained; peak FBGs >126 mg/dL were most often transient – except of course in the 23 patients who were discontinued because of unacceptable hyperglycemia
---many patients demonstrated FBG increases 2-4 weeks after starting Serostim, but, over time, mean FBG levels returned to normal without discontinuing the drug
---it is well documented that the difference in the change from baseline to Week 12 in FBG after 12 weeks of treatment with Serostim 4 mg QD vs. placebo is ~6 mg/dL; however, the Week 12 FBG level is still usually <100 mg/dL
---in patients treated with Serostim 4 mg QD as induction therapy for 12 weeks followed by 24 weeks of Serostim 2 mg QOD as maintenance therapy, all glucose/insulin parameters of interest become insignificantly different from pre-treatment values by Week 36
- With respect to changes in serum IGF I SDS
---the difference in the change from baseline to Week 12 in serum IGF I SDS after treatment with Serostim 4 mg QD vs. placebo was highly significant and quite robust (+5.7)
---both Serostim 4 mg QD and Serostim 4 mg QOD increased the proportion of subjects with serum IGF I SDS >+2 from <10% to >80% after 12 weeks of treatment
---when subjects were rerandomized to placebo for 24 weeks after 12 weeks of induction therapy, IGF I SDS return to baseline; however, if patients were rerandomized to Serostim 2 mg QOD as maintenance therapy for 24 weeks, a substantial proportion (~50%) of them still had serum IGF I levels >+2 at Week 36. The oncogenic potential of this phenomena remains unknown and controversial. Some authors believe that the concomitant increase in serum IGFBP-3 after treatment with rhGH is in fact cancer-protective.

- There were no changes from baseline in HIV-1 RNA copies or CD4+ lymphocyte counts after treatment

1.3.4 Dosing Regimen and Administration

As suggested for the package insert:

(b) (4)

1.3.5 Drug-Drug Interactions

None have been documented. However, **I agree with this sponsor-proposed addition** to the PRECAUTIONS section of the package insert:

Published in vitro data indicate that growth hormone may be an inducer of cytochrome P450 3A4. In clinical trials of HIV-infected patients with wasting or HARS who were receiving antiretroviral therapy, Serostim did not adversely alter antiretroviral effectiveness, such as mean circulating levels of CD4 counts or HIV-1 RNA (viral load). When Serostim is administered in combination with drugs known to be metabolized by CYP P450 3A4 hepatic enzymes, such as some antiretroviral drugs, it is advisable to monitor the clinical effectiveness of these drugs.

1.3.6 Special Populations

See Efficacy Conclusions and Recommendations regarding gender considerations (i.e., the lack of a VAT response in women treated with any dose of Serostim.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information, Currently Approved Indication and Proposed Indication

Serostim (somatropin [rDNA origin] for injection) is a lyophilized formulation of rhGH.

It is currently indicated for HIV-Associated Wasting or Cachexia - 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.

The sponsor has submitted this supplement in support of the following proposed additional indication:

HIV-Associated Adipose Redistribution Syndrome (HARS) - the reduction of abnormal trunk fat, including visceral adipose tissue, and associated body image distress in patients infected with the human immunodeficiency virus (HIV) being treated concomitantly with antiretroviral therapy.

2.2 Currently Available Treatment for Proposed Indication

None of 7 other rhGH formulations (currently approved for miscellaneous other indications including pediatric and adult growth hormone deficiency [GHD]) are approved for the treatment of patients with HARS. Of note, if a sufficient amount of rhGH was administered, these 7 other rhGH formulations could readily be used to treat patients with HARS.

2.3 Availability of Proposed Active Ingredient in the United States

The rhGH formulations of 7 other sponsors (including Saizen marketed by EMD Serono, Inc.) are available in the United States.

2.4 Important Issues With Pharmacologically Related Products

Not applicable to this supplement.

2.5 Presubmission Regulatory Activity

The original approval of Serostim for the treated of HIV-associated wasting or cachexia (NDA 20-604) occurred on 8/23/96 under Subpart(h). The required Subpart(h) confirmatory study was reviewed by this Medical Officer, and approved by the Division in the summer of 2003.

Following an End-of-Phase II meeting with DMEP on 5/22/02, it was mutually agreed that HARS was a clinical entity worth treating (i.e., a pathological condition warranting intervention), and that the HARS patient population defined in the Phase III clinical development plan was adequately representative of HIV patients with excessive, pathological accumulation of central fat. Therefore, this group of patients was studied in the clinical development program for Serostim for the treatment of HARS. It was agreed that change in VAT would be the primary efficacy endpoint, but that validated PRO outcome data (reflecting the patient's perception of belly size and belly appearance distress) would be essential supporting information.

A pre-sNDA meeting was conducted on 2/18/06 during which the Division and the sponsor fundamentally agreed on the content of the NDA submission.

In addition, Serono's request for orphan drug designation for Serostim for the treatment of patients with HARS was granted by the Office of Orphan Products Development (OOPD) on 3/16/04.

2.6 Other Relevant Background Information

2.6.1 Background Regarding the Targeted Indication - HARS

2.6.1.1 Definition of the HARS Syndrome (and Abnormal Adipose Tissue Accumulation in Patients with HARS)

HARS is a disorder that developed after the advent of HAART in the mid-1990s in the United States and elsewhere. On HAART, many patients with HIV/AIDS display dramatic reductions in viral load and, as a consequence, marked decreases in the frequency of life-threatening AIDS-defining complications, including opportunistic infections, neoplasms, and wasting or cachexia (1-2).

However, advances in antiretroviral therapy have been accompanied by (and may at least in part have directly caused) the emergence of disturbing morphologic and metabolic complications, frequently referred to as HIV lipodystrophy syndrome. Some of these complications (i.e., excess accumulation of VAT and trunk fat) have been referred to as HARS. **HARS is characterized by the abnormal accumulation of trunk fat[a] including VAT[b] (lipohypertrophy)[c] with or without lipoatrophy[d] (SAT depletion primarily in the face and limbs, but also the buttocks and the abdomen) (3-9). HARS, in fact, is a subtype of the HIV lipodystrophy syndrome. Patients with HARS present with central lipohypertrophy, with (~2/3) or without (~1/3) accompanying lipoatrophic features (6-7), and fit within the "lipohypertrophic" or "mixed" subcategories of the HIV lipodystrophy syndrome**. A survey of studies reporting on patients with the HIV lipodystrophy syndrome (through 2003) revealed that the prevalence of HARS was less than 200,000 patients - which qualified this NDA supplement submission for the treatment of HARS with Serostim for an orphan drug designation by the Agency in 2004.

(a) **Trunk fat consisting of all VAT and SAT in the abdomino-pelvic and upper torso area** is usually measured with a DEXA scan. The DEXA scan is also used to measure limb fat (the sum of SAT in the extremities and buttocks). HARS patients also have elevated waist circumferences and waist-to-hip ratios (WHRs) compared to HIV-infected individuals who have not experienced such changes (10).
(b) VAT is usually measured in cm^2 by abdominal CT or magnetic resonance imaging (MRI) scans at the L4-5 level.
(c) Some HARS patients also present with an enlarged dorsocervical fat pad and/or excess accumulation of chest or breast fat (much less frequently than excess VAT) (5, 11-12).
(d) Typically the lipoatrophy observed in patients with HARS (13) is not as severe as that in HIV-infected patients with lipoatrophy alone (4, 14).

2.6.1.2 Factors Associated with the Development of HARS

The pathogenesis for the abnormal central fat accumulation in HARS remains uncertain. HARS develops primarily in HIV-infected individuals who have been receiving HAART, and, more than likely, both antiretroviral drug-related and non-drug/host factors (in the patient being treated with HAART) contribute to the etiology of the syndrome. In this regard, factors found to be associated with abnormal central fat accumulation in HIV-infected patients include 1) longer duration of treatment with antiretroviral agents; 2) lower viral load prior to antiretroviral therapy and viral load below the level of detection during antiretroviral treatment; and 3) older age and higher body mass index (BMI) (15-16).

Initially, it was hypothesized that HIV PIs were the sole agents responsible for the development of HARS and the HIV lipodystrophy syndrome (3, 6). However, it is now believed that the HIV lipodystrophy syndromes can develop in HIV patients treated with any class of antiretroviral therapy, and that the NRTIs, may accelerate the development of the HIV lipodystrophy syndrome (especially SAT lipoatrophy) in patients receiving PIs (17).

Furthermore, HARS and the HIV lipodystrophy syndrome have occasionally been reported in HIV patients who have never been treated with PIs, or any other antiretroviral therapy (5, 18). Patients with documented severe organic GHD (19) and the omnipresent metabolic syndrome (associated with secondary functional GHD) also present with excess VAT (20) (with/without excess abdominal/limb SAT). Therefore, secondary functional GHD (21), as well as paracrine

mechanisms (22), have been postulated as possible etiologic factors for increased VAT in these patients.

2.6.1.3 Clinical Abnormalities & Symptomatology/Consequences in Patients with HARS

2.6.1.3.1 Clinical Symptomatology/Consequences of Abnormal Adipose Tissue Accumulation in Patients with HARS (see Section 2.6.1.1)

Patients with HARS who develop abnormal adipose tissue accumulation in the abdomen may report uncomfortable physical symptoms, including early satiety, gastro-esophageal reflux, peptic ulcer, abdominal distension, abdominal cramping, constipation, diarrhea, respiratory difficulties, and umbilical herniation (5, 12).

HARS patients with dorsocervical fat pads may present with neck/back pain, headache, and decreased mobility at the level of the neck, while patients with huge lipomata in the chest/breast area also report discomforting symptoms (12).

Also see Sections 2.6.1.3.2 and 2.6.1.3.3 with regard to the potential cardiovascular consequences of abnormal adipose tissue accumulation in patients with HARS.

2.6.1.3.2 Metabolic Abnormalities in HARS

HARS patients have a number of cardiovascular risk factors, including: insulin resistance (occasionally leading to the development of impaired glucose tolerance/impaired fasting glucose and even overt non-insulin dependent diabetes mellitus), lipid abnormalities (e.g., elevated total, LDL, or non-HDL cholesterol, reduced HDL cholesterol, and elevated triglycerides – which are often difficult to treat [23]), and hypertension. See references 16, 23-28 as a group.

All of these abnormalities are cardiovascular risk factors and potentially related, at least in part, to the abnormal accumulation of VAT described above in Section 2.6.1.1.

2.6.1.3.3 Cardiovascular Considerations in Patients with HARS

As a consequence of the risk factors discussed in Sections 2.6.1.3.2 and 2.6.1.1 above, HARS patients as a group appear to have a greater than average risk of developing cardiovascular disease.

There have been reports of increased carotid artery intima media thickening and endothelial dysfunction in patients with HIV (28-30). **Increased coronary artery calcifications have been observed on electron beam CT scanning in patients who had developed visceral adiposity after initiating PI therapy** (31). Furthermore, case reports have been published which document the occurrence of myocardial infarction in relatively young HIV infected individuals on PI therapy (23, 32). Large surveys have shown that HIV-infected persons not only have multiple risk factors for premature atherosclerosis, but a higher risk for myocardial infarction

than age-matched HIV-negative controls (27, 33-34). **Other studies have found that HIV-infected persons with fat distribution abnormalities are particularly at risk** (35-36).

2.6.1.3.4 Patient-Reported Outcomes/Psychological Considerations in HARS

A review by Mann et al in 1999 summarized the first 65 post-marketing adverse event reports describing abnormal fat distribution in association with antiretroviral therapy that were voluntarily reported to the Agency (37). Case reports used terms such as "disabling" and "devastating", and described appearances like "a pregnant skeleton," an "apple on a stick," and "having an inner tube-like abdominal distension with butt and legs that were bird-like skinny." (37). In a sample of 105 HIV-infected patients with fat distribution abnormalities, Goetzenich et al. found that 71% reported that the changes in their bodies had an impact on the adequacy of their performance of daily activities. In this sample, ratings of the difficulty of performing daily activities showed a significant correlation with changes in the abdomen ($r = 0.43$, $p < 0.05$) (38). In addition, these patients reported low self-esteem (83%) and an impact of body changes on social contacts (69%) (38).

HIV patients with fat distribution abnormalities may be readily identified by others and therefore experience shame and stigmatization in the workplace and in private life (5, 12).

Another concern regarding HIV/AIDS patients with fat maldistribution is that they are often depressed. Some develop severe depression or suicidal ideation requiring treatment with antidepressant medications and/or psychiatric hospitalization.

2.6.1.3.5 <u>Issue of Potential Non-Compliance with HAART Related to the Body Dysmorphia Associated with HARS</u>

In that the deforming, and often stigmatizing, manifestations of HARS have been attributed, at least in part, to antiretroviral medications, caretakers have become very concerned that HIV patients who have HARS, or who fear developing it, might abandon otherwise effective, lifesaving antiretroviral therapy. In this regard, Kasper et al evaluated the perceptions of HIV-infected patients who claimed that they had experienced body composition alterations (39). Thirty percent had changed drug regimens and 7% had stopped therapy, while more than 50% had thought about changing or stopping therapy, and the remainder claimed they planned to stop or switch therapies if their alterations became worse (39). Other more recent publications have confirmed these findings (40-41).

2.6.1.4 Rationale for the Use of rhGH in Patients with HARS

2.6.1.4.1 Lack of other medical therapies

At the present time, **physicians have no approved medical therapies to treat patients with HARS**. In addition, until recently, it has not been shown that abnormal accumulation of trunk fat/VAT and associated dyslipidemia can be <u>consistently</u> reversed by substituting for, or by discontinuing, the antiretroviral agents which have been linked to central fat accumulation, such

as first generation PIs (12). **However, in the last few years, newer generation antiretroviral medications have been reported not to result in as much VAT accumulation or dyslipidemia as the HAART regimens administered earlier (42-43). This is further evidenced by the significantly smaller baseline levels of VAT and various lipids (including non-HDL cholesterol) in the subjects enrolled in 2004 for the sponsor's second pivotal study (Study 24380) compared with the baseline values observed in the subjects enrolled in 2001 for the sponsor's first pivotal study (Study 22388)** (see Section 6.1.4.2).

2.6.1.4.2 Surgical Considerations in HARS

Surgical procedures may be feasible for the removal of lipomata and dorsocervical fat pads, but these techniques have not been recommended for removal of excess VAT, due to the risk of bowel perforation and other surgical risks. There are also reports that surgically excised adipose tissue reaccumulates (44).

2.6.1.4.3 Lipolytic Effects of rhGH in Patients Without HIV/AIDS and HARS – Adult GHD and the Metabolic Syndrome

Growth hormone has been known to be lipolytic since the earliest days of research into its metabolic effects. Since rhGH first became commercially available in 1985, numerous clinical trials in adult GHD patients have consistently shown that it reduces total body fat, trunk fat, **VAT** and various lipid parameters including total, non-HDL and LDL cholesterol, as well as increasing LBM (45 [2006 Clinical Practice Guideline issued by the Endocrine Society]). In addition, Johannsson et al have reported that rhGH selectively reduces VAT in HIV-negative patients with the metabolic syndrome presenting with excess VAT (46).

2.6.1.4.4 Effect of rhGH in Patients with HIV-Associated Wasting/Cachexia

The lipolytic effects of growth hormone were also noted in Serono's pivotal trials which led to the approval of Serostim for the treatment of patients with HIV-associated wasting/cachexia. In addition to a producing a significant increase in LBM (and work capacity) in these severely underweight patients **without** visceral adiposity, treatment with Serostim 0.1 mg/kg ((up to 6 mg QD) for 12 weeks resulted in a modest reduction in total body fat (47-48).

2.6.1.4.5 Effect of rhGH in Patients with HARS - Early Observations

To date, there have been 5 important preliminary published trials evaluating the efficacy (and safety) of Serostim for the treatment of patients with HARS, 3 in 1999 (49-51), 1 in 2001 (52) and 1 in 2002 (53). Engelson et al published the most significant of these trials in 2002 and demonstrated that treatment with rhGH 6 mg QD (the dose approved for HIV-associated wasting/cachexia) significantly decreased VAT, but also resulted in an unacceptable amount of rhGH-related adverse events (i.e., glucose intolerance, fluid retention) (53). The incidence of rhGH-related adverse events in this trial clearly exceeded the incidence of rhGH-related adverse events previously observed in the pivotal trials wherein patients with HIV-associated

wasting/cachexia were treated with the same dosage of Serostim. This study influenced the sponsor to evaluate the efficacy and safety of a lesser amount of Serostim for the treatment of HARS. The sponsor's 2 sequential pivotal trials are contained in this submission and the results from one of them (Study 22388) has already been published (13).

2.6.1.5 Summary Statement Regarding HARS and Rationale for Treatment with rhGH

In summary, HARS is a clinical entity for which treatment is warranted. As discussed above, the morphological abnormalities associated with HARS impact the physical/psychosocial well-being and self-image of afflicted patients, and may discourage patients from adhering to life-saving, effective antiretroviral therapy. Although the long-term health consequences of HARS are unknown, the presence of numerous metabolic abnormalities (i.e., increased VAT, insulin resistance, dyslipidemia) which are well established cardiovascular risk factors (shared by adults with GHD and the metabolic syndrome) and preliminary observational studies suggest that patients with HARS have an increased risk for cardiovascular disease.
No medical therapies are currently approved for the treatment of HARS. Preliminary studies to date all support the hypothesis that treatment with rhGH significantly reduces trunk fat, especially VAT, in patients with HARS. The sponsor has therefore submitted 2 large pivotal studies for review by the Division in an attempt to gain an indication for Serostim for the treatment of patients with HARS.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

This Medical Officer collaborated extensively and frequently with the Division's Statistical Reviewer/Statistical Team Leader, as well as the consultant from CDER's Study Endpoints and Labeling Development Team (SEALD) (with respect to the instrument utilized to assess patient reported outcomes regarding body image). The most important findings of the Division's Statistical Reviewer and the SEALD consultant have been incorporated in this Medical Officer's review.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data and Review Strategy

The Clinical Overview, Summary of Efficacy, Summary of Safety and individual Clinical Study Reports on Original electronically submitted by the sponsor on 6/12-13/06, the Safety Update electronically submitted by the sponsor on 9/28/06, and revised labeling electronically submitted by the sponsor on 2/6/07 were thoroughly and comprehensively reviewed by this Medical Officer.

In addition, there were multiple phone call conversations between the sponsor and this Medical Officer in February and March 2007 - during which requests for additional information/analyses were made by this Medical Officer. The sponsor responded to these requests with secure email submissions on 2/27/07, 3/2/07, 3/5/07, 3/7/07, 3/8/07, 3/9/07, 3/12/07, 3/13/07, 3/14/07, 3/15/07, 3/16/07, 3/19/07 (twice), 3/20/07 (twice), 3/21/07 (thrice) and 3/22/07 (all of which

material will be submitted to the NDA archive in the near future). All of this material was also thoroughly and comprehensively reviewed by this Medical Officer.

4.2 Tables of Clinical Studies

The pivotal studies (Studies 22388 and 24380) and their extension studies (Studies 23056 and 25373) are briefly described in Table 1. Study designs will be discussed in more detail in Section 6.1.3 below.

Table 1: Listing of Studies Designed to Provide Information Regarding the Efficacy and Safety of Serostim for the Treatment of HARS

Study Number	Number of Study Centers; Start-Completion; Number Treated	Study Design	Primary Efficacy Endpoint(s)
22388 (pivotal)	23 centers in the USA; March 2001/May 2002; 240 received drug	24 week double-blind, randomized, placebo controlled, parallel group, dose finding study. During Weeks 0-12, patients randomized to 3 arms: Serostim 4 mg SC QD (DD) vs. Serostim 4 mg SC QOD (AD) vs. placebo (PL). During Weeks 12-24, patients initially treated with DD were rerandomized to 2 arms (**DD to PL, DD to AD**), PL patients were treated with DD, and AD patients continued to be treated with AD	Change from baseline to Week 12 in 1) cross-sectional area of VAT (measured by CT scan); and 2) trunk:limb fat ratio (measured by DEXA)
23056 (extension study to 22388)	23 centers in the USA; September 2001/ February 2003; 141 received drug	36 week open label, partially randomized, parallel group, dose finding study in patients who completed Study 22388. During Weeks 0-12 patients were randomized to 2 arms: Serostim 4 mg SC QD or Serostim 2 mg SC QD. During Weeks 12-36, patients were rerandomized to Serostim 2 mg SC QD or Serostim 1 mg SC QD (except for patients who had by then been dose reduced)	Percent change in trunk fat (measured by DEXA) from Week 12 to Week 36
24380 (pivotal)	34 centers in the USA; May 2004/ September 2005; 325 received drug	36 week double-blind, randomized, placebo controlled, parallel group study. During Weeks 0-12, patients randomized to 2 arms: Serostim 4 mg SC QD (DD) vs. placebo (PL). During Weeks 12-36, 1) patients initially treated with DD were rerandomized to 2 arms: Serostim 2 mg SC QOD or PL QOD; and 2) patients initially treated with PL received PL QOD for 12 weeks followed by Serostim 4 mg SC QD for 12 weeks	Change from baseline to Week 12 in cross-sectional area of VAT) (measured by CT scan)

25373 (extension study to 24380)	26 centers in the USA; February 2005/?; Results still being analyzed	12 week open label study in patients who completed Study 24380. All patients were treated with Serostim 4 mg SC QD	Change from baseline to Week 12 in trunk fat (measured by DEXA)

4.4 Data Quality and Integrity

Monitoring visits by the sponsor were adequate. Case report forms (CRFs) were compared with source documents and checked for completeness and accuracy. 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 Division's Statistical Reviewer expressed confidence in the raw SAS data provided by the sponsor.

4.4.1 DSI Inspections

Two inspections were performed. The performance of Dr. Steven Brown (Investigator in West Hollywood, CA - 32 patients randomized) **revealed no deficiencies**. CRFs accurately reflected source documents at the site. The performance of Dr. Gary Richmond (investigator in Ft. Lauderdale, FL - 29 patients randomized) revealed **will take place last week in March 2007 – delayed** because of a shortage of Agency inspectors in the South Florida area.

4.5 Compliance with Good Clinical Practices

The sponsor appeared to adhere to appropriate clinical practices in conducting the clinical trials. The sponsor states that frequent inspections and audits were performed to ensure that investigators at various were complying with all of the protocols and their amendments - including protocol-specified procedures for ensuring patient compliance with study drug administration.

4.6 Financial Disclosures

Complete financial disclosure information was submitted by the sponsor and reviewed by this Medical Officer. **With 1 exception (see below*), none** of the 8 primary investigators or 37 subinvestigators who participated in Study 22388, 13 primary investigators or 62 subinvestigators who participated in Study 23056, or 18 primary investigators or 100 subinvestigators who participated in Study 24380 **had any financial information to disclose**.

More specifically, none of these investigators 1) had compensation potentially affected by the outcome of the studies; 2) received significant payments of other sorts by the sponsor of the studies; 3) had proprietary interest in the tested products; or 4) had significant equity interest in the sponsor of the tested product.

(b) (4) applied for a grant in excess of $25,000 from the sponsor in November 2005. He had participated (b) (4) in

Studies [redacted] (b) (4) His last patient contact [redacted] (b) (4) was in September 2005 (which made him eligible for grant consideration 1 year later in September 2006). **As of this time, the sponsor has not considered** [redacted] (b) (4) **grant request**.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication Proposed by the Sponsor

HIV-Associated Adipose Redistribution Syndrome (HARS)

Serostim is also indicated for the reduction of abnormal trunk fat, including visceral adipose tissue, and associated body image distress in patients infected with the human immunodeficiency virus (HIV) being treated concomitantly with antiretroviral therapy.

6.1.1 Methods

See Section 4.1 above.

6.1.2 General Discussion of Endpoints

6.1.2.1 Efficacy Endpoints

The primary efficacy endpoint for both pivotal studies (Studies 22388 and 24380) **was change in the cross-sectional area of VAT (cm^2)** (measured by CT scan at the L4-5 level). Other consequential secondary efficacy endpoints (common to both pivotal studies) included additional measures of body composition (changes in abdominal SAT by CT scan, **trunk fat** by DEXA scan, and dorsocervical fat pad), and changes in various lipid parameters. As discussed earlier in Section 2.6, patients with HARS are thought to be at greater risk for cardiovascular disease because of increased amounts of VAT, adverse lipid profiles and insulin resistance; **however, long-term outcome data correlating a reduction in VAT with decreased cardiovascular risk are not currently available**. In addition, as noted/referenced earlier in Section 2.6, the body dysmorphia and attendant psychological distress associated with the accumulation of VAT and central obesity per se has been reported to result in non-compliance with life-sustaining HAART. Therefore, for both of these reasons, **the Division and the sponsor mutually agreed prior to the initiation of the 2 pivotal studies that improvement in endpoints obtained with a validated PRO instrument reflecting the patient's perception of changes in his/her body image would be extremely important to support an indication for HARS**. As a result, the sponsor submitted validation data for the BIIM [redacted] (b) (4) prior to launching the second Phase III pivotal study (Study 24380), and also within this supplemental NDA submission. **Changes in BAD, BSE and BPA were mutually agreed to be the most consequential components of the BIIM, and this Medical Officer will therefore focus almost exclusively on these particular PRO results**.

6.1.2.2 Safety Endpoints

The primary safety endpoints for both pivotal studies were **measures of glucose tolerance**, serum IGF I levels, the well known rhGH-related adverse events related to fluid retention (i.e., edema, arthralgia, myalgia, carpal tunnel syndrome, etc), and measures reflecting the activity of preexisting HIV infection, i.e. viral load (HIV-1 RNA) and CD4 T-helper lymphocyte count.

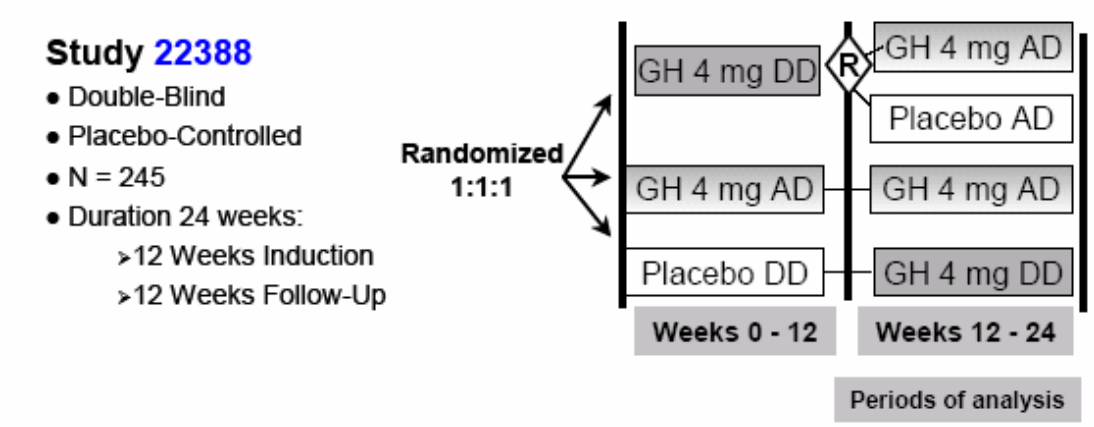
6.1.3 Study Designs for Studies 22388 (& 23056) and Studies 24380 (& 25373)

6.1.3.1 Study Design for Study 22388 (and Study 23056 - the extension study for completers of Study 22388)

6.1.3.1.1 General Description (including rationale for dosing)

Study 22388 was a 24 week, randomized, double blind, placebo controlled, parallel group, **dose finding** study. During Weeks 0-12 (induction phase), patients were randomized to 3 arms: Serostim 4 mg SC QD (DD) vs. Serostim 4 mg SC QOD (AD) vs. placebo (PL). As discussed earlier in Section 2.6, treatment of HARS patients with Serostim 6 mg SC QD (the dose of Serostim approved for AIDS wasting) was associated with an excessive amount of adverse effects and glucose intolerance); **therefore, it was decided to compare the efficacy Serostim 4 mg SC QD and Serostim 4 mg SC QOD vs. placebo - in order to ascertain the best dose for induction**. During Weeks 12-24, patients initially treated with DD were rerandomized to 2 arms (DD to PL and DD to AD), PL patients were treated with DD, and AD patients continued to be treated with AD. **The primary focus of this Medical Officer's review of Study 22388 will be on the results from the induction period, Weeks 0-12**. Only brief descriptive comments will be made regarding the results from Weeks 12-24. See Figure 1 below and also Table 1 above.

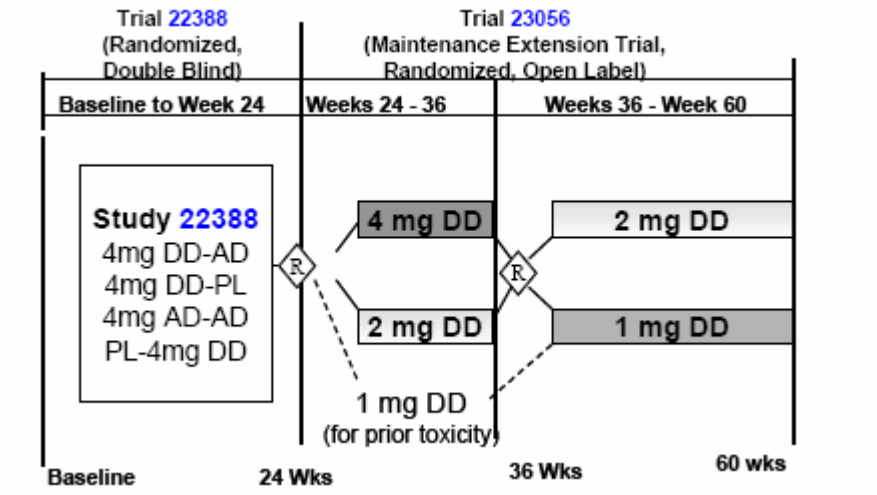
Figure 1: Schematic Study Design – Study 22388



Study 23056 was 36 week, open label, partially randomized, parallel group, dose finding study in **patients who completed Study 22388**. During Weeks 0-12 (equivalent to Weeks 24-36 of Studies 22388-23056 combined), patients were randomized to 2 arms: Serostim 4 mg SC QD or Serostim 2 mg SC QD (a "reinduction" of sorts for certain patients). **During Weeks 12-36**

(equivalent to Weeks 36-60 of Studies 22388-23056 combined), patients were rerandomized to Serostim 2 mg SC QD or Serostim 1 mg SC QD (except for patients who had by then been dose reduced because of adverse events). **The objective of Study 23056 was to determine the best 6 month maintenance dose of Serostim following treatment with a larger dose of Serostim during the induction period**. **This Medical Officer will therefore briefly describe the results of Weeks 12-36 (which led to the selection of the maintenance dose used in the second pivotal study, Study 24380) in this review**. See Figure 2 below and also Table 1 above.

Figure 2: Schematic Study Design – Studies 22388-23056 Combined



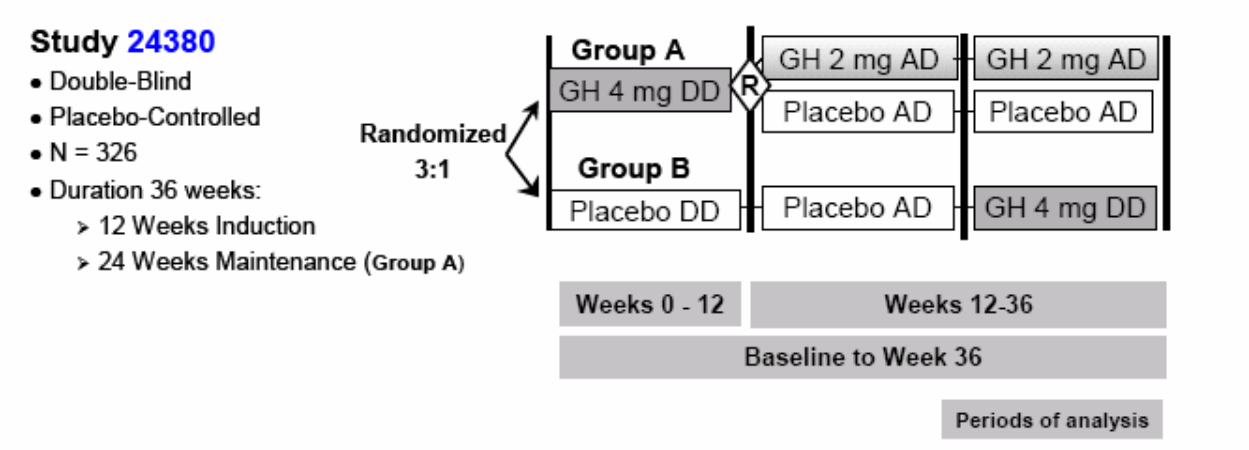
6.1.3.2 Study Design for Study 24380 (and Study 25373 - the extension study for completers of Study 24380)

6.1.3.2.1 General Description (including rationale for dosing)

Study 24380 was a 36 week, double blind, randomized, placebo controlled, parallel group study. During Weeks 0-12 (induction phase), patients were randomized to 2 arms: Serostim 4 mg SC QD (DD) vs. placebo (PL). **Serostim 4 mg SC QD (rather than Serostim 4 mg SC QOD) was chosen as the preferred dose for induction based on the results observed during Study 22388**. With respect to most efficacy parameters (except reduction in VAT), Serostim 4 mg SC QD appeared to be more efficacious than Serostim 4 mg SC QOD in Study 22388. The safety profile of Serostim 4 mg SC QOD was (not unexpectedly) clearly more "benign" than that of Serostim 4 mg SC QD; however, the safety profile of Serostim 4 mg SC QD was felt to be tolerable and acceptable for a 12 week induction period, given the better overall efficacy observed with Serostim 4 mg SC QD. **The efficacy and safety results comparing Serostim 4 mg SC QD and Serostim 4 mg SC QOD during the 12 week induction period in Study 22388 (which led to the sponsor's decision to use Serostim 4 mg SC QD as the induction dose in Study 24380) will be presented in detail in this Medical Officer's review**. See Figure 2 below and also Table 1 above.

During Weeks 12-36, 1) patients initially treated with Serostim 4 mg QD were rerandomized to 2 arms: Serostim 2 mg SC QOD or PL QOD (in effect, a blinded randomized withdrawal); and 2) patients initially treated with PL received PL QOD for 12 weeks followed by Serostim 4 mg SC QD for 12 weeks. **Serostim 2 mg SC QOD was chosen as the 6 month maintenance dose in Study 24380 because the efficacy results observed during Weeks 12-36 in Study 23056 showed no difference between Serostim 1 mg SC QD and Serostim 2 mg SC QD. The results from the 6 month maintenance period (Weeks 12-36) in Study 24380 will be summarized in this review**. See Figure 3 below and also Table 1 above.

Figure 3: Schematic Study Design - Study 24380



Study 25373 was a 12 week open label study for patients who completed Study 24380. All patients were treated with Serostim 4 mg SC QD in order to gather additional efficacy and safety data.

6.1.3.3 Major Inclusion/Exclusion Criteria/Discontinuation Criteria for Studies 22388 and 24380

The major inclusion/exclusion/discontinuation criteria for Studies 22388 and 24380 **were almost identical**. The major criteria are bulleted below:

Inclusion Criteria:

- Between 18 and 60 years of age
- **Evidence of excess abdominal adipose deposition using the following cut-points (54):**
  − Men: Waist circumference >88.2 cm (34.7 inches) and waist/hip ratio ≥0.95
  − Women: Waist circumference >75.3 cm (29.6 inches) AND waist/hip ratio ≥0.9
- Weigh ≥36 kg (79.3 lb)
- HIV infection documented either by viral load measured by polymerase chain reaction (PCR) amplification; or by the presence of HIV antibodies with confirmation by one of the following: western blot, immunofluorescence assay, branched DNA (bDNA) signal amplification, or 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's monitor prior to randomization.

- Under therapy with antiretroviral medication(s) which is (are) approved or is (are) available under a Treatment IND. The regimen must have remained stable for the 30 days prior to study entry. Patients must also have agreed not to discontinue or change their regimen for the duration of the study, except as judged medically necessary.
- **Fasting glucose <110 mg/dL and 2 hour (120 minute) post-prandial glucose <140 mg/dL**
- Fasting triglycerides ≤1,000 mg/dL
- AST, ALT, and amylase ≤3 times the upper limit of normal
- If female, post-menopausal, surgically sterilized, or using an appropriate contraceptive method for the duration of the study, and not pregnant or breast-feeding

Exclusion Criteria:

- Presence of an active AIDS-defining opportunistic infection as defined by the Center for Disease Control; or an untreated or suspected serious systemic infection, or persistent fever ≥101°F (38.3°C) during the 30 days prior to study entry
- History of any active malignancy, except for localized cutaneous Kaposi's sarcoma (fewer than 10 lesions none of which are larger than 2 cm, and not on active therapy)
- History of central nervous system (CNS) mass or active CNS process associated with neurological findings
- Presence of unstable or untreated hypertension, defined as ≥140/90 mm Hg, and/or has initiated or changed antihypertensive therapy in the 30 days prior to Day 1
- Presence of coronary artery disease/angina pectoris
- Presence of an acute critical illness treated in an intensive care unit, e.g. due to complications following open heart surgery/abdominal surgery/multiple accidental trauma, or acute respiratory failure
- History of any of the following: diabetes mellitus, any disorder associated with moderate to severe edema, carpal tunnel syndrome (unless resolved by surgical release), pancreatitis, allergy/hypersensitivity to rhGH
- Recent history of sleep apnea or intermittent upper respiratory obstruction (Study 24380 only)
- Presence of any condition which interferes with informed consent or protocol compliance including, but not limited to, active substance abuse and/or dementia

Discontinuation Criteria:

- AEs/Toxicity (see Section 6.1.3.4 ahead regarding **severe AEs/rhGH-related toxicity leading to <u>immediate study/drug discontinuation</u>; severe AEs/rhGH-related toxicity leading to drug suspension (and <u>study/drug discontinuation</u> if the toxicity did not resolve within 7 days or if the toxicity reoccurred after resumption of treatment at a reduced dose); and moderate AEs/rhGH-related toxicity leading to dose**

reduction/adjustment (and study/drug discontinuation if moderate AEs/rhGH-related toxicity did not resolve within 7 days S/P dose reduction)
- New or recurrent malignancy
- Acute critical illnesses treated in an intensive care unit, e.g. due to complications following open heart surgery/abdominal surgery/multiple accidental trauma, or acute respiratory failure
- Serious intercurrent illness or significant worsening of intercurrent illness
- **Violation of concomitant therapy restrictions, including discontinuation of antiretroviral therapy**
- Missing 7 consecutive doses or a total of 20 doses of study drug
- Protocol violations, including non-compliance and loss to follow-up
- Failure to undergo the Week 12 CT Scan
- Pregnancy

6.1.3.4 Dose Adjustment Criteria for Studies 22388 and 24380

The dose adjustment criteria (discontinuation, hold/suspend dosing, reduction) for Studies 22388 and 24380 **were almost identical**. The major criteria are bulleted below:

Study participants experiencing any of the following were to be discontinued immediately and were not allowed to resume the 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 the appearance of any new lesions)
- Severe systemic allergic manifestations (e.g., bronchospasm, laryngospasm, desquamation) thought to be related to Serostim administration

Severe Toxicity:

Study drug treatment was to be **suspended** for the following severe toxicities:

- **Severe hyperglycemia (symptomatic, any fasting blood glucose ≥140 mg/dL, or any 2 hour post-prandial/random glucose ≥240 mg/dL)**
- Severe paresthesias
- Marked hypertension (symptomatic, or ≥200/110 mm Hg)
- Congestive heart failure
- Pancreatitis
- Serum triglycerides ≥1,800 mg/dL

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 or, if the severe toxicity reoccurred at the reduced dose, the individual was to be removed from the study**.

Moderate Toxicity:

Study drug treatment was to be **reduced by 50%** for the following moderate toxicities:

- **Any fasting blood glucose level between 125 and 140 mg/dL or any 2 hour post-prandial/random blood glucose between 199 and 240 mg/dL**
- Intolerable tissue turgor
- Intolerable arthralgias - not responsive to anti-inflammatory therapy
- Carpal tunnel syndrome
- Asymptomatic hypertension (between 140/90 and 200/110 mm Hg)
- Serum triglyceride levels between 1200 mg/dL and 1800 mg/dL
- Moderate systemic allergic reaction (e.g., pruritus, erythema)

If symptoms did not resolve within 7 days of the initial dose reduction, treatment was to be withheld completely and the patient was to be removed from the study. If all symptoms resolved within 7 days of initiating the reduced dose (50% of initial), the patient was to continue dosing at 50% of the initial dose. If symptoms recurred, the patient was to be withdrawn from the study.

6.1.3.5 Prior and Concomitant Therapy for Studies 22388 and 24380

During Studies 22388 and 24380, investigators may have prescribed any medications considered necessary for the subject's welfare, unless the medications interfered with the study medication. **All subjects must have adhered to the antiretroviral therapy requirements described in the inclusion criteria**. In addition, patients were specifically allowed to continue LLAs, anti-hypertensive medications and anti-depressant medications.

The following medications were not allowed during the trial or for the **3** months prior to the screening visit (unless otherwise indicated below):

- **Anti-diabetic medications**
- Therapy for obesity including anorexigenic or fat reducing drugs
- Liposuction or other elective plastic surgery
- Systemic glucocorticoids
- Appetite stimulants such as dronabinol (Marinol), megestrol acetate (Megace), or cyproheptadaine (Periactin)
- **Prior treatment with a rhGH formulation other than Serostim**, or other AIDS wasting therapy (for **12** months prior to the screening visit)
- Androgenic agents* including, but not limited to, testosterone, nandrolone (Decadurabolin), oxandrolone (Oxandrin), oxymetholone (Anadrol), dehydroepiandrosterone (DHEA), etc
  ***Testosterone replacement therapy for hypogonadism was the exception to this exclusion and was to be allowed if started >30 days prior to study Day 1**

- Progestational agents, unless used for oral contraception or post-menopausal hormone replacement therapy
- Systemic chemotherapy, interferon or radiation therapy treatment

6.1.3.6 Efficacy and Safety Endpoints for Studies 22388 (& 23056) and 24380

See Section 6.1.2.1 (and 6.1.2.2 as well) for an overview of the most consequential endpoints. The efficacy and safety endpoints for Studies 22388 and 24380 **were almost identical**. **This review will focus on the endpoints measured during the induction phase (Weeks 0-12) of Studies 24380 and 22388**. Similar endpoints were monitored during the placebo-controlled maintenance phase (Weeks 12-36) of the second pivotal study, Study 24380.

6.1.3.6.1 Efficacy Endpoints

6.1.3.6.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint was change in **VAT** (cm^2) measured by CT scan at the L4-5 level (in Study 22388, trunk fat/limb fat ratio was a co-primary efficacy endpoint).

6.1.3.6.1.2 Non-PRO Secondary Efficacy Endpoints

The non-PRO secondary efficacy endpoints were **changes in other measures of body composition and lipid parameters**:

- **Abdominal SAT** (cm^2) measured by CT scan at the L4-5 level
- **Trunk Fat** measured by DEXA
- Trunk fat/Limb fat ratio, Limb Fat, and Total Fat measured by DEXA
- LBM measured by DEXA
- Anthropometric indices including Waist Circumference and WHR
- **Cervicodorsal Fat Pad** (cm^2) measured with a tape measure (in Study 22388, cervicodorsal fat pad [when present] was quantitated with a CT scan at the T1-2 level)
- Total Cholesterol, LDL cholesterol, HDL cholesterol, **non-HDL cholesterol**, HDL cholesterol/LDL cholesterol ratio

The focus of this Medical Officer's review with regard to the non-PRO secondary efficacy endpoints will be on changes in Abdominal SAT, Trunk Fat, Total Body Fat, Dorsocervical Fat Pad, non-HDL cholesterol and LBM.

CT scans and DEXA scans were performed at baseline and Week 12 with regard to the induction phase in Studies 24380 and 22388, and Week 36 with regard to the maintenance phase in Study 24380. DEXA scans were also performed at Weeks 24, 36 and 60 of Studies 22388-23056 combined (equivalent to Baseline, Week 12 and Week 36 of Study 23056).

Lipid profiles and anthropometric measurements were obtained at baseline and every 12 weeks thereafter during Studies 24380 and 22388/23056.

6.1.3.6.1.3 PRO Secondary Efficacy Endpoints

See Section 6.1.2.1 for a discussion of the rationale for including validated PRO measurements in these studies, i.e. the lack of outcome data demonstrating that reduction in VAT in patients with HARS diminishes adverse cardiovascular outcomes, and the reported relationship between the body dysmorphia observed in patients with HARS and non-compliance with life-sustaining HAART. Toward this end, the sponsor subcontracted [redacted] (b) (4) to assess the impact of HARS-associated body dysmorphia (e.g., big belly +/- dorsocervical fat pad +/- thin extremities, face, & buttocks) on the patient's psyche/emotional well being (and perhaps compliance with HAART) at baseline and after treatment with Serostim vs. placebo. [redacted] (b) (4). As discussed in Section 6.1.2.1, the sponsor submitted validation data for the BIIM prior to launching the second Phase III pivotal study (Study 24380). These data were extensively reviewed by the Agency's SEALD team at that time at the request of this Medical Officer and DMEP. It was mutually agreed at that time and also at the pre-NDA meeting that **changes in BAD, BSE and BPA were the most validated and consequential components of the BIIM. This Medical Officer will therefore focus almost exclusively on these particular PRO results in this review** (although in fact the sponsor included analyses of the many other facets of the BIIM, as well as results from the health-related quality of life module in its submission). **The SEALD team was again consulted and actively assisted this Medical Officer with 1) the review of the additional validation data included by the sponsor in this NDA supplement submission; and 2) how to best label these findings**.

A brief description of the methodology employed to obtain BAD, BSE and BPA scores follows:

Change in BSE

The BSE component of the BIIM was designed to assess the patient's perception of the difference between his/her "current appearance" belly size and his/her "healthy look" belly size (at baseline and various post-treatment endpoints, i.e. Week 12 at the completion of the induction phase of both studies). Specifically, patients were asked the following question

The following statements are about your appearance. Think about how you would look if you were "healthy". Now consider your "current appearance". Compared to your "healthy look", please comment about how you feel regarding the current size of your belly. Compared to my "healthy look", my current belly size is....(the patient then was asked to select a phrase and was assigned a score):

Number	Meaning
1. (-100)	= A great deal less/very much smaller or thinner
2. (-75)	= A lot less/much smaller or thinner
3. (-50)	= Somewhat less, smaller or thinner
4. (-25)	= A little less, smaller or thinner
5. 0	= About right
6. (+25)	= A little more or bigger
7. (+50)	= Somewhat more or bigger
8. (+75)	= A lot more or much bigger
9. (+100)	= A great deal more or very much bigger

Numbers 1 through 9 map to a continuous scale of -100 to +100 with a midpoint of 0 (number 5). For BSE, 1 scale unit or number = 25 points. The bi-directional responses measured deviation from "healthy look".

Change in BAD

Once again using "current appearance" as the reference point, patients indicated **the degree of distress associated with belly size**. The question was phrased as follows:

Think about your "current appearance". The following statements are about how you feel about the size of your belly....(the patient then was asked to select a phrase and was assigned a score):

Number	Meaning
1. (0)	= Extremely upsetting and distressing
2. (12.5)	= Very upsetting and distressing
3. (25)	= Quite upsetting and distressing
4. (37.5)	= A little upsetting
5. (50)	= No feeling either way
6. (62.5)	= A little encouraging
7. (75)	= Quite encouraging
8. (87.5)	= Very encouraging
9. (100)	= Extremely encouraging

Numbers 1 through 9 map to a continuous scale of 0 to 100 with a midpoint of 50 (number 5). For BAD, 1 scale unit or number = 12.5 points. The bi-directional responses measured deviation from "healthy look".

BPA at Baseline and Change in BPA

The patient selected from 6 belly profile images/cartoons (which reflected an increasingly large belly area wherein number 0 was normal, and numbers 1 through 5 projected a progressive increase in belly size) the images best reflecting answers to the following questions:

- **Most how you think you look today? - the "current look" profile**
- You would most like to look? – the "ideal" or "goal" profile
- **Smallest amount of improvement that you consider beneficial to your health and well being? – the "minimum benefit" or "minimal beneficial improvement" profile**

The numerical product of the "minimum benefit" for the BPA at baseline (prior to any treatment) and the change score from baseline to Week 12 in BPA was used an anchor to calibrate/validate the "minimum benefit" for BAD and BSE (using a regression line derived from blinded data). The "minimum benefits" for BAD and BSE were then used as responder criteria for responder analyses comparing treatment groups (see Sections 6.1.3.7.3 and 6.1.4.4.1.8.1). It is important to note that the Division's SEALD consultant completely agreed with the above described derivation of responder criteria.

It should be noted that the "minimum benefit" for the BPA and the change score for the BPA was also generated based on the perceptions of the patient's treating physician; however, it was felt by the Agency's SEALD consultant that patient-derived data (as described above) would be more appropriate for these analyses.

PRO measurements were obtained at baseline and every 12 weeks thereafter during Studies 24380 and 22388/23056.

6.1.3.6.2 Safety Endpoints

In Study 24380, basic safety laboratory evaluations (including **fasting blood glucose [FBG] levels**) were obtained at baseline and Weeks 2, 4, 12, 16, 24, 26, 28 and 36. In Study 22388, basic safety laboratory evaluations (including **fasting blood glucose levels**) were obtained at baseline and Weeks 2, 4, 12, 14, 16 and 24. In both Studies 24380 and 22388, **glucose tolerance tests (GTT) (with insulin levels)** were performed at baseline and every 12 weeks thereafter; and **hemoglobin A1C levels, serum IGF I and IGF I SDS, anti-rhGH antibody titers, and HIV-1 RNA/CD4 T-helper lymphocyte counts** were obtained at baseline and every 12 weeks thereafter. In Study 23056, these same measurements were obtained at similar intervals.

6.1.3.7 Statistical Methods for Studies 24380 and 22388/23056

6.1.3.7.1 Sample Size Calculations for the Induction Phase

Study 22388: A total of 228 patients would provide 97% power to detect a significant difference in reduction from baseline to Week 12 in the absolute area of VAT between each Serostim treatment group and the placebo group when in fact the difference in reduction is 48.3 cm^2. This calculation was performed using a two-sided Wilcoxon Rank-Sum test assuming a 2.5% overall Type I error in order to ensure the study was powered for a significant difference for at least 1 Serostim dose vs. placebo. The calculation assumed a 85.6% common standard deviation for the change from baseline to Week 12 in the absolute area of VAT. The standard deviation estimate was derived from data obtained from 24 patients in an investigator-initiated pilot study sponsored by the company (53). The sample size calculations assumed a 25% unevaluable/withdrawal rate so that the original calculation of 171 (57 per group) total patients was increased by 25% in order for **both** the modified ITT **and** evaluable/completer populations to be sufficiently powered.

Study 24380: A sample size of 300 subjects was needed (225 subjects assigned to Serostim 4 mg daily, and 75 subjects assigned to placebo). Assuming a drop out rate of 20%, a total of 240 subjects at Week 12 would provide 91% power to detect the difference in change from baseline to Week 12 in VAT between the Serostim 4 mg daily and placebo groups when in fact the difference in change existed (for **both** the ITT **and** evaluable/completer populations). The calculation was based on a two-sided t-test with unequal "n" (180 subjects in the Serostim 4 mg daily group and 60 subjects in the placebo group), a 5% type I error rate, a mean difference of the changes in VAT of 25 cm^2, and a common standard deviation of the changes in VAT of 50 cm^2. The standard deviation was based on the actual value from Study 22388.

6.1.3.7.2 Definitions of Populations for Analysis

In both studies, the intent-to-treat (ITT)/safety population consisted of all patients who received at least 1 dose of study drug. The “non-specific” modified ITT population consisted of all patients who received at least 1 dose of study drug, and who had at least 1 post-baseline assessment of any kind. The number of patients in the “specific” modified ITT populations varied according to the efficacy or safety parameter measured. **The modified ITT populations were the protocol-designated primary/preferred populations for all efficacy analyses in both studies**. The evaluable/completer population was of secondary interest..

6.1.3.7.3 Efficacy Analyses

Induction Phase

The statistical methods used to analyze the induction phase efficacy results for Studies 22388 and 24380 **were similar**. (b) (4)

The Division’s Statistical Reviewer

and Statistical Team Leader disagreed with this approach (i.e., standard operating procedure in DMEP is to perform (b) (4) **and reperformed the analyses on the primary endpoint (change in VAT) for each pivotal study using non-proportionally weighted, standard ANCOVA models (with baseline VAT as the single covariate, and effects for treatment, gender, and the treatment by gender interaction)**. The sponsor reperformed the analyses on the most consequential non-PRO secondary efficacy endpoints for each pivotal study (and both studies combined*) using non-proportionally weighted, standard ANOVA models (with effects for treatment, gender, and the treatment by gender interaction). All of the reperformed analyses generated **ordinary** (b) (4) least squares means for within-group changes from baseline to Week 12 and between-group differences vs. placebo.

*Since there were differences in several baseline parameters by study (including VAT and non-HDL cholesterol), all statistical models used by the sponsor in the efficacy analyses of the pooled/integrated data included an effect parameter for study.

The Division's Statistical Reviewer also performed a gender subgroup analysis for VAT, and constructed **cumulative distribution functions (CDFs) for the change in VAT** (as well as the changes in BAD and BSE, the most consequential PRO secondary efficacy endpoints).

The sponsor utilized Fisher's exact t-test to perform responder analyses for BAD and BSE (see Section 6.1.3.6.1.3 and 6.1.4.4.1.8.1 for a description of how responder criteria were derived), and an ANCOVA model (adjusted for baseline score and age with effects for treatment, gender and their interaction) for changes in BAD and BSE (as well as BPA).

Maintenance Phase

The statistical methods used by the sponsor to analyze the maintenance phase efficacy results for Study 24380 (Weeks 12-36) are described in Section 6.1.4.4.2 ahead (together with the results of these analyses).

Therefore, the efficacy results reflected in this Medical Officer's review derive from analyses performed by both the Division's Statistical Reviewer and the sponsor as well.

6.1.3.7.4 Safety

Safety results were presented utilizing descriptive statistics. Analyses of the glycemic response after treatment with Serostim vs. placebo were also presented with shift tables. Distribution of response analyses for the serum IGF I SDS response after treatment with Serostim vs. placebo were also presented with "stacked bar graphs".

6.1.4 Efficacy Findings

6.1.4.1 Enrollment and Disposition

As seen in Table 2, 946 subjects were screened in both studies. Given that glucose intolerance is a common finding in patients with HARS, it is not surprising that the most common reason for "screening failure" was a glucose abnormality (exclusion criteria for both studies included fasting glucose >110 mg/dL, 2 hour post-prandial glucose >140 mg/dL or both) (~50% of the 375 screening failures).

Overall, 327 subjects were randomized to Serostim 4 mg QD (82 in Study 22388 and 245 in Study 24380) and 162 were randomized to placebo (81 in each of Studies 22388 and 24380). Eighty two patients randomized to Serostim 4 mg SC QOD in Study 22388 are not included in Table 2.

82 subjects in Study 22388 and 244 subjects in Study 24380 (overall, 326) received at least 1 dose of Serostim 4 mg QD, and **78 subjects in Study 22388 and 81 in Study 24380 (overall, 159)** received at least 1 dose of placebo (**the safety population or ITT population**).

82 subjects in Study 22388 and 243 subjects in Study 24380 (overall, 325) received at least 1 dose of Serostim 4 mg QD **and had at least 1 post-baseline assessment of ANY kind,** and **78 subjects in Study 22388 and 79 in Study 24380 (overall, 157)** received at least one dose of placebo and had at least 1 post-baseline assessment of ANY kind (**the modified ITT population for ANY post-baseline assessment**).

With regard to the modified ITT population, the percentage of subjects completing the 12 week induction period was similar across the 2 studies. In Study 22388, 70/82 subjects (85.4%) in the Serostim 4 mg QD group and 76/78 subjects (97.4%) in the placebo group completed 12 weeks, while in Study 24380, 200/243 subjects (82.3%) in the Serostim 4 mg QD group and 74/79 subjects (93.7%) in the placebo group completed 12 weeks.

Table 2: Subject Disposition During Weeks 0 to 12 for Studies 22388 and 24380, Separately and Combined, by Treatment Group

	Study 22388		Study 24380		All Subjects	
Disposition	**Placebo n (%)**	**Serostim 4 mg daily n (%)**	**Placebo n (%)**	**Serostim 4 mg daily n (%)**	**Placebo n (%)**	**Serostim 4 mg daily n (%)**
Subjects Screened	409		537		946	
Subjects Not Randomized (Screen Failures) (denominator for %)	**164 (40.1)**		**211 (39.3)**		**375 (39.6)**	
Glucose Abnormality at Screen	**78 (47.6)**		**119 (56.4)**		**197 (52.5)**	
Fasting Glucose >110 mg/dL	8 (4.9)		19 (9.0)		27 (7.2)	
120 Minute Glucose >140 mg/dL	49 (29.9)		73 (34.6)		122 (32.5)	
Both Glucose Abnormalities Met	21 (12.8)		27 (12.8)		48 (12.8)	
Anthropometric Criteria Not Met	23 (14.0)		19 (9.0)		42 (11.2)	
Other Inclusion/Exclusion Criteria Not Met	42 (25.6)		27 (12.8)		69 (18.4)	
Subject Decision	11 (6.7)		30 (14.2)		41 (10.9)	
Other	10 (6.1)		16 (7.6)		26 (6.9)	
Subjects Randomized[a]	**81 (19.8)**	**82 (20.0)**	**81 (15.1)**	**245 (45.6)**	**162 (17.1)**	**327 (34.6)**
Subjects Did Not Receive Study Drug	3 (3.7)	0	0	1 (0.4)	3 (1.9)	1 (0.3)
Protocol Violation	1 (33.3)	0	0	0	1 (33.3)	0
Subject Decision	1 (33.3)	0	0	1 (100.0)	1 (33.3)	1 (100.0)
Other	1 (33.3)	0	0	0	1 (33.3)	0
Subjects Received Study Drug (Safety) (ITT)[b]	**78 (96.3)**	**82 (100.0)**	**81 (100.0)**	**244 (99.6)**	**159 (98.1)**	**326 (99.7)**
Subjects Without Post-Baseline Assessment	0	0	2 (2.5)	1 (0.4)	2 (1.3)	1 (0.3)
Subject Decision	0	0	2 (100.0)	1 (100.0)	2 (100.0)	1 (100.0)
Subjects With *ANY* Post-Baseline Assessment (Modified ITT)[c]	**78 (100.0)**	**82 (100.0)**	**79 (97.5)**	**243 (99.6)**	**157 (98.7)**	**325 (99.7)**
Subjects Did Not Complete Week 12	**2 (2.6)**	**12 (14.6)**	**5 (6.3)**	**43 (17.7)**	**7 (4.5)**	**55 (16.9)**
Subjects Completed Week 12	**76 (97.4)**	**70 (85.4)**	**74 (93.7)**	**200 (82.3)**	**150 (95.5)**	**270 (83.1)**
Subjects Withdrew after Week 12[d]	2 (2.6)	5 (7.1)	1 (1.4)	15 (7.5)	3 (2.0)	20 (7.4)
Subjects Continued into Period II[e]	74 (97.4)	65 (92.9)	73 (98.6)	185 (92.5)	147 (98.0)	250 (92.6)

(a) 82 subjects who were randomized to Serostim 4 mg SC QOD in Study 22388 are not included.
(b) 80 subjects treated with Serostim 4 mg SC QOD in Study 22388 are not included in the Safety/ITT population in this table.
(c) 79 subjects treated with Serostim 4 mg SC QOD in Study 22399 are not included in the Modified ITT population in this table.
(d) This category includes subjects who may have been randomized into Period II (post Week 12), but who neither received study drug nor had a Period II study visit.
(e) This category includes subjects who were randomized into Period II and who either received study drug or had a Period II study visit.

As seen in Table 3, overall, a significantly greater percentage of subjects withdrew or were withdrawn prematurely in the Serostim 4 mg QD treatment group (23.5%, 77/327 randomized subjects) than in the placebo group (9.3%, 15/162 randomized subjects) during Weeks 0 to 12. This difference was largely due to a greater percentage of subjects in the Serostim 4 mg SC QD treatment group withdrawing or being withdrawn **due to AEs** compared to the placebo group (13.1% versus 1.2%). Fewer than 5.0% of subjects in each treatment group withdrew for other reasons, i.e. protocol violation, lost to follow-up, subject decision. Similar premature withdrawal data was observed in each pivotal study. Table 4 demonstrates that almost twice as many subjects (Modified ITT population) treated with Serostim 4 mg SC QD withdrew prematurely compared with subjects treated with Serostim 4 mg SC QOD during Weeks 0-12 in Study 22388, **primarily because of AEs (11% vs. 5.1%, respectively)**. **Please see Section 7.1.3 in Safety Results regarding delineation of the AEs that resulted in premature withdrawal, and further discussion of this issue**.

Table 3: Studies 22388 and 24380 - Subject Withdrawals During Weeks 0 to 12 for Each Study and Overall by Treatment Group Summarized by Primary Withdrawal Reason (Randomized Population)

	Study 22388		Study 24380		All Subjects	
	Placebo (n=81) n (%)	Serostim 4 mg daily (n=82) n (%)	Placebo (n=81) n (%)	Serostim 4 mg daily (n=245) n (%)	Placebo (n=162) n (%)	Serostim 4 mg daily (n=327) n (%)
Randomized Subjects Withdrawn During Weeks 0-12	**7 (8.6)**	**17 (20.7)**	**8 (9.9)**	**60 (24.5)**	**15 (9.3)**	**77 (23.5)**
Adverse Event	**0**	**9 (11.0)**	**2 (2.5)**	**34 (13.9)**	**2 (1.2)**	**43 (13.1)**
Protocol Violation	3 (3.7)	0	0	4 (1.6)	3 (1.9)	4 (1.2)
Lost to Follow-up	2 (2.5)	3 (3.7)	1 (1.2)	4 (1.6)	3 (1.9)	7 (2.1)
Subject Decision	1 (1.2)	4 (4.9)	3 (3.7)	12 (4.9)	4 (2.5)	16 (4.9)
Administrative Reasons	0	0	0	2 (0.8)	0	2 (0.6)
Other	1 (1.2)	1 (1.2)	2 (2.5)	4 (1.6)	3 (1.9)	5 (1.5)

Table 4: Study 22388 - Subject Withdrawals During Weeks 0-12 by Treatment Group Summarized by Primary Withdrawal Reason (Modified ITT Population)

Withdrawal Reason	Placebo (n=78) n (%)	Serostim 4 mg QOD (n=79) n (%)	Serostim 4 mg daily (n=82) n (%)	All Patients (n=239) n (%)
Number of Patients Withdrawn From Study	**4 (5.1)**	**8 (10.1)**	**17 (20.7)**	**29 (11.7)**
Adverse Event	**0**	**4 (5.1)**	**9 (11.0)**	**13 (5.4)**
Protocol Violation	2 (2.6)	0	0	2 (0.8)
Lost to Follow-Up	2 (2.6)	1 (1.3)	3 (3.7)	5 (2.1)
Subject Decision	0	2 (2.5)	4 (4.9)	6 (2.5)
Administrative Reason	0	1 (1.3)	0	1 (0.4)
Other	0	0	1 (1.2)	1 (0.4)

6.1.4.2 Demographics and Baseline Characteristics

6.1.4.2.1 Comparison of Basic and AIDS-Related Demographic Characteristics Between Treatment Groups

The basic demographic characteristics at study entry (age, gender, race, weight and BMI) of subjects in the modified ITT population for Weeks 0 to 12, for each study and overall, **by treatment group** (placebo vs. Serostim 4 mg QD), are presented in Table 5. **Overall (pooled data) and for each study**, the Serostim 4 mg QD and placebo treatment groups **were similar** with regard to these basic demographic characteristics, **except for weight at entry**. The mean baseline weight of subjects in the pooled placebo group was significantly greater than that of subjects in the pooled Serostim 4 mg QD treatment group (85.3±13.8 vs. 82.4±12.2 kg; p=0.018). Mean body mass indices (**BMIs**), however, **were very similar** across the pooled treatment groups and the treatment groups in each study. At baseline, the age of subjects in the pooled Serostim 4 mg QD treatment group ranged from 21 to 62 years, with a mean of 44.6 ±7.0 years, and in the pooled placebo group, age at baseline ranged from 30 to 62 years, with a mean of 44.9±7.5 years. The majority of subjects were male and Caucasian in the pooled Serostim 4 mg QD treatment group (85.5% and 74.8%, respectively) and very similar in the pooled placebo group.

Table 5: Studies 22388 and 24380 - Basic Demographic Characteristics at Study Entry for Weeks 0 to 12, for Each Study and Overall, by Treatment Group (Modified ITT Population)

	Study 22388		Study 24380		Pooled Data	
Characteristic	Placebo n=78	Serostim 4 mg daily n=82	Placebo n=79	Serostim 4 mg daily n=243	Placebo n=157	Serostim 4 mg daily n=325
Age (yrs)						
Mean (SD)	44.3 (7.5)	44.8 (7.0)	45.5 (7.5)	44.5 (7.0)	**44.9 (7.5)**	**44.6 (7.0)**
Range	(30.0, 59.0)	(29.0, 60.0)	(31.0, 62.0)	(21.0, 62.0)	(30.0, 62.0)	(21.0, 62.0)
Gender, n (%)						
Male	68 (87.2)	71 (86.6)	68 (86.1)	207 (85.2)	**136 (86.6)**	**278 (85.5)**
Female	10 (12.8)	11 (13.4)	11 (13.9)	36 (14.8)	21 (13.4)	47 (14.5)
Race, n (%)						
White	60 (76.9)	62 (75.6)	60 (75.9)	181 (74.5)	**120 (76.4)**	**243 (74.8)**
Black	4 (5.1)	12 (14.6)	8 (10.1)	22 (9.1)	12 (7.6)	34 (10.5)
Asian	1 (1.3)	0	0	0	1 (0.6)	0
Hispanic	13 (16.7)	6 (7.3)	11 (13.9)	38 (15.6)	24 (15.3)	44 (13.5)
Other	0	2 (2.4)	0	2 (0.8)	0	4 (1.2)
Weight (kg)						
Mean (SD)	84.8 (15.1)	81.4 (11.3)	85.8 (12.5)	82.7 (12.6)	**85.3 (13.8)**	**82.4 (12.2)**
Range	(57.0, 121.1)	(54.0, 111.1)	(48.8, 117.9)	(52.6, 130.0)	(48.8, 121.1)	(52.6, 130.0)
BMI (kg/m²)						
Mean (SD)	27.5 (4.1)	26.4 (2.7)	27.8 (4.4)	27.2 (3.7)	**27.7 (4.2)**	**27.0 (3.5)**
Range	(20.5, 40.8)	(22.0, 33.5)	(21.0, 50.8)	(20.0, 41.7)	(20.5, 50.8)	(20.0, 41.7)

Overall (using pooled data), **the Serostim 4 mg QD and placebo treatment groups were also similar with regard to AIDS-related demographic characteristics** (data not shown in a table). The majority of subjects in the Serostim 4 mg QD and placebo groups had a **baseline HIV-1 RNA level** of ≤400 copies (78.5% and 79.6%, respectively). The **mean baseline CD4 T helper lymphocyte count** for subjects in the Serostim 4 mg QD treatment group was 497.3±282.3 cells/mm^3, while in the placebo group, it was 461.7±255.5 cells/mm3. The mean time since HIV diagnosis was ~11-12 years in both groups. The most common HIV risk factor in both groups was men having sex with men, reported by 77.8% of subjects in the Serostim 4 mg QD treatment group and 81.5% of subjects in the placebo group. In the pooled Serostim 4 mg QD treatment group, 47.7% of all subjects had a past history of HIV-related medical conditions and 70.2% had current ongoing medical conditions at the time of study entry. Similarly, in the pooled placebo group, 51.0% of all subjects had a past history of HIV-related medical conditions and 63.1% had current ongoing medical conditions at the time of study entry. **The treatment groups in each study were similar with regard to these parameters as well**.

6.1.4.2.2 Comparison of Basic and AIDS-Related Demographic Characteristics Between Studies

The sponsor also performed analyses to determine if there were any differences between the protocol populations with respect to basic and AIDS-related demographic characteristics at baseline (Study 22388 vs. Study 24380) (data not shown in a table). Baseline differences between study populations were observed with respect to 1) HIV-1 RNA ≤400 copies; and 2) frequency of past HIV-related conditions. In Studies 22388 and 24380, 73.1% vs. 81.7% of subjects (p=0.009), respectively, had an HIV-1 RNA level ≤400 copies at baseline. In addition, the percentages of subjects with past HIV-related conditions were 67.5% vs. 39.4% in Studies 22388 and 24380, respectively (p<0.001). **These differences are probably related to the fact that more potent, second generation antiretroviral drugs were introduced between the initiation of Study 22388 in 2001 and Study 24380 in 2004**. Indeed, when analyzed by overall category, more subjects in Study 24380 were being treated with newer generation PIs and NRTIs.

6.1.4.2.3 Comparison of Baseline Levels of Efficacy Parameters Between Studies

In addition, the sponsor performed analyses to determine if there were any differences between the protocol populations with respect to baseline efficacy parameters. As seen in Table 6, statistically significant differences at baseline between study populations were observed for VAT, non-HDL cholesterol, total cholesterol, VLDL cholesterol, and triglycerides.

Mean VAT levels at baseline (±SE) were 153.0±6.2 cm^2 and 135.6±3.7 cm^2 for Studies 22388 and 24380, respectively (p=0.012). Table 7 depicts the clearly lower baseline VAT levels in Study 24380 (compared to Study 22388) <u>by gender</u>. Of interest, in both studies, VAT levels were greater in men compared to women (a previously reported observation that we will be discussing again later in this review with respect to the non-significant treatment effect for VAT observed in women in both studies).

Also seen in Table 6, mean baseline levels of non-HDL cholesterol, total cholesterol, VLDL cholesterol, and triglycerides were all significantly greater in Study 22388 compared to Study 24380 ($p \leq 0.002$ for each parameter). However, there were no significant differences between studies in the proportions of subjects who were receiving or not receiving any of the commonly prescribed LLAs. At baseline, 28% of the subjects in Study 22388 and 32% of the subjects in Study 24380 were receiving lipid-lowering agents (LLAs) (yet, like most of the patients in these studies, they were dyslipidemic at baseline, according to established guidelines [55]). Furthermore, there were no differences in mean baseline lipid levels across treatment groups in either study - irrespective of whether or not patients were receiving LLAs at the time of enrollment.

The **explanation** for the baseline differences in **VAT** across the studies probably relates to the fact that the patients enrolled in Study 24380 **were being treated more often with newer generation antiretroviral medications** (such as the PI atazanavir and NRTI tenofovir), which have been reported to result in less VAT accumulation (42-43). The **explanation** for the baseline differences in **lipid levels** across the studies also probably relates to the fact that the patients enrolled in Study 24380 **were being treated more often with newer generation, more "lipid-friendly" antiretroviral medications** (42-43, 56). Nonetheless, despite treatment with newer generation antiretroviral agents, HARS remains associated with a number of clinically significant metabolic abnormalities and an increased risk of atherosclerosis and myocardial infarction (57). Furthermore, the **greater mean baseline VAT level** in Study 22388 (which many believe contributes significantly to the dyslipidemia seen in HARS patients) in and of itself **may partially explain the greater mean baseline lipid levels** in Study 22388.

None of the differences in the baseline parameters across the 2 studies were considered significant enough to preclude the performance of integrated analyses. **However, since there were differences in important baseline parameters by study, all statistical models used by the sponsor in the efficacy analyses of the pooled/integrated data included an effect parameter for study** (see Section 6.1.3.7.3).

Table 6: Studies 22388 and 24380 -Analysis Comparing Body Composition and Lipid Parameters at Baseline (Modified ITT Population - Weeks 0-12)

Parameter	Study 22388 n=160* Mean (SE)	Study 24380 n=322 Mean (SE)	All Subjects n=482 Mean (SE)	p-value[(a)]
VAT (cm^2)	**153.0 (6.2)**	**135.6 (3.7)**	**141.1 (3.2)**	**0.012**
Abdominal SAT (cm^2)	167.8 (9.2)	177.8 (6.6)	174.7 (5.3)	0.338
Trunk Fat (kg)	10.8 (0.4)	11.9 (0.3)	11.6 (0.2)	0.073
Limb Fat (kg)	5.6 (0.3)	5.7 (0.2)	5.7 (0.2)	0.668
Trunk/Limb Fat Ratio	2.3 (0.1)	2.5 (0.1)	2.4 (0.0)	0.166
Total Body Fat (kg)	17.3 (0.7)	18.4 (0.5)	18.1 (0.4)	0.217
Lean Body Mass (kg)	62.8 (0.9)	61.7 (0.6)	62.0 (0.5)	0.835
Non-HDL Cholesterol (mg/dL)	**174.3 (3.5)**	**155.0 (2.3)**	**161.4 (1.9)**	**<0.001**
Total Cholesterol (mg/dL)	**211.6 (3.7)**	**193.5 (2.5)**	**199.5 (2.1)**	**0.002**
HDL Cholesterol (mg/dL)	37.3 (0.8)	38.5 (0.6)	38.1 (0.5)	0.339
LDL Cholesterol (mg/dL)	120.7 (3.3)	115.1 (2.0)	116.9 (1.7)	0.280
HDL/LDL Ratio	34.7 (1.2)	36.2 (0.8)	35.7 (0.7)	0.069
VLDL Cholesterol (mg/dL)	**61.5 (3.3)**	**36.0 (1.0)**	**45.0 (1.5)**	**<0.001**
Triglycerides (mg/dL)	**307.4 (16.6)**	**221.3 (9.1)**	**249.9 (8.4)**	**<0.001**

*Only includes patients randomized to placebo or Serostim 4 mg QD, i.e. 79 subjects randomized to Serostim 4 mg QOD not included
(a) p-value derived by the sponsor from a CMH analysis

Table 7: Studies 22388 and 24380 - Baseline Efficacy Parameters by Protocol and Gender (Modified ITT Population)

Mean (SD)	Study 22388			Study 24380		
Parameter	Male n=207	Female n=32	All n=239*	Male n=275	Female n=47	All n=322
Age (yr)	44.9 (6.8)	41.4 (7.9)	44.4 (7.0)	45.1 (6.8)	42.7 (8.2)	44.8 (7.1)
BMI (kg/m^2)	27.0 (3.4)	26.8 (4.0)	26.9 (3.5)	27.2 (3.5)	28.0 (5.4)	27.3 (3.9)
VAT (cm^2)	**156.0 (67.9)**	**105.8 (37.2)**	**149.1 (66.8)**	**143.9 (62.5)**	**85.1 (37.3)**	**135.6 (63.0)**
SAT (cm^2)	153.8 (95.2)	259.4 (109.0)	168.5 (103.6)	159.6 (93.8)	288.7 (139.0)	177.8 (110.6)
Trunk Fat (kg)	10.2 (4.3)	13.1 (4.2)	10.6 (4.4)	11.5 (4.7)	14.4 (5.3)	11.9 (4.9)
Limb Fat (kg)	5.1 (3.4)	8.4 (3.4)	5.5 (3.6)	5.1 (3.1)	9.5 (5.3)	5.7 (3.8)
Total Fat (kg)	16.3 (7.5)	22.6 (7.4)	17.1 (7.7)	17.3 (7.5)	24.8 (10.3)	18.4 (8.4)
% Body Fat	18.7 (6.6)	31.2 (6.8)	20.3 (7.8)	20.0 (6.9)	32.7 (8.1)	21.8 (8.4)

*Includes 79 patients randomized to Serostim 4 mg QOD

6.1.4.4 Efficacy Results

This Medical Officer's review of efficacy results contains the following:

- **A comparison of the results for the primary efficacy endpoint (change in VAT) and consequential non-PRO and PRO secondary efficacy endpoints after treatment with Serostim 4 mg QD vs. placebo during the 12 week induction period in each of the pivotal studies (Studies 24380 and 22388)**. Given the similarities in the 12 week induction phase design and inclusion/exclusion criteria between these 2 studies, an integrated analysis for VAT and the most consequential non-PRO secondary efficacy endpoints (performed by the sponsor and **adjusted for differences in baseline values across studies**) is presented as well.
- **A comparison of the results for the primary efficacy endpoint (change in VAT) and consequential non-PRO and PRO secondary efficacy endpoints after treatment with Serostim 4 mg QD <u>and</u> Serostim 4 mg QOD vs. placebo during the 12 week induction period in Study 22388 (which led to the sponsor's decision to use Serostim 4 mg QD as the induction dose in Study 24380).**
- **A brief description of the efficacy results during Weeks 12-36 in Study 23056 (equivalent to Weeks 36-60 of Studies 22388-23056 combined) - which led to the selection of the maintenance dose used in Study 24380 during Weeks 12-36.**
- **Placebo-controlled efficacy results from the 6 month maintenance period (Weeks 12-36) in Study 24380.**
- **CDF curves for the change and percent change in VAT during the induction phase.**
- **Gender subgroup analyses for the change in VAT (as well as the changes in abdominal SAT and trunk fat) during the induction phase.**
- **Non-HDL cholesterol subgroup analyses during the induction phase for subjects treated with or not treated with LLAs at the time of enrollment.**
- **Responder analyses and CDF curves for the PRO secondary efficacy endpoints.**

6.1.4.4.1 Induction Phase Results - Weeks 0-12

6.1.4.4.1.1 Change in VAT - Primary Efficacy Endpoint

The mean differences in the change from baseline to Week 12 in VAT between the Serostim 4 mg QD group and the placebo group were significant in Study 24380 (**-17.0 cm^2; p=0.005**; see Table 8 and Figure 4), Study 22388 (**-18.2 cm^2; p=0.031**; see Table 9 and Figure 5), and in the integrated analysis (**-18.1 cm^2; p<0.001**; see Table 10). As expected, the mean differences in the percent change from baseline to Week 12 in VAT between these 2 treatment groups were also significant in Study 24380 (**-17.2%; p=0.0005**; see Table 8), Study 22388 (**-14.0%; p=0.022**; see Table 9), and in the integrated analysis (**-15.0%; p<0.001**; see Table 10).

CDF curves (see Figure 6) show a clear separation of the subjects in the Serostim 4 mg QD and placebo groups. With respect to change from baseline to Week 12 in VAT, the cumulative percentages of patients who were **non-responders** (defined as a response >0) **were ~50% for the placebo group in both studies vs. ~20% and ~25% for the Serostim 4 mg QD groups** in Studies 24380 and 22388, respectively. With respect to percent change from baseline to Week 12 in VAT, the cumulative percentages of patients who were **non-responders** (defined as a response >0) **were ~50% for the placebo group in both studies vs. ~10% and ~25% for the Serostim 4 mg QD groups** in Studies 24380 and 22388, respectively. Furthermore, if one selects a within-group change of **-25 cm^2** (a number more negative than the mean between-group differences of -17-18 cm^2 noted in the preceding paragraph) **as a cutpoint**, the cumulative percentages of patients **with changes more negative than -25 cm^2 were ~60% for the Serostim 4 mg QD groups in both studies, vs. ~25% and ~30% for the placebo groups** in Studies 24380 and 22388, respectively. Finally, if one selects a within-group percent change of **-15%** (a number approximating the robust, mean between-group differences noted in the preceding paragraph) **as a cutpoint**, the cumulative percentages of patients **with changes more negative than 15% were ~70% and ~60% for the Serostim 4 mg QD groups in Studies 24380 and 22388, respectively vs. ~25% for the placebo groups in both studies**.

As seen in Table 9 and Figure 5, **the mean differences in the change and percent change from baseline to Week 12 in VAT between the Serostim 4 mg QOD group and the placebo group (-19.7 cm^2 and -16.7%) were very similar to those observed between the Serostim 4 mg QD group and the placebo group (-18.2 cm^2 and -14.0%)**. This is **confirmed by the CDF curves** for Study 22388 wherein the **"plots"** for the Serostim 4 mg QD group and the Serostim 4 mg QOD group **were identical** and overlap each other. **In other words, there was no dose-response observed with respect to change from baseline to Week 12 in VAT**.

Table 8: Study 24380 - Change & Percent Change from Baseline to Week 12 in VAT (cm^2) by Treatment Group (Modified ITT Population w/ LOCF)

	Placebo n=74	Serostim 4 mg daily n=210
Baseline (SE)[a]	109.87 (10.64)	115.86 (5.82)
Week 12 (SE)[a]	**123.93 (5.33)**	**106.93 (2.94)**
Change from Baseline (SE)[b]	**-11.69 (5.33)**	-28.69 (2.94)
Difference from Placebo for Change (CI)		**-17.00 (-28.84, -5.16) p=0.005**
% Change from Baseline (SE)[b]	**1.50 % (4.35)**	**-15.70 % (2.40)**
Difference from Placebo for % Change (CI)		**-17.21% (-26.87, -7.55) p=0.0005**

(a) Ordinary LSM from ANOVA model including effects for gender, treatment and their interaction
(b) Ordinary LSM from ANCOVA model with effects for gender, treatment, their interaction with baseline VAT as the single covariate

(b) (4)

Table 9: Study 22388 - Change & Percent Change from Baseline to Week 12 in VAT (cm^2) by Treatment Group (Modified ITT Population w/ LOCF)

	Placebo n=57	Serostim 4 mg QOD n=58	Serostim 4 mg daily n=61
Baseline (SE)[a]	136.33 (11.62)	120.88 (12.23)	135.44 (11.16)
Week 12 (SE)[a]	128.46 (10.61)	106.40 (12.59)	113.64 (10.54)
Change from Baseline (SE)[b]	-8.63 (5.98)	-28.38 (7.10)	-26.87 (5.93)
Difference from Placebo for Change (CI)		**-19.74 (-37.96, -1.53) p=0.034**	**-18.24 (-34.79, -1.69) p=0.031**
% Change from Baseline (SE)[b]	-2.36% (4.29)	-19.09% (5.09)	-16.31% (4.25)
Difference from Placebo for % Change (CI)		**-16.73% (-29.80, -3.67) p=0.012**	**-13.95% (-25.82, -2.08) p=0.022**

(a) Ordinary LSM from ANOVA model including effects for gender, treatment and their interaction
(b) Ordinary LSM from ANCOVA model with effects for gender, treatment, their interaction with baseline VAT as covariate

(b) (4)

Figure 4: Study 24380 - Change from Baseline to Week 12 in VAT (cm^2) by Treatment Group (Modified ITT Patients)

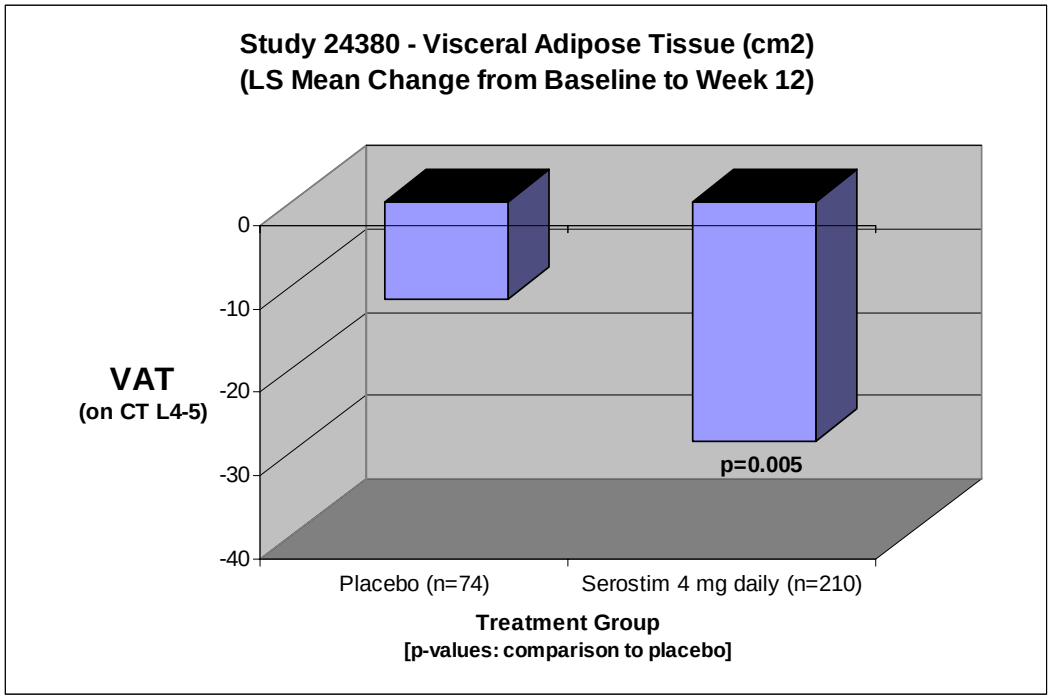


Figure 5: Study 22388 - Change from Baseline to Week 12 in VAT (cm^2) by Treatment Group (Modified ITT Patients)

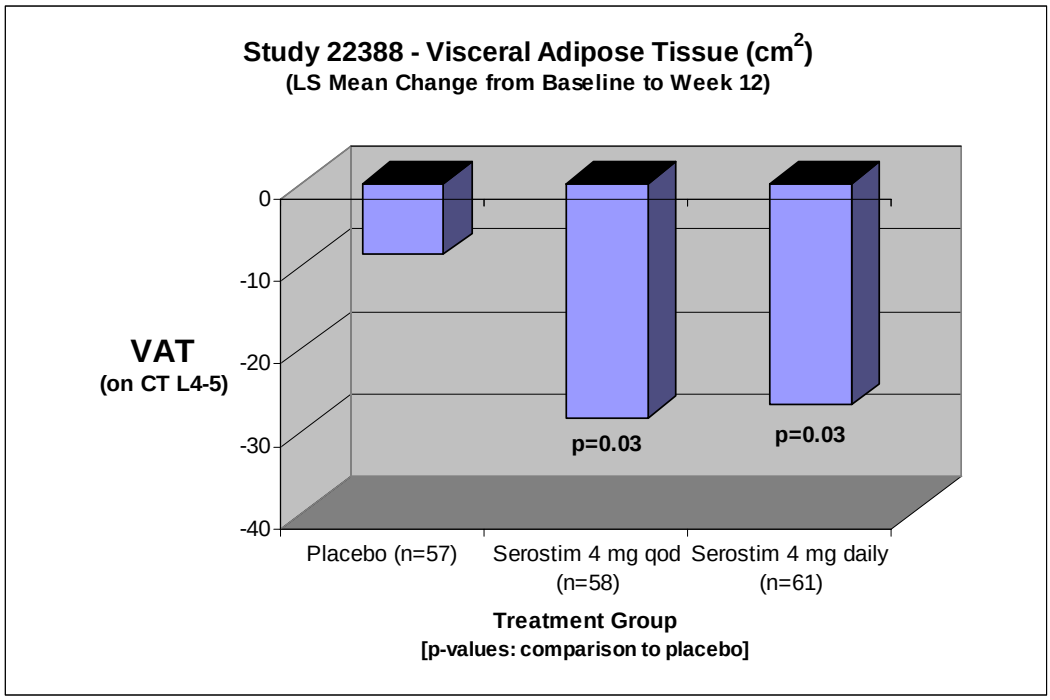


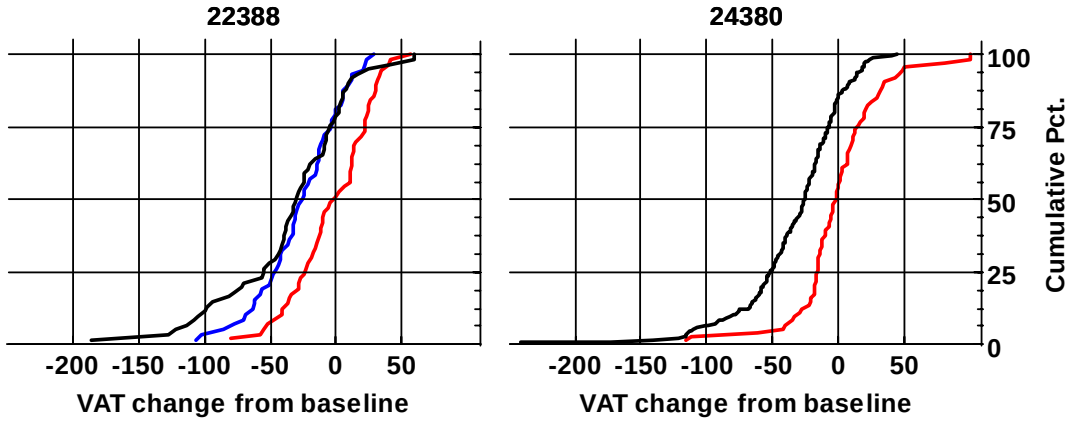
Table 10: Studies 22388 and 24380 - Changes from Baseline to Week 12 in VAT (cm^2) for Each Study and Integrated Overall by Treatment Group (Modified ITT Population) - Integrated ANCOVA Performed by the Sponsor

		Study 22388		Study 24380		All Subjects	
Time Point		**Placebo (n=57)**	**Serostim 4 mg daily (n=61)**	**Placebo (n=74)**	**Serostim 4 mg daily (n=210)**	**Placebo (n=131)**	**Serostim 4 mg daily (n=271)**
Baseline	Mean (SD)	143.3 (69.4)	158.5 (68.3)	134.7 (57.3)	135.9 (65.0)	138.5 (62.7)	141.0 (66.3)
	Range	(22.8, 392.8)	(22.8, 321.4)	(30.9, 333.0)	(13.0, 406.7)	(22.8, 392.8)	(13.0, 406.7)
Week 12	Mean (SD)	140.8 (63.0)	124.2 (63.5)	135.2 (59.6)	103.4 (48.0)	137.6 (60.9)	108.1 (52.5)
	Range	(46.0, 377.1)	(24.9, 317.9)	(31.1, 305.6)	(4.7, 269.1)	(31.1, 377.1)	(4.7, 317.9)
Change from Baseline to Week 12	Mean (SD)	**-2.5** (29.3)	**-34.3** (46.1)	0.5 (34.5)	-32.6 (37.9)	-0.8 (32.3)	-33.0 (39.8)
	Range	(-79.6, 56.1)	(-186.5, 60.1)	(-115.5, 100.6)	(-240.9, 45.3)	(-115.5, 100.6)	(-240.9, 60.1)
	Mean (SE)	-8.6 (6.0)[c]	-26.9 (5.9)[c]	-11.7 (5.3)[c]	-28.7 (2.9)[c]	-9.3 (4.0)[a]	-27.4 (2.9)[a]
	Mean Diff. vs. Placebo (SE)	**-18.2 (-34.8, -1.7)[c]**		**-17.0 (-28.8, -5.2)[c]**		**-18.1 (4.9)[a]**	
	p-value	**0.03[c]**		**0.005[c]**		**<0.001[b]**	
% Change from Baseline to Week 12	Mean (SD)	3.6 (27.9)	-18.6 (25.8)	3.6 (30.5)	-20.3 (23.6)	3.6 (29.3)	-19.9 (24.1)
	Range	(-59.1, 102.0)	(-79.4, 57.3)	(-67.6, 114.4)	(-89.5, 78.1)	(-67.6, 114.4)	(-89.5, 78.1)
	Mean (SE)	-2.4 (4.3)[c]	-16.3 (4.3)[c]	1.5 (4.4)[c]	-15.7 (2.4)[c]	-0.3 (3.1)[a]	-15.3 (2.2)[a]
	Mean Diff. vs. placebo (SE)	**-14.0 (-25.8, -2.1)[c]**		**-17.2 (26.9, -7.6)[c]**		**-15.0 (3.8)[a]**	
	p-value	**0.02[c]**		**0.0005[c]**		**<0.001[b]**	

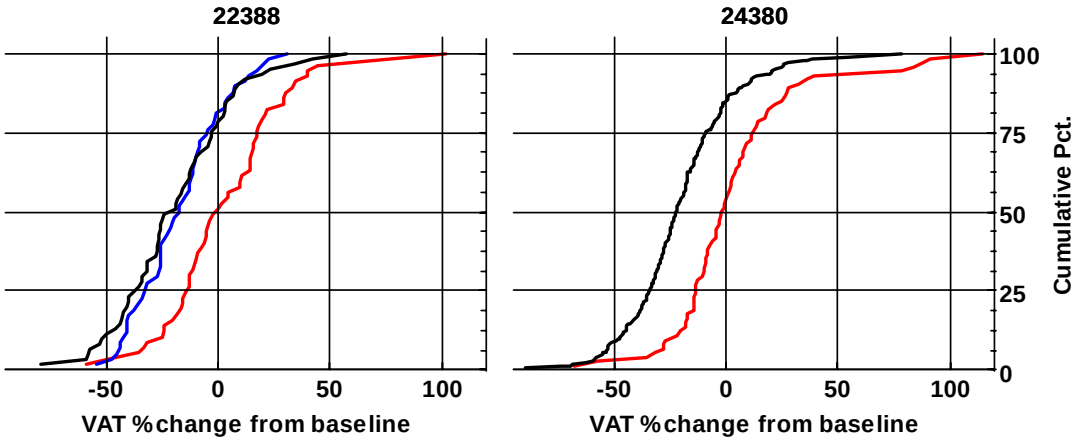
(a) Ordinary least squares means from a three-way ANCOVA model on raw data including effects for **study**, treatment, gender and the treatment by gender interaction with the baseline value of VAT as the single covariate
(b) p-value from a non-parametric ANCOVA model with effects for **study**, treatment, and gender with the baseline value of VAT as the single covariate
(c) **See Tables 8 and 9 earlier in review - ANCOVA performed by the Division's Statistical Reviewer**

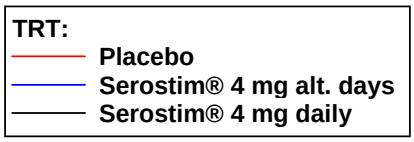
Figure 6: Studies 22388 and 24380 - Cumulative Distribution Functions for Change and Percent Change from Baseline to Week 12 in VAT (cm^2) for Each Study

VAT - Change from Baseline to Week 12



VAT - % Change from Baseline to Week 12

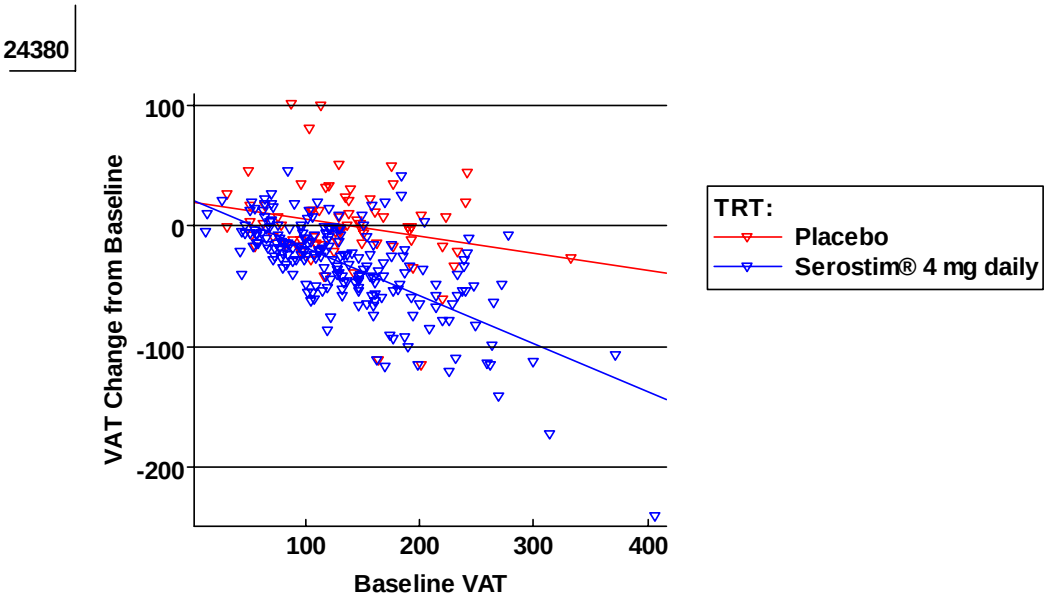




6.1.4.4.1.1.1 Covariate Analysis for Change from Baseline to Week 12 in VAT (During the Induction Phase)

The treatment by baseline VAT interaction was significant (p=0.0002) for change from baseline to Week 12 in VAT for Study 24380, but not for Study 22388 (data not shown) in the analyses presented earlier in Section 6.1.4.4.1.1. Figure 7 displays the linear regression lines for the Serostim 4 mg QD treatment group (r value was significant) and the placebo group for Study 24380. **As baseline VAT decreased, the reduction from baseline to Week 12 in VAT decreased in the Serostim 4 mg QD group**. In Study 24380, **the difference in VAT reduction** from baseline to Week 12 between the Serostim 4 mg QD treatment group and the placebo group **significantly increased as the baseline VAT increased**. Of note, the interaction was quantitative in nature. **In other words, a lower baseline VAT predicts a smaller treatment effect (Serostim 4 mg QD vs. placebo)**. This has been reported previously (13, 58-59).

Figure 7: Change from Baseline to Week 12 in VAT (cm^2) vs. Baseline VAT



6.1.4.4.1.1.2 Subgroup Analyses by Gender for Change from Baseline to Week 12 in VAT (During the Induction Phase)

The treatment by gender interactions were highly significant (p=0.0006) and minimally significant p=0.1) in Studies 24380 and 22388, respectively, **for the Serostim 4 mg QD treatment group vs. the placebo group in the analyses of the entire population** presented earlier in Section 6.1.4.4.1.1. Tables 11 and 12 display descriptive statistics for VAT by gender. **Mean VAT levels at baseline in female treatment groups were clearly smaller than in the male treatment groups in both studies** - as previously reported by several authors in HIV (13, 60-61) and non-HIV infected populations (59-61). The results of ANCOVA analyses for the change and percent change from baseline to Week 12 in VAT by gender are presented in Tables 13-16. **The treatment effects (Serostim 4 mg QD vs. placebo) for the change and percent change from baseline to Week 12 in VAT in males were significant in both studies, and very similar to the treatment effects derived from the analyses of all patients** presented earlier in Section 6.1.4.4.1.1 (see Tables 13-16). This is not surprising in that **~85% of the patients** in the modified ITT population treated with Serostim 4 mg QD vs. placebo in each study **were male**.

On the other hand, the treatment effects (Serostim 4 mg QD vs. placebo) for the change and percent change from baseline to Week 12 in VAT in females were not significant, i.e. the responses of women treated with Serostim 4 mg QD and placebo were similar in both studies (see Tables 13-16). As seen in Tables 14 and 16, in Study 22388, the Serostim 4 mg QOD vs. placebo treatment effect was somewhat greater than the Serostim 4 mg QD vs. placebo treatment effect. However, neither treatment effect was significant.

The CDF curves for change from baseline to Week 12 in VAT by gender are presented in Figures 8 and 9, and **support the ANCOVA findings described above**. In both studies, ~10% of men treated with Serostim 4 mg QD vs. ~50% of men treated with placebo were non-responders (i.e., arbitrarily defined as an increase rather than a decrease in VAT). These findings mirror the non-responder rates for the entire population (see Section 6.1.4.4.1.1 above). **In contrast, ~50% of the women treated with Serostim 4 mg QD or placebo in Study 24380, and ~40% of the women treated with Serostim 4 mg QD or placebo in Study 22388 were non-responders**. The response curves for women treated with Serostim 4 mg QD and placebo were essentially identical in both studies.

In summary, the treatment of women with Serostim 4 mg QD (or 4 mg QOD) vs. placebo during the induction phases of Studies 24380 and 22388 did not result in significant treatment effects/differences.

Table 11: Study 24380 - VAT Descriptive Statistics by Gender

Treatment	Gender	n	**Baseline VAT**	Week 12 VAT	**Change from Baseline**
Placebo	Female	**9**	**77.06 (49.81)**	69.78 (20.44)	**-7.29 (43.98)**
Serostim 4 mg QD	Female	**31**	**87.37 (33.55)**	80.55 (30.42)	**-6.82 (19.41)**
Placebo	Male	**65**	**142.68 (53.82)**	144.23 (57.59)	**1.54 (33.27)**
Serostim 4 mg QD	Male	**179**	**144.35 (65.49)**	107.32 (49.46)	**-37.03 (38.61)**

Table 12: Study 22388 - VAT Descriptive Statistics by Gender

Treatment	Gender	n	**Baseline VAT**	Week 12 VAT	**Change from Baseline**
Placebo	Female	**9**	**118.5 (29.84)**	110.46 (41.87)	**-8.04 (31.28)**
Serostim 4 mg QOD	Female	**6**	**94 (44.19)**	94.94 (30.25)	**-19.79 (18.53)**
Serostim 4 mg QD	Female	**9**	**103.89 (37.42)**	98.67 (39.45)	**-9.66 (17.45)**
Placebo	Male	**48**	**154.15 (76.52)**	143.21 (62.84)	**-1.52 (29.13)**
Serostim 4 mg QOD	Male	**52**	**147.75 (57.42)**	119.63 (49.02)	**-27.78 (31.86)**
Serostim 4 mg QD	Male	**52**	**166.98 (68.32)**	127.05 (64.80)	**-38.57 (48.20)**

(b) (4)

Treatment	Gender	n	Baseline VAT	Week 12 VAT	**Change from Baseline**
Placebo	Female	**9**	**118.5 (29.84)**	110.46 (41.87)	**-8.04 (31.28)**
Serostim 4 mg QOD	Female	**6**	(b) (4)	(b) (4)	**-19.79 (18.53)**
Serostim 4 mg QD	Female	**9**		98.67 (39.45)	**-9.66 (17.45)**
Placebo	Male	**48**		(b) (4)	**-1.52 (29.13)**
Serostim 4 mg QOD	Male	**52**			**-27.78 (31.86)**
Serostim 4 mg QD	Male	**52**			**-38.57 (48.20)**

Table 13: Study 24380 - ANCOVA Analysis* by Gender for VAT Change from Baseline to Week 12

Treatment	Gender	n	Within-Group Change from Baseline LSM (SE)	**Difference from Placebo LSM (CI)**	**p-value**
Placebo	Female	9	-27.34 (10.04)		
Serostim 4 mg QD	Female	31	-23.34 (5.51)	**4.00 (-18.12, 26.11)**	**0.722**
Placebo	Male	65	3.96 (3.68)		
Serostim 4 mg QD	Male	179	-34.04 (2.23)	**-38.00 (-46.45, -29.54)**	**<0.001**

*ANCOVA Model: Treatment, gender and treatment by gender interaction as fixed effects, and the baseline VAT as covariate

Table 14: Study 22388 - ANCOVA Analysis* by Gender for VAT Change from Baseline to Week 12

Treatment	Gender	n	Within-Group Change from Baseline LSM (SE)	**Difference from Placebo LSM (CI)**	**p-value**
Placebo	Female	9	-15.47 (10.98)		
Serostim 4 mg QOD	Female	6	-28.88 (13.44)	**-13.41 (-47.47, 20.65)**	**0.4381**
Serostim 4 mg QD	Female	9	-19.56 (11.03)	**-4.09 (-34.56, 26.38)**	**0.7914**
Placebo	Male	48	-1.79 (4.73)		
Serostim 4 mg QOD	Male	52	-27.87 (4.54)	**-26.08 (-39.01, -13.14)**	**<0.001**
Serostim 4 mg QD	Male	52	-34.18 (4.59)	**-32.39 (-45.41, -19.37)**	**<0.001**

*ANCOVA Model: Treatment, gender and treatment by gender interaction as fixed effects, and the baseline VAT as covariate

Table 15: Study 24380 - ANCOVA Analysis* by Gender for VAT Percent Change from Baseline to Week 12

Treatment	Gender	n	Within-Group Change from Baseline LSM (SE)	**Difference from Placebo LSM (CI)**	**p-value**
Placebo	Female	9	-1.1 (8.19)		
Serostim 4 mg QD	Female	31	-9.3 (4.50)	**-8.2 (-26.25, 9.84)**	**0.372**
Placebo	Male	65	4.1 (3.01)		
Serostim 4 mg QD	Male	179	-22.11 (1.82)	**-26.22 (-33.11, -19.32)**	**<0.001**

*ANCOVA Model: Treatment, gender and treatment by gender interaction as fixed effects, and the baseline VAT as covariate

Table 16: Study 22388 - ANCOVA Analysis* by Gender for VAT Percent Change from Baseline to Week 12

Treatment	Gender	n	Within-Group Change from Baseline LSM (SE)	**Difference from Placebo LSM (CI)**	**p-value**
Placebo	Female	9	-10.06 (7.87)		
Serostim 4 mg QOD	Female	6	-21.22 (9.64)	**-11.16 (-35.59, 13.26**	**0.368**
Serostim 4 mg QD	Female	9	-14.67 (7.91)	**-4.61 (-26.46, 17.24)**	**0.678**
Placebo	Male	48	5.34 (3.39)		
Serostim 4 mg QOD	Male	52	-16.97 (3.26)	**-22.31 (-31.58, 13.03)**	**<0.001**
Serostim 4 mg QD	Male	52	-17.95 (3.29)	**-23.29 (-32.62, -13.95)**	**<0.001**

*ANCOVA Model: Treatment, gender and treatment by gender interaction as fixed effects, and the baseline VAT as covariate

Figure 8: Study 24380 - Cumulative Distribution Functions for Change from Baseline to Week 12 in VAT (cm^2) by Gender

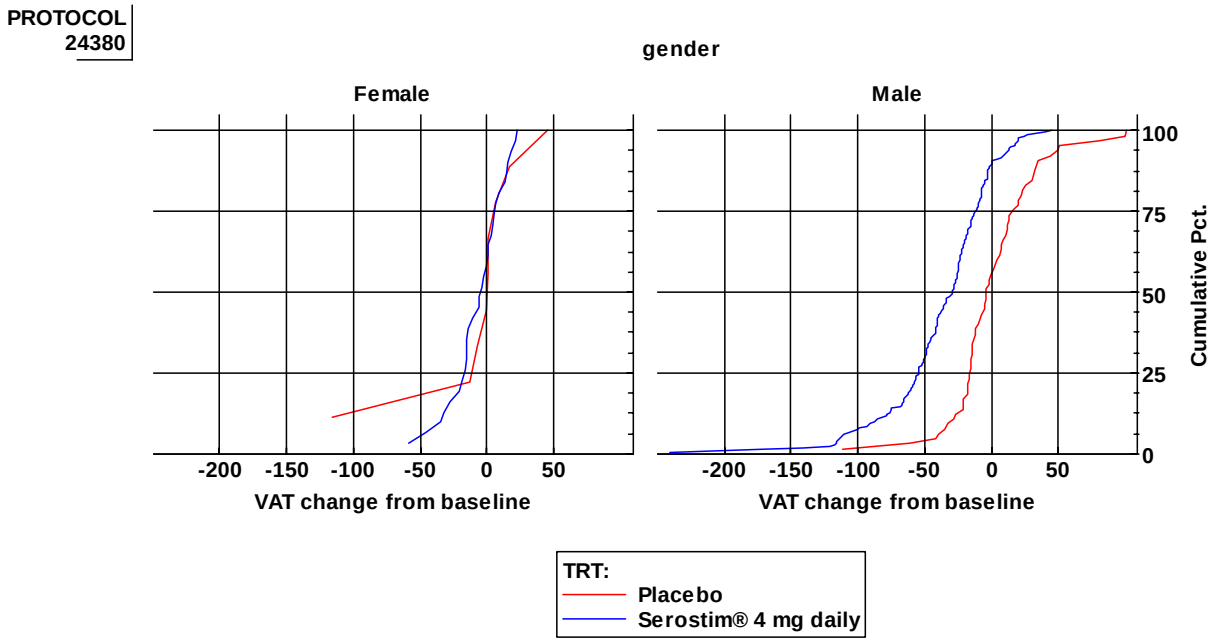
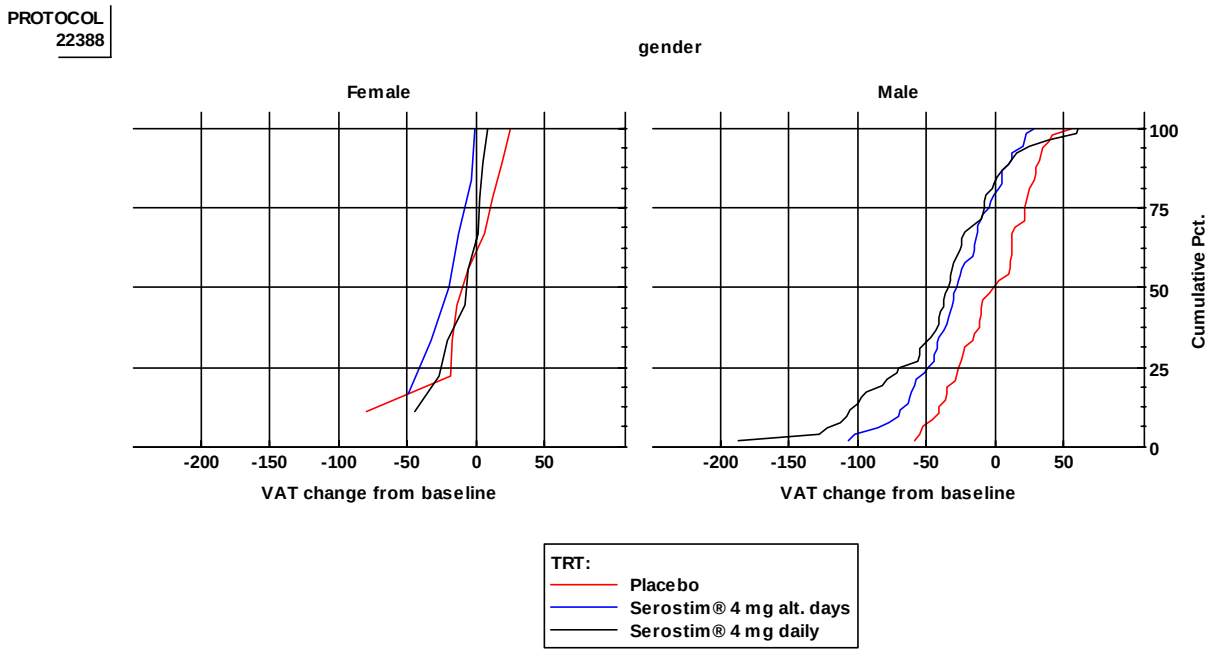


Figure 9: Study 22388 - Cumulative Distribution Functions for Change from Baseline to Week 12 in VAT (cm^2) by Gender



6.1.4.4.1.1.3 Subgroup Analyses by Gonadal Status for Change from Baseline to Week 12 in VAT (During the Induction Phase)

In Study 22388, the sponsor compared the responses of eugonadal men (without hypogonadism or with hypogonadism on appropriate testosterone replacement therapy) and unreplaced hypogonadal men to Serostim 4 mg QOD and Serostim 4 mg QD vs. placebo. Both treatment effects (vs. placebo) were statistically significant in eugonadal men, and comparable to the treatment effects observed in the whole population of patients. On the other hand, in hypogonadal men, only Serostim 4 mg QD elicited a statistically significant treatment effect (vs. placebo), i.e. hypogonadal men did not respond to Serostim 4 mg QOD (vs. placebo). Data not shown.

6.1.4.4.1.2 Change in Abdominal SAT - Consequential Secondary Efficacy Endpoint

The mean differences in the change from baseline to Week 12 in abdominal SAT between the Serostim 4 mg QD group and the placebo group were significant in Study 24380 (**-17.0 cm^2; p=0.008**; see Table 17 and Figure 10), Study 22388 (**-26.9 cm^2; p=0.002**; see Table 18 and Figure 11), and in the integrated analysis (**-20.8 cm^2; p<0.001**; see Table 19). As expected, the mean differences in the percent change from baseline to Week 12 in abdominal SAT between these 2 treatment groups were also significant in Study 24380 (**-8.3%; p=0.021**; see Table 17), Study 22388 (**-11.5%; p=0.039**; see Table 18), and in the integrated analysis (**-9.6%; p<0.001**; see Table 19).

As seen in Table 18 and Figure 11, **the mean difference in the change from baseline to Week 12 in abdominal SAT between the Serostim 4 mg QOD group and the placebo group was not significant, and clearly smaller than the difference observed after treatment with Serostim 4 mg QD vs. placebo (-10.4 cm^2 vs. -26.9 cm^2, respectively).**

<u>In other words, there was a dose-response observed with respect to change from baseline to Week 12 in abdominal SAT</u>.

Table 17: Study 24380 - Change & Percent Change from Baseline to Week 12 in Abdominal SAT (cm^2) by Treatment Group (Modified ITT Population w/ LOCF)

	Placebo n=74	Serostim 4 mg daily n=210
Baseline (SD)	188.1 (114.9)	174.2 (109.2)
Baseline (SE)[a]	241.1 (18.0)	218.8 (9.9)
Week 12 (SD)	190.1 (118.8)	159.9 (106.2)
Week 12 (SE)[a]	240.2 (18.1)	200.8 (9.9)
Change from Baseline (SD)	2.0 (30.2)	-14.3 (31.8)
Change from Baseline (SE)[a]	-0.9 (5.6)	-18.0 (3.0)
Raw Mean Difference from Placebo for Change (CI)		**-16.3 (-24.6, -7.9)**
Difference from Placebo for Change (CI)		**-17.0 (-29.5, -4.5) p=0.008**
% Change from Baseline (SD)	1.6 (16.9)	-7.1 (17.7)
% Change from Baseline (SE)[a]	0.3 (3.1)	-7.9 (1.7)
Raw Mean Difference from Placebo for % Change (CI)		**-8.7 (-13.4, -4.1)**
Difference from Placebo for % Change (CI)		**-8.3 (-15.3, -1.3) 0.021**

(a) Ordinary LSM from ANOVA model including effects for gender, treatment and their interaction

Table 18: Study 22388 - Change & Percent Change from Baseline to Week 12 in Abdominal SAT (cm^2) by Treatment Group (Modified ITT Population w/ LOCF)

	Placebo n=57	Serostim 4 mg QOD n=58	Serostim 4 mg daily n=61
Baseline (SD)	177.0 (110.5)	171.5 (100.1)	166.2 (103.1)
Baseline (SE)[a]	212.3 (17.6)	234.4 (20.9)	201.5 (17.5)
Week 12 (SD)	174.8 (108.3)	162.9 (104.7)	143.5 (87.3)
Week 12 (SE)[a]	210.6 (17.0)	222.2 (20.1)	172.9 (16.9)
Change from Baseline (SD)	-2.2 (31.8)	-8.6 (24.5)	-22.7 (41.9)
Change from Baseline (SE)[a]	**-1.7 (6.1)**	**-12.1 (7.3)**	**-28.6 (6.1)**
Raw Mean Difference from Placebo for Change (CI)		**-6.4 (-21.3, 8.5)**	**-20.5 (-35.2, -5.8)**
Difference from Placebo for Change (CI)		**-10.4 (-29.2, 8.4) p=0.276**	**-26.9 (-43.9, -9.8) p=0.002**
% Change from Baseline (SD)	0.6 (18.3)	-7.8 (20.8)	-10.1 (24.4)
% Change from Baseline (SE)[a]	0.4 (3.9)	-9.3 (4.6)	-11.0 (3.9)
Raw Mean Difference from Placebo for % Change (CI)		**-8.4 (-17.9, 1.1)**	**-10.7 (-20.1, -1.3)**
Difference from Placebo for % Change (CI)		**-9.7 (-21.7, 2.3) p=0.111**	**-11.5 (-22.4, -0.6) p=0.039**

(a) Ordinary LSM from ANOVA model including effects for gender, treatment and their interaction

Figure 10: Study 24380 - Change from Baseline to Week 12 in Abdominal SAT (cm^2) by Treatment Group (Modified ITT Patients)

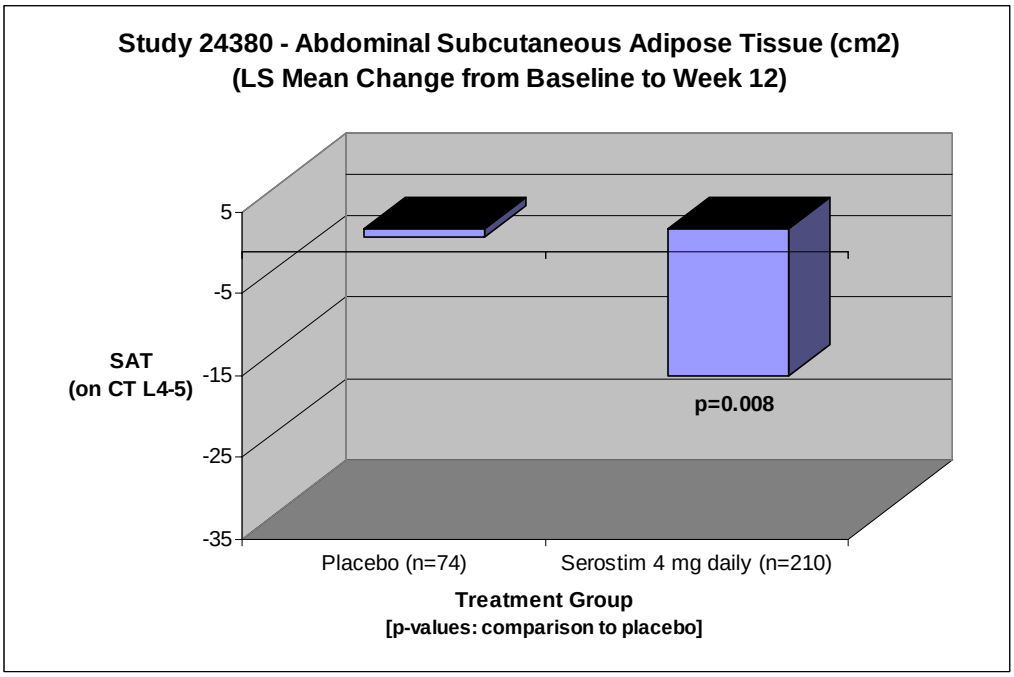


Figure 11: Study 22388 - Change from Baseline to Week 12 in Abdominal SAT (cm^2) by Treatment Group (Modified ITT Patients)

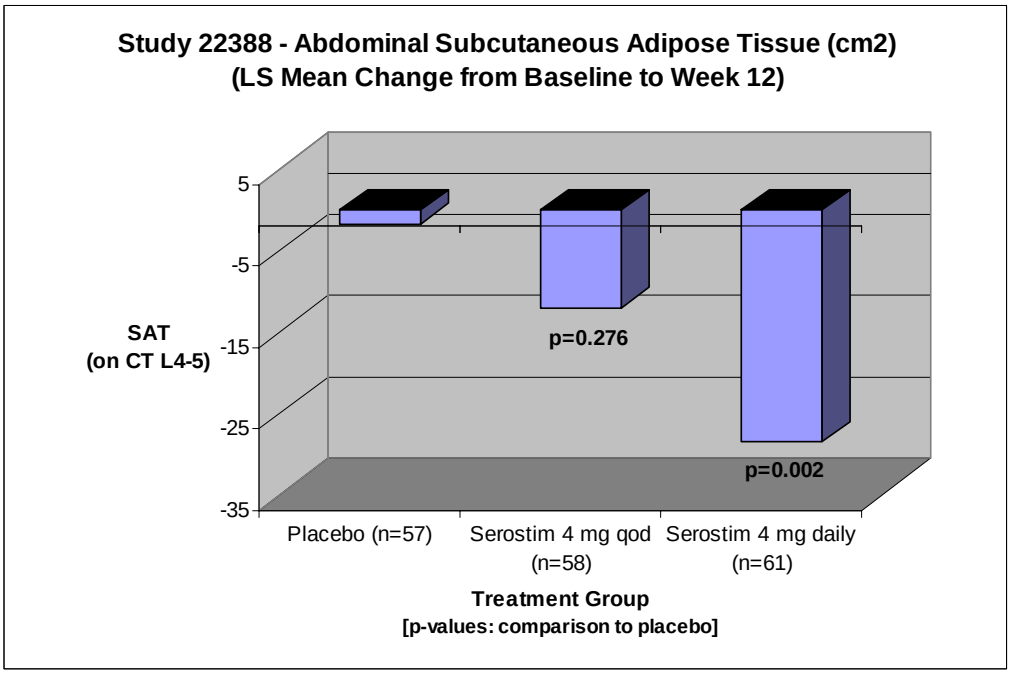


Table 19: Studies 22388 and 24380 - Changes from Baseline to Week 12 in Abdominal SAT (cm^2) for Each Study and Integrated Overall by Treatment Group (Modified ITT Population) - Integrated ANOVA Performed by the Sponsor

		Study 22388		Study 24380		All Subjects	
Time Point		**Placebo (n=57)**	**Serostim 4 mg daily (n=61)**	**Placebo (n=74)**	**Serostim 4 mg daily (n=210)**	**Placebo (n=131)**	**Serostim 4 mg daily (n=271)**
Baseline	Mean (SD)	177.0 (110.5)	166.2 (103.1)	188.1 (114.9)	174.2 (109.2)	183.3 (112.7)	172.4 (107.7)
	Range	(18.7, 471.7)	(34.2, 519.9)	(24.0, 565.1)	(0.9, 750.6)	(18.7, 565.1)	(0.9, 750.6)
Week 12	Mean (SD)	174.8 (108.3)	143.5 (87.3)	190.1 (118.8)	159.9 (106.2)	183.4 (114.2)	156.2 (102.3)
	Range	(23.4, 470.4)	(25.6, 472.2)	(8.5, 601.4)	(0.5, 730.4)	(8.5, 601.4)	(0.5, 730.4)
Change from Baseline to Week 12	Mean (SD)	-2.2 (31.8)	-22.7 (41.9)	2.0 (30.2)	-14.3 (31.8)	0.2 (30.9)	-16.2 (34.4)
	Range	(-133.4, 79.6)	(-196.1, 92.9)	(-150.2, 82.7)	(-215.5, 88.4)	(-150.2, 82.7)	(-215.5, 92.9)
	Mean (SE)	-1.7 (6.1)[c]	-28.6 (6.1)[c]	-0.9 (5.6)[c]	-18.0 (3.0)[c]	-1.4 (4.2)[a]	-22.2 (3.0)[a]
	Mean Diff. vs. Placebo (SE)	**-26.9 (-43.9, -9.8)[c]**		**-17.0 (-29.5, -4.5)[c]**		**-20.8 (5.1)[a]**	
	p-value	**0.002[c]**		**0.008[c]**		**<0.001[b]**	
% Change from Baseline to Week 12	Mean (SD)	0.6 (18.3)	-10.1 (24.4)	1.6 (16.9)	-7.1 (17.7)	1.2 (17.4)	-7.8 (19.4)
	Range	(-47.3, 49.5)	(-53.7, 105.6)	(-64.5, 42.0)	(-53.3, 42.3)	(-64.5, 49.5)	(-53.7, 105.6)
	Mean (SE)	0.4 (3.9)[c]	-11.0 (3.9)[c]	0.3 (3.1)[c]	-7.9 (1.7)[c]	0.4 (2.4)[a]	-9.2 (1.7)[a]
	Mean Diff. vs. Placebo (SE)	**-11.5 (-22.4, -0.6)[c]**		**-8.3 (-15.3, -1.3)[c]**		**-9.6 (2.9)[a]**	
	p-value	**0.039[c]**		**0.02[c]**		**<0.001[b]**	

(a) Ordinary least squares means from a three-way ANOVA model on raw data including effects for **study**, treatment, gender, and the treatment by gender interaction
(b) p-value from a three-way ANOVA model on ranked data including effects for **study**, treatment, gender, and the treatment by gender interaction
(c) **See Tables 17 and 18 earlier in review – ANOVA performed by the sponsor**

6.1.4.4.1.2.1 Subgroup Analysis by Gender for Change from Baseline to Week 12 in Abdominal SAT (During the Induction Phase)

The treatment by gender interactions were not significant in Studies 24380 and 22388 **for the Serostim 4 mg QD treatment group vs. the placebo group in the analyses of the entire population** presented earlier in Section 6.1.4.4.1.2.

Tables 20 and 21 depict the descriptive statistics by gender for abdominal SAT in each study. Not surprisingly, mean baseline abdominal SAT levels were substantially greater in women for each treatment group in each study. **The responses to treatment with Serostim 4 mg QD vs. placebo in women appear to be similar to or even greater than the responses observed in men**.

Table 20: Study 24380 - Abdominal SAT Descriptive Statistics by Gender

Treatment	Gender	n	Baseline SAT	Week 12 SAT	Change from Baseline
Placebo	Female	**9**	**311.2 (127.2)**	306.4 (144.0)	**-4.8 (72.8)**
Serostim 4 mg QD	Female	**31**	**282.2 (143.5)**	258.9 (151.0)	**-23.2 (39.4)**
Placebo	Male	**65**	**171.1 (103.0)**	174.0 (106.5)	**2.9 (19.3)**
Serostim 4 mg QD	Male	**179**	**155.5 (90.2)**	142.7 (85.9)	**-12.7 (30.2)**

Table 21: Study 22388 - Abdominal SAT Descriptive Statistics by Gender

Treatment	Gender	n	Baseline SAT	Week 12 SAT	Change from Baseline
Placebo	Female	**9**	**263.9 (118.9)**	262.9 (118.3)	**-1.0 (33.0)**
Serostim 4 mg QOD	Female	**6**	**313.7 (118.0)**	297.1 (161.8)	**-16.5 (48.0)**
Serostim 4 mg QD	Female	**9**	**251.6 (97.9)**	214.7 (77.1)	**-36.9 (34.3)**
Placebo	Male	**48**	**160.7 (102.1)**	158.3 (99.2)	**-2.4 (31.9)**
Serostim 4 mg QOD	Male	**52**	**155.0 (84.7)**	147.4 (85.5)	**-7.7 (20.8)**
Serostim 4 mg QD	Male	**52**	**151.5 (97.4)**	131.2 (83.6)	**-20.3 (42.9)**

6.1.4.4.1.3 Change in Trunk Fat - Consequential Secondary Efficacy Endpoint (as well as change in several other body composition parameters)

The mean differences in the change from baseline to Week 12 in trunk fat between the Serostim 4 mg QD group and the placebo group were significant in Study 24380 (**-2.3 kg; p<0.001**; see Table 22 and Figure 12), Study 22388 (**-2.2 kg; p<0.001**; see Table 23 and Figure 13), and in the integrated analysis (**-2.2 kg; p<0.001**; see Table 24). As expected, the mean differences in the percent change from baseline to Week 12 in trunk fat between these 2 treatment groups were also significant in Study 24380 (**-19.9%; p<0.001**; see Table 22), Study 22388 (**-20.0%; p<0.001**; see Table 23), and in the integrated analysis (**-20.0%; p<0.001**; see Table 24).

As seen in Table 23 and Figure 13, **the mean difference in the change from baseline to Week 12 in trunk fat between the Serostim 4 mg QOD group and the placebo group**

was significant (-1.3 kg; p<0.001), but clearly smaller than the difference observed after treatment with Serostim 4 mg QD vs. placebo (-2.2 kg).

In other words, there was a dose-response observed with respect to change from baseline to Week 12 in trunk fat.

Table 22: Study 24380 - Change & Percent Change from Baseline to Week 12 in Trunk Fat (kg) by Treatment Group (Modified ITT Population w/ LOCF)

	Placebo n=75	Serostim 4 mg daily n=213
Baseline (SD)	12.0 (4.5)	11.7 (4.9)
Baseline (SE)[a]	12.9 (0.8)	12.7 (0.4)
Week 12 (SD)	12.2 (4.9)	9.6 (4.9)
Week 12 (SE)[a]	13.2 (0.9)	10.7 (0.5)
Change from Baseline (SD)	0.2 (1.3)	-2.2 (1.7)
Change from Baseline (SE)[a]	**0.3 (0.3)**	**-2.0 (0.2)**
Raw Mean Difference from Placebo for Change (CI)		**-2.4 (-2.8, -1.9)**
Difference from Placebo for Change (CI)		**-2.3 (-2.9, -1.7) p<0.001**
% Change from Baseline (SD)	1.4 (11.9)	-20.0 (14.5)
% Change from Baseline (SE)[a]	2.3 (2.4)	-17.6 (1.3)
Raw Mean Difference from Placebo for % Change (CI)		**-21.3 (-25.0, -17.7)**
Difference from Placebo for % Change (CI)		**-19.9 (-25.4, -14.5) p<0.001**

(a) Ordinary LSM from ANOVA model including effects for gender, treatment and their interaction

Stat reviewer: Change from Baseline (SE)[a] 0.4 (0.2) -2.0 (0.1)
Difference from Placebo for Change (CI) -2.4 (-2.8, -2.0)

Table 23: Study 22388 - Change & Percent Change from Baseline to Week 12 in Trunk Fat (kg) by Treatment Group (Modified ITT Population w/ LOCF)

	Placebo n=63	Serostim 4 mg QOD n=60	Serostim 4 mg daily n=59
Baseline (SD)	11.3 (4.9)	10.1 (4.0)	10.1 (4.0)
Baseline (SE)[a]	12.1 (0.7)	11.8 (0.8)	10.3 (0.9)
Week 12 (SD)	11.4 (5.0)	8.8 (3.7)	7.9 (3.8)
Week 12 (SE)[a]	12.2 (0.7)	10.7 (0.8)	8.3 (0.9)
Change from Baseline (SD)	0.2 (1.0)	-1.2 (1.2)	-2.2 (1.9)
Change from Baseline (SE)[a]	**0.2 (0.2)**	**-1.1 (0.3)**	**-2.0 (0.3)**
Raw Mean Difference from Placebo for Change (CI)		**-1.4 (-2.0, -0.8)**	**-2.4 (-3.0, -1.8)**
Difference from Placebo for Change (CI)		**-1.3 (-2.0, -0.6)** **p<0.001**	**-2.2 (-3.0, -1.4)** **p<0.001**
% Change from Baseline (SD)	2.1 (11.5)	-12.6 (13.0)	-22.5 (17.5)
% Change from Baseline (SE)[a]	1.5 (2.4)	-10.0 (2.7)	-18.6 (3.0)
Raw Mean Difference from Placebo for % Change (CI)		**-14.7 (-20.7, -8.7)**	**-24.5 (-30.6, -18.5)**
Difference from Placebo for % Change (CI)		**-11.4 (-18.6, -4.3)** **p=0.002**	**-20.0 (-27.7, -12.4)** **p<0.001**

(a) Ordinary LSM from ANOVA model including effects for gender, treatment and their interaction

Stat reviewer: Change from Baseline (SE)[a] 0.4 (0.2) -1.1 (0.2) -2.1 (0.2)
Difference from Placebo for Change (CI) -1.5 (-2.0, -1.0) -2.5 (-3.0, -2.0)

Figure 12: Study 24380 - Change from Baseline to Week 12 in Trunk Fat by Treatment Group (Modified ITT Population)

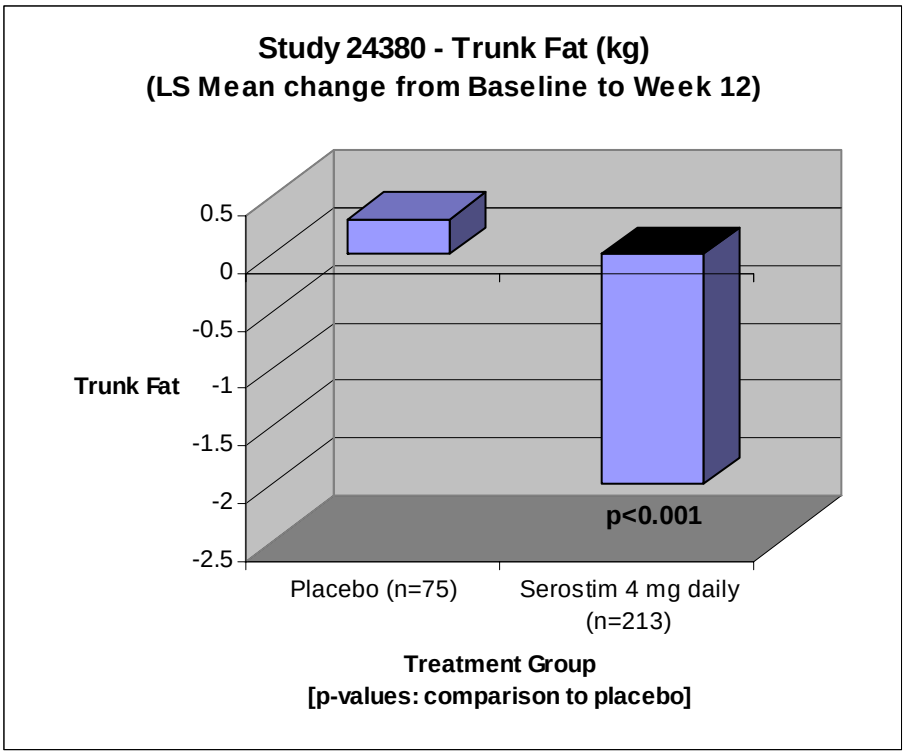


Figure 13: Study 22388 - Change from Baseline to Week 12 in Trunk Fat, Total Fat and Limb Fat by Treatment Group (Modified ITT Patients)

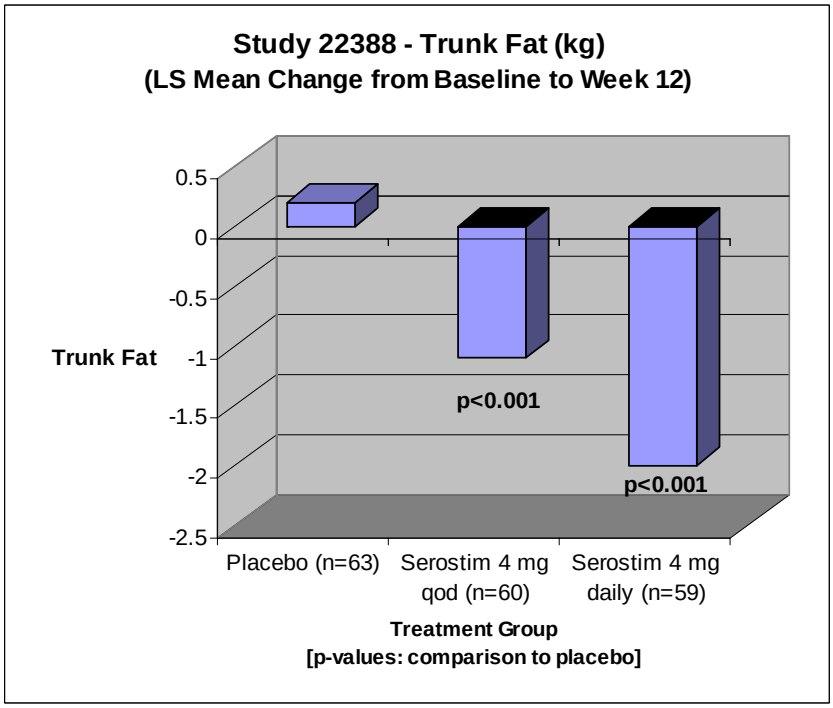


Table 24: Studies 22388 and 24380 - Changes from Baseline to Week 12 in Trunk Fat (kg) for Each Study and Integrated Overall by Treatment Group (Modified ITT Population) - Integrated ANOVA Performed by the Sponsor

		Study 22388		Study 24380		All Subjects	
Time Point		**Placebo (n=63)**	**Serostim 4 mg daily (n=59)**	**Placebo (n=75)**	**Serostim 4 mg daily (n=213)**	**Placebo (n=138)**	**Serostim 4 mg daily (n=272)**
Baseline	Mean (SD)	11.3 (4.9)	10.1 (4.0)	12.0 (4.5)	11.7 (4.9)	11.7 (4.7)	11.4 (4.8)
	Range	(2.8, 24.5)	(2.9, 22.8)	(5.1, 24.0)	(1.8, 28.1)	(2.8, 24.5)	(1.8, 28.1)
Week 12	Mean (SD)	11.4 (5.0)	7.9 (3.8)	12.2 (4.9)	9.6 (4.9)	11.9 (4.9)	9.2 (4.8)
	Range	(3.6, 24.4)	(2.0, 21.8)	(4.4, 27.5)	(1.3, 32.8)	(3.6, 27.5)	(1.3, 32.8)
Change from Baseline to Week 12	Mean (SD)	0.2 (1.0)	-2.2 (1.9)	0.2 (1.3)	-2.2 (1.7)	0.2 (1.2)	-2.2 (1.7)
	Range	(-2.3, 2.6)	(-7.1, 2.1)	(-3.3, 5.9)	(-7.9, 4.7)	(-3.3, 5.9)	(-7.9, 4.7)
	Mean (SE)	0.2 (0.2)[c]	-2.0 (0.3)[c]	0.3 (0.3)[c]	-2.0 (0.2)[c]	0.2 (0.2)[a]	-2.0 (0.1)[a]
	Mean Diff. vs. Placebo (SE)	**-2.2 (-3.0, -1.4)[c]**		**-2.3 (-2.9, -1.7)[c]**		**-2.2 (0.2)[a]**	
	p-value	**<0.001[c]**		**<0.001[c]**		**<0.001[b]**	
% Change from Baseline to Week 12	Mean (SD)	2.1 (11.5)	-22.5 (17.5)	1.4 (11.9)	-20.0 (14.5)	1.7 (11.7)	-20.5 (15.2)
	Range	(-19.1, 37.2)	(-54.6, 15.1)	(-32.1, 32.2)	(-58.4, 20.2)	(-32.1, 37.2)	(-58.4, 20.2)
	Mean (SE)	1.5 (2.4)[c]	-18.6 (3.0)[c]	2.3 (2.4)[c]	-17.6 (1.3)[c]	1.8 (1.7)[a]	-18.1 (1.3)[a]
	Mean diff. vs. Placebo (SE)	**-20.0 (-27.7, -12.4)[c]**		**-19.9 (-25.4, -14.5)[c]**		**-20.0 (2.2)[a]**	
	p-value	**<0.001[c]**		**<0.001[c]**		**<0.001[b]**	

(a) Ordinary least squares means from a three-way ANOVA model on raw data including effects for **study**, treatment, gender, and the treatment by gender interaction
(b) p-value from a three-way ANOVA model on ranked data including effects for **study**, treatment, gender, and the treatment by gender interaction
(c) **See Tables 22 and 23 earlier in review – ANOVA performed by the sponsor**

6.1.4.4.1.3.1 Subgroup Analysis by Gender for Change from Baseline to Week 12 in Trunk Fat (During the Induction Phase)

The treatment by gender interactions were not significant in Studies 24380 and 22388 **for the Serostim 4 mg QD treatment group vs. the placebo group in the analyses of the entire population** presented earlier in Section 6.1.4.4.1.3.

Tables 25 and 26 depict the descriptive statistics by gender for trunk fat. Not surprisingly, mean baseline trunk fat levels were greater in women for each treatment group in each study. **The responses to treatment with Serostim 4 mg QD vs. placebo in women appear to be similar to the responses observed in men**.

Table 25: Study 24380 - Trunk Fat Descriptive Statistics by Gender

Treatment	Gender	n	Baseline Trunk Fat	Week 12 Trunk Fat	Change from Baseline
Placebo	Female	**9**	**14.0 (4.9)**	14.5 (5.1)	**0.5 (0.8)**
Serostim 4 mg QD	Female	**33**	**14.1 (5.4)**	12.4 (5.8)	**-1.7 (1.3)**
Placebo	Male	**66**	**11.7 (4.4)**	11.9 (4.8)	**0.2 (1.4)**
Serostim 4 mg QD	Male	**180**	**11.3 (4.7)**	9.0 (4.6)	**-2.2 (1.7)**

Table 26: Study 22388 - Trunk Fat Descriptive Statistics by Gender

Treatment	Gender	n	Baseline Trunk Fat	Week 12 Trunk Fat	Change from Baseline
Placebo	Female	**10**	**13.2 (4.2)**	13.4 (4.7)	**0.2 (0.9)**
Serostim 4 mg QOD	Female	**8**	**14.2 (4.5)**	13.2 (4.1)	**-0.9 (1.2)**
Serostim 4 mg QD	Female	**6**	**10.7 (3.7)**	8.9 (2.3)	**-1.8 (1.6)**
Placebo	Male	**53**	**10.9 (5.0)**	11.0 (5.0)	**0.2 (1.1)**
Serostim 4 mg QOD	Male	**52**	**9.4 (3.6)**	8.1 (3.2)	**-1.3 (1.2)**
Serostim 4 mg QD	Male	**53**	**10.0 (4.0)**	7.8 (3.9)	**-2.3 (2.0)**

(b) (4)

- [redacted] (b) (4)

6.1.4.4.1.4 Change in Total Body Fat (Equal to Trunk Fat + Limb Fat) - Consequential Secondary Efficacy Endpoint

The mean differences in the change from baseline to Week 12 in total body fat between the Serostim 4 mg QD group and the placebo group were significant in Study 24380 (**-3.0 kg; p<0.001**; see Table 27 and Figure 14), Study 22388 (**-2.8 kg; p<0.001**; see Table 27 and Figure 15), and in the integrated analysis (**-3.0 kg; p<0.001**; data not shown in a table). As expected, the mean differences in the percent change from baseline to Week 12 in total body fat between these 2 treatment groups were also significant in Study 24380 (**-16.3%; p<0.001**; see Table 27), Study 22388 (**-16.0%; p<0.001**; see Table 27), and in the integrated analysis (**-16.3%; p<0.001**; see Table 27).

As seen in Table 27 and Figure 15, **the mean difference in the change from baseline to Week 12 in total body fat between the Serostim 4 mg QOD group and the placebo group was significant (-1.7 kg; p<0.001), but clearly smaller than the difference observed after treatment with Serostim 4 mg QD vs. placebo (-2.8 kg).**

In other words, there was a dose-response observed with respect to change from baseline to Week 12 in total body fat.

Table 27: Studies 22388 and 24380 – Treatment Difference vs. Placebo for Change and Percent Change from Baseline to Week 12 in Total Body Fat

Study	22388	22388	24380	22388 + 24380
Total Body Fat	**Serostim 4 mg QOD**	**Serostim 4 mg QD**	**Serostim 4 mg QD**	**Serostim 4 mg QD**
Study 22388[a]	**-1.7 kg** (-2.8, -0.6)[c] (p=0.003) **-9.2%** (-16.5, -1.9) (p=0.014)	**-2.8 kg** (-4.0, -1.6)[c] (p<0.001) **-16.0%** (-23.9, -8.1) (p<0.001)	XX	XX
Study 24380[a]	XX	XX	**-3.0 kg** (-3.9, -2.2)[d] (p<0.001) **-16.3%** (-21.1, -11.4) (p<0.001)	XX
Studies 22388 & 24380 Combined/ Integrated[a]	XX	XX	XX	**-3.0 kg**[b] (p<0.001) **-16.3%** (p<0.001)

(a) Ordinary least squares mean (CI) and p-values from ANOVA with effects for treatment, gender and treatment by gender interaction
(b) LSM Change from Baseline (SE) = 0.4 (0.3) for placebo and -2.5 (0.2) for Serostim 4 mg QD; LSM % Change from Baseline (SE) = 1.7 (1.6) for placebo and -14.6 (1.2) for Serostim 4 mg QD in the Integrated Analysis
(c) LSM Change from Baseline (SE) = 0.3 (0.4) & -1.5 (0.4) & -2.5 (0.5) for placebo & Serostim 4 mg QOD & Serostim 4 mg QD, respectively, in Study 22388
(d) LSM Change from Baseline (SE) = 0.6 (0.4) & -2.4 (0.2) for placebo & Serostim 4 mg QD, respectively, in Study 24380

Figure 14: Study 24380 - Change from Baseline to Week 12 in Total Body Fat by Treatment Group (Modified ITT Population)

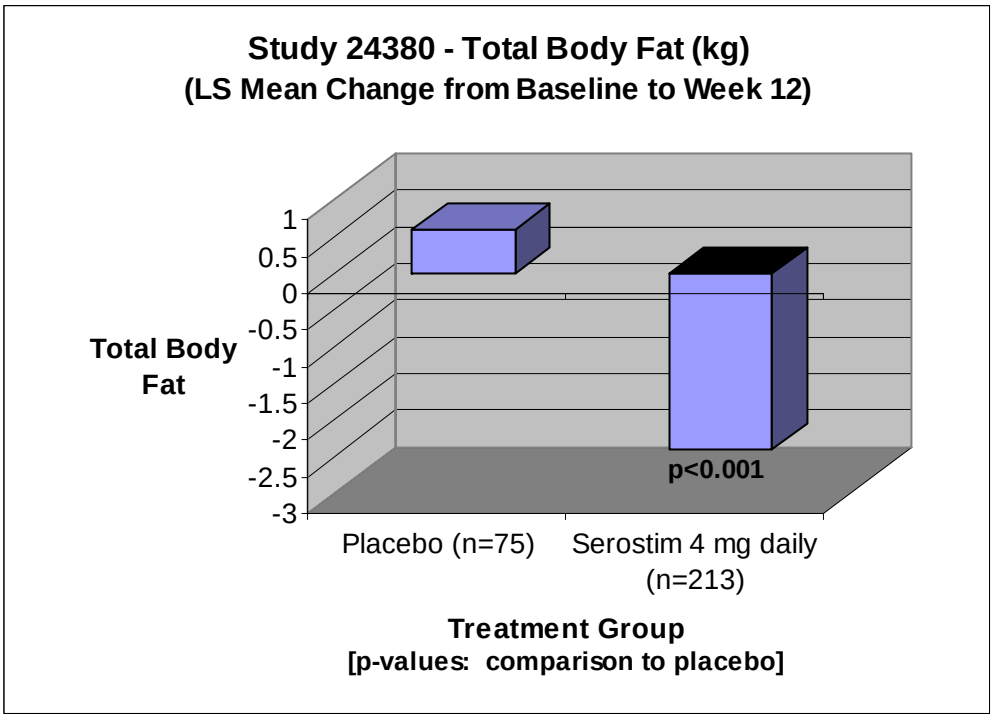
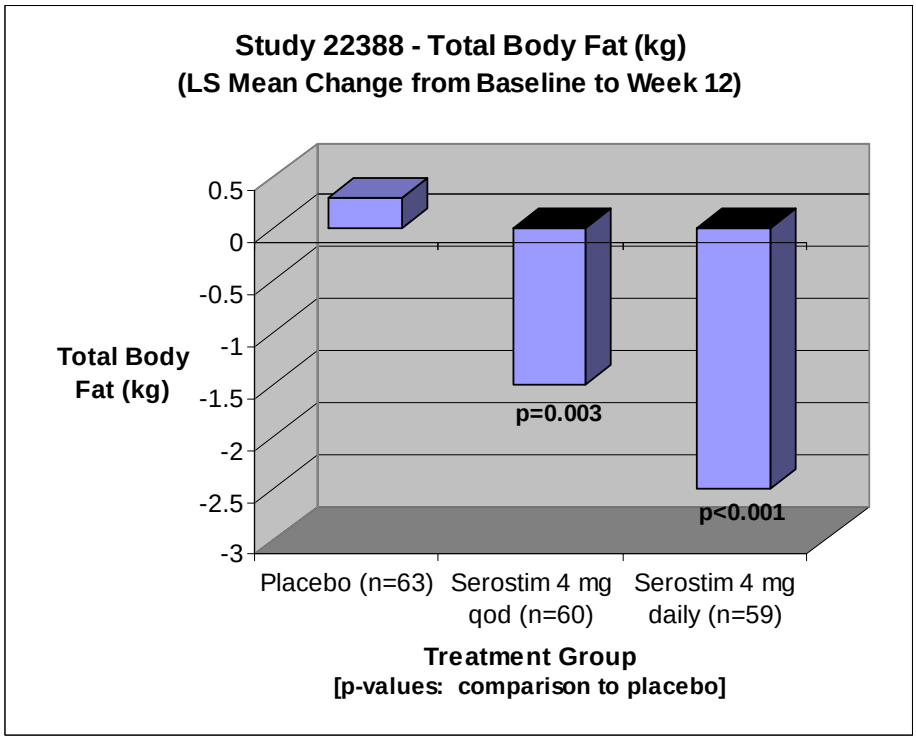


Figure 15: Study 22388 - Change from Baseline to Week 12 in Total Body Fat by Treatment Group (Modified ITT Population)



6.1.4.4.1.5 Change in Dorsocervical Fat Pad - Consequential Secondary Efficacy Endpoint

None of the mean differences in the change and percent change from baseline to Week 12 in dorsocervical fat pad between the Serostim 4 mg QD group and the placebo group in Studies 24380 and 22388, or between the Serostim 4 mg QOD group and the placebo group in Study 22388, were significant when equally weighted ANOVA models were used to reanalyze the data - although 1) the LSM treatment differences were of substantial magnitude for Serostim 4 mg QD vs. placebo in both studies; and 2) there appeared to be a dose-response in Study 22388 (see Tables 28 and 29). On the other hand, **when the data were pooled, mean differences** in the change and percent change from baseline to Week 12 in dorsocervical fat pad between the Serostim 4 mg QD group and the placebo group **were significant (-15.6 cm^2 [p=0.05] and -17.8% [p=0.029], respectively)** (see Table 30).

Table 28: Study 24380 - Change & Percent Change from Baseline to Week 12 in Dorsocervical Fat (cm^2) by Treatment Group (Modified ITT Population w/ LOCF)

	Placebo n=23	Serostim 4 mg daily n=74
Baseline (SD)	120.5 (96.4)	130.9 (99,4)
Baseline (SE)[a]	122.3 (27.4)	132.3 (14.4)
Week 12 (SD)	96.9 (60.7)	99.7 (87.7)
Week 12 (SE)[a]	102.4 (22.8)	100.3 (12.0)
Change from Baseline (SD)	-23.7 (61.9)	-31.2 (48.1)
Change from Baseline (SE)[a]	-19.8 (14.3)	-32.0 (7.5)
Raw Mean Difference from Placebo for Change (CI)		**-7.5 (-32.2, 17.2)**
Difference from Placebo for Change (CI)		**-12.1 (-44.3, 20.1) p=0.457**
% Change from Baseline (SD)	-13.0 (39.6)	-27.4 (34.1)
% Change from Baseline (SE)[a]	-8.9 (9.8)	-28.8 (5.2)
Raw Mean Difference from Placebo for % Change (CI)		**-14.3 (-31.3, 2.6)**
Difference from Placebo for % Change (CI)		**-19.9 (-41.9, 2.1) p=0.075**

(a) Ordinary LSM from ANOVA model including effects for gender, treatment and their interaction

Table 29: Study 22388 - Change & Percent Change from Baseline to Week 12 in Dorsocervical Fat (cm^2) by Treatment Group (Modified ITT Population w/ LOCF)

	Placebo n=22	Serostim 4 mg QOD n=29	Serostim 4 mg daily n=22
Baseline (SD)	125.4 (52.2)	113.7 (49.5)	137.1 (59.9)
Baseline (SE)[a]	122.8 (13.3)	98.8 (11.3)	133.8 (19.4)
Week 12 (SD)	125.5 (80.1)	96.8 (55.8)	103.0 (71.7)
Week 12 (SE)[a]	114.2 (17.6)	90.8 (15.0)	93.9 (25.6)
Change from Baseline (SD)	0.0 (42.5)	-17.0 (44.9)	-34.1 (41.7)
Change from Baseline (SE)[a]	-8.6 (10.8)	-8.0 (9.2)	-40.0 (15.7)
Raw Mean Difference from Placebo for Change (CI)		**-17.0 (-45.7, 11.7)**	**-34.2 (-64.8, -3.6) p<0.05**
Difference from Placebo for Change (CI)		**0.6 (-27.7, 28.9) p=0.965**	**-31.4 (-69.4, 6.6) p=0.104**
% Change from Baseline (SD)	-3.2 (29.9)	-9.4 (48.9)	-29.1 (29.3)
% Change from Baseline (SE)[a]	-10.9 (9.1)	4.4 (7.7)	-33.2 (13.2)
Raw Mean Difference from Placebo for % Change (CI)		**-6.2 (-30.4, 18.0)**	**-25.9 (-51.7, -0.1) p<0.05**
Difference from Placebo for % Change (CI)		**15.3 (-8.6, 39.1) p=0.205**	**-22.4 (-54.4, 9.7) p=0.168**

(a) Ordinary LSM from ANOVA model including effects for gender, treatment and their interaction

Table 30: Studies 22388 and 24380 - Changes from Baseline to Week 12 in Dorsocervical Fat Pad for Each Study and Integrated Overall by Treatment Group (Modified ITT Population) - Integrated ANOVA Performed by the Sponsor

Time Point		Study 22388		Study 24380		All Subjects	
		Placebo (n=22)	Serostim 4 mg daily (n=22)	Placebo (n=23)	Serostim 4 mg daily (n=74)	Placebo (n=45)	Serostim 4 mg daily (n=96)
Baseline	Mean (SD)	125.4 (52.2)	137.1 (59.9)	120.5 (96.4)	130.9 (99.4)	122.9 (77.2)	132.3 (91.6)
	Range	(35.3, 256.0)	(38.1, 251.6)	(12.3, 471.3)	(10.2, 440.4)	(12.3, 471.3)	(10.2, 440.4)
Week 12	Mean (SD)	125.5 (80.1)	103.0 (71.7)	96.9 (60.7)	99.7 (87.7)	110.8 (71.5)	100.4 (83.9)
	Range	(40.6, 319.1)	(17.9, 298.3)	(0.0, 191.7)	(0.0, 355.9)	(0.0, 319.1)	(0.0, 355.9)
Change from Baseline to Week 12	Mean (SD)	0.0 (42.5)	-34.1 (41.7)	-23.7 (61.9)	-31.2 (48.1)	-12.1 (54.1)	-31.9 (46.5)
	Range	(-66.6, 78.6)	(-123.3, 60.3)	(-279.6, 31.4)	(-203.5, 147.6)	(-279.6, 78.6)	(-203.5, 147.6)
	Mean (SE)	-8.6 (10.8)[c]	-40.0 (15.7)[c]	-19.8 (14.3)[c]	-32.0 (7.5)[c]	-15.1 (9.2)[a]	-30.6 (7.2)[a]
	Mean Diff. vs. Placebo (SE)	**-31.4 (-69.4, 6.6)[c]**		**-12.1 (-44.3, 20.1)[c]**		**-15.6 (11.7)[a]**	
	p-value	**0.104[c]**		**0.457[c]**		**0.050[b]**	
% Change from Baseline to Week 12	Mean (SD)	-3.2 (29.9)	-29.1 (29.3)	-13.0 (39.6)	-27.4 (34.1)	-8.2 (35.1)	-27.8 (32.9)
	Range	(-50.8, 43.1)	(-77.5, 25.3)	(-100.0, 95.2)	(-100.0, 70.9)	(-100.0, 95.2)	(-100.0, 70.9)
	Mean (SE)	-10.9 (9.1)[c]	-33.2 (13.2)[c]	-8.9 (9.8)[c]	-28.8 (5.2)[c]	-10.8 (6.3)[a]	-28.6 (5.0)[a]
	Mean Diff. vs. Placebo (SE)	**-22.4 (-54.4, 9.7)[c]**		**-19.9 (-41.9, 2.1)[c]**		**-17.8 (8.0)[a]**	
	p-value	**0.168[c]**		**0.075[c]**		**0.029[b]**	

(a) Ordinary least squares means from a three-way ANOVA model on raw data including effects for **study**, treatment, gender, and the treatment by gender interaction
(b) p-value from a three-way ANOVA model on ranked data including effects for **study**, treatment, gender, and the treatment by gender interaction
(c) **See Tables 28 and 29 earlier in review – ANOVA performed by sponsor**

6.1.4.4.1.6 Change in Non-HDL Cholesterol - Consequential Secondary Efficacy Endpoint (and a brief comment about changes in other lipid parameters)

The mean differences in the change from baseline to Week 12 in non-HDL cholesterol between the Serostim 4 mg QD group and the placebo group were significant in Study 24380 (**-15.0 mg/dL; p=0.034**; see Table 31 and Figure 16), and in the integrated analysis (**-13.1 mg/dL; p=0.002**; see Table 33), but not in Study 22388 (**-12.4 mg/dL; p=0.154**; see Table 32). As expected, the mean differences in the percent change from baseline to Week 12 in non-HDL cholesterol between these 2 treatment groups were also significant in Study 24380 (**-9.4%; p=0.024**; see Table 31), and in the integrated analysis (**-7.7%; p=0.001**; see Table 33), but not in Study 22388 (**-8.1%; p=0.093**; see Table 32). As seen in Table 32, **there was no apparent dose-response in Study 22388** (when the data were reanalyzed using an equally weighted ANOVA model).

Table 31: Study 24380 - Change & Percent Change from Baseline to Week 12 in Non-HDL Cholesterol (mg/dL) by Treatment Group (Modified ITT Population w/ LOCF)

	Placebo n=74	Serostim 4 mg daily n=226
Baseline (SD)	151.1 (37.1)	155.3 (41.5)
Baseline (SE)[a]	142.9 (7.2)	153.4 (3.8)
Week 12 (SD)	148.3 (40.0)	142.3 (38.9)
Week 12 (SE)[a]	147.5 (7.0)	143.0 (3.7)
Change from Baseline (SD)	-2.8 (28.1)	-13.0 (37.1)
Change from Baseline (SE)[a]	4.6 (6.2)	-10.4 (3.3)
Raw Mean Difference from Placebo for Change (CI)		**-10.2 (-19.4, -1.0)**
Difference from Placebo for Change (CI)		**-15.0 (-28.8, -1.2) p=0.034**
% Change from Baseline (SD)	-0.3 (18.6)	-6.1 (21.5)
% Change from Baseline (SE)[a]	5.6 (3.7)	-3.7 (1.9)
Raw Mean Difference from Placebo for % Change (CI)		**-5.8 (-11.2, -0.3)**
Difference from Placebo for % Change (CI)		**-9.4 (-17.5, -1.2) p=0.024**

(a) Ordinary LSM from ANOVA model including effects for gender, treatment and their interaction

Table 32: Study 22388 - Change & Percent Change from Baseline to Week 12 in Non-HDL Cholesterol (mg/dL) by Treatment Group (Modified ITT Population w/ LOCF)

	Placebo n=76	Serostim 4 mg QOD n=75	Serostim 4 mg daily n=74
Baseline (SD)	174.2 (43.9)	181.3 (46.0)	173.3 (45.3)
Baseline (SE)[a]	178.2 (7.7)	182.1 (7.7)	170.0 (7.7)
Week 12 (SD)	176.9 (40.2)	170.1 (45.4)	158.0 (41.9)
Week 12 (SE)[a]	179.3 (7.3)	170.8 (7.3)	158.8 (7.3)
Change from Baseline (SD)	2.7 (29.8)	-11.3 (39.7)	-15.4 (37.5)
Change from Baseline (SE)[a]	1.2 (6.1)	-11.4 (6.1)	-11.2 (6.1)
Raw Mean Difference from Placebo for Change (CI)		**-14.0 (-27.8, -0.1) p<0.05**	**-18.1 (-31.9, -4.2) p<0.05**
Difference from Placebo for Change (CI)		**-12.5 (-29.6, 4.5) p=0.149**	**-12.4 (-29.4, 5.7) p=0.154**
% Change from Baseline (SD)	3.4 (17.8)	-4.5 (21.5)	-6.7 (20.1)
% Change from Baseline (SE)[a]	2.2 (3.4)	-5.1 (3.4)	-5.9 (3.4)
Raw Mean Difference from Placebo for % Change (CI)		**-7.8 (-15.5, -0.2) p<0.05**	**-10.1 (-17.7, -2.4) p<0.05**
Difference from Placebo for % Change (CI)		**-7.3 (-16.7, 2.1) p=0.129**	**-8.1 (-17.5, 1.4) p=0.093**

(a) Ordinary LSM from ANOVA model including effects for gender, treatment and their interaction

Figure 16: Study 24380 - Change from Baseline to Week 12 in Non-HDL Cholesterol (mg/dL) by Treatment Group (Modified ITT Population)

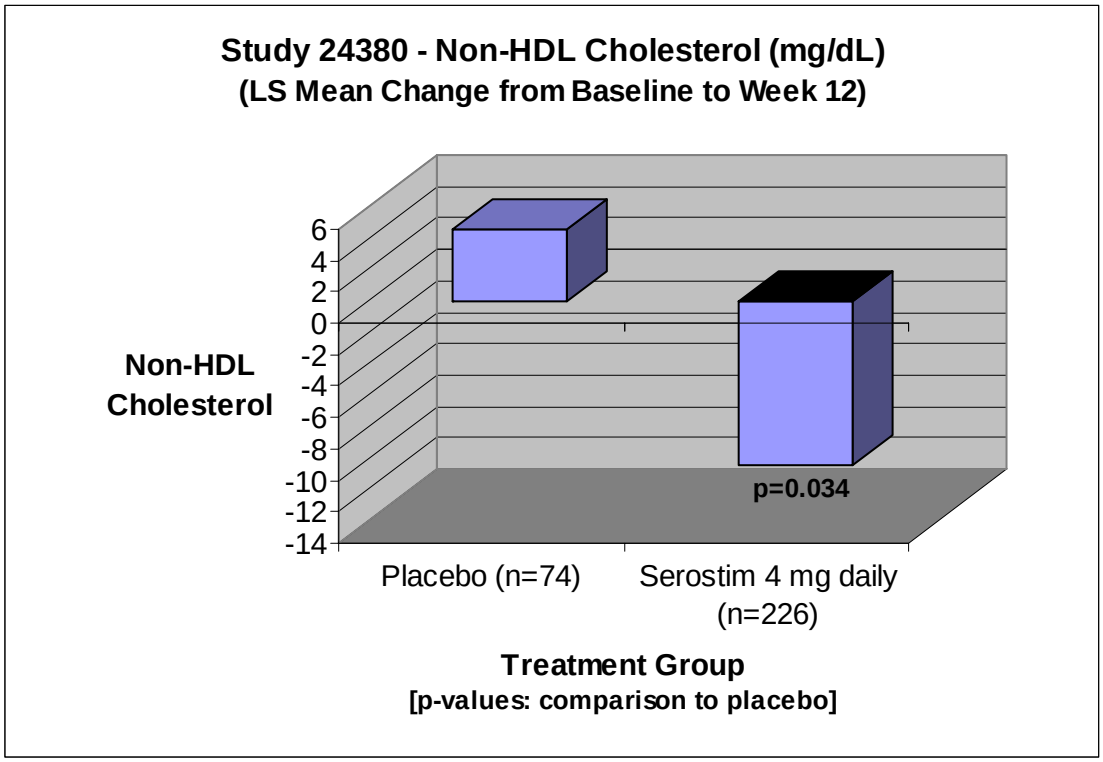


Table 33: Studies 22388 and 24380 - Changes from Baseline to Week 12 in Non-HDL Cholesterol (mg/dL) for Each Study and Integrated Overall by Treatment Group (Modified ITT Population) – Integrated ANOVA Performed by the Sponsor

Time Point		Study 22388		Study 24380		All Subjects	
		Placebo n=76	Serostim 4 mg daily (n=74)	Placebo (n=74)	Serostim 4 mg daily (n=226)	Placebo (n=150)	Serostim 4 mg daily (n=300)
Baseline	Mean (SD)	174.2 (43.9)	173.3 (45.3)	151.1 (37.1)	155.3 (41.5)	162.8 (42.2)	159.7 (43.1)
	Range	(79.0, 325.0)	(98.0, 269.0)	(81.0, 288.0)	(69.0, 311.0)	(79.0, 325.0)	(69.0, 311.0)
Week 12	Mean (SD)	176.9 (40.2)	158.0 (41.9)	148.3 (40.0)	142.3 (38.9)	162.8 (42.5)	146.2 (40.2)
	Range	(79.0, 274.0)	(74.0, 305.0)	(90.0, 363.0)	(51.0, 291.0)	(79.0, 363.0)	(51.0, 305.0)
Change from Baseline to Week 12	Mean (SD)	2.7 (29.8)	-15.4 (37.5)	-2.8 (28.1)	-13.0 (37.1)	0.0 (29.0)	-13.6 (37.2)
	Range	(-93.0, 63.0)	(-141.0, 63.0)	(-71.0, 75.0)	(-169.0, 118.0)	(-93.0, 75.0)	(-169.0, 118.0)
	Mean (SE)	1.2 (6.1)[c]	-11.2 (6.1)[c]	4.6 (6.2)[c]	-10.4 (3.3)[c]	2.7 (4.3)[a]	-10.4 (3.0)[a]
	Mean Diff. vs. Placebo (SE)	**-12.4 (-29.4, 5.7)[c]**		**-15.0 (-28.8, -1.2)[c]**		**-13.1 (5.2)[a]**	
	p-value	**0.154[c]**		**0.034[c]**		**0.002[b]**	
% Change from Baseline to Week 12	Mean (SD)	3.4 (17.8)	-6.7 (20.1)	-0.3 (18.6)	-6.1 (21.5)	1.6 (18.2)	-6.2 (21.1)
	Range	(-35.6, 61.2)	(-52.6, 54.1)	(-40.1, 43.2)	(-58.7, 95.2)	(-40.1, 61.2)	(-58.7, 95.2)
	Mean (SE)	2.2 (3.4)[c]	-5.9 (3.4)[c]	5.6 (3.7)[c]	-3.7 (1.9)[c]	3.7 (2.5)[a]	-3.9 (1.7)[a]
	Mean Diff. vs. Placebo (SE)	**-8.1 (-17.5, 1.4)[c]**		**-9.4 (-17.5, -1.2)[c]**		**-7.7 (3.0)[a]**	
	p-value	**0.093[c]**		**0.024[c]**		**0.001[b]**	

(a) Ordinary least squares means from a three-way ANOVA model on raw data including effects for **study**, treatment, gender, and the treatment by gender interaction
(b) p-value from a three-way ANOVA model on ranked data including effects for **study**, treatment, gender, and the treatment by gender interaction
(c) **See Tables 31 and 32 earlier in review – ANOVA performed by the sponsor**

6.1.4.4.1.6.1 Subgroup Analyses by Use or Non-Use of LLAs Prior to Study Entry/During the Study for Change from Baseline to Week 12 in Non-HDL Cholesterol - In Subjects With or Without Dyslipidemia at Baseline

As seen in Tables 34 and 35, in Study 22388, the mean differences in change and percent change from baseline to Week 12 in non-HDL cholesterol between the Serostim 4 mg QOD treatment group and the placebo group were significant when subjects were receiving concomitant LLAs (-27.5 mg/dL; p=0.008 & -13.0%; p=0.008), but were not significant when subjects were not receiving concomitant LLAs (data for the Serostim 4 mg QD group is not shown because of the integrated results described in the next sentence). As seen in Table 36, in an integrated analysis of Studies 22388 and 24380, the mean differences in change and percent change from baseline to Week 12 in non-HDL cholesterol between the Serostim 4 mg QD treatment group and the placebo group were highly significant when subjects were receiving concomitant LLAs (-26.8 mg/dL; p<0.001 & -13.7%; p<0.001), and were modestly significant when subjects were not receiving concomitant LLAs (-7.5 mg/dL; p=0.027 & -4.8%; p=0.027). **Taken together, these results suggest that Serostim (rhGH) and LLAs may act synergistically in lowering levels of non-HDL cholesterol in these subjects with HARS**.

Table 34: Study 22388 - Change & Percent Change from Baseline to Week 12 in Non-HDL Cholesterol (mg/dL) by Treatment Group (Modified ITT Population) (Subjects Being Treated with Lipid Lowering Agents)

Time Point		Placebo n=22	Serostim 4 mg QOD n=25
Baseline	Mean (SD) Range	194.1 (42.6) (121.0, 325.0)	188.0 (59.1) (103.0, 324.0)
	Mean (SE)[a]	194.1 (10.7)	188.0 (10.0)
Week 12	Mean (SD) Range	205.2 (35.4) (154.0, 274.0)	171.6 (53.6) (89.0, 272.0)
	Mean (SE)[a]	205.2 (9.3)	171.6 (8.7)
Change from Baseline to Week 12	Mean (SD) Range	11.1 (29.7) (-81.0, 56.0)	-16.4 (54.4) (-154.0, 91.0)
	Mean (SE)[a]	11.1 (10.1)	-16.4 (9.5)
	Mean Diff. vs. Placebo (SE)[a]		**-27.5 (13.9)**
	p-value vs. Placebo[b]		**0.008**
% Change from Baseline to Week 12	Mean (SD) Range	7.5 (15.3) (-24.9, 46.3)	-5.5 (28.2) (-47.5, 60.3)
	Mean (SE)[a]	7.5 (5.2)	-5.5 (4.9)
	Mean Diff. vs. Placebo (SE)[a]		**-13.0 (7.1)**
	p-value vs. Placebo[b]		**0.008**

(b) (4)

Table 35: Study 22388 - Change & Percent Change from Baseline to Week 12 in Non-HDL Cholesterol (mg/dL) by Treatment Group (Modified ITT Population) (Subjects Not Being Treated with LLAs)

Time Point		Placebo n=54	Serostim 4 mg QOD n=50
Baseline	Mean (SD) Range	166.1 (42.1) (79.0, 261.0)	178.0 (38.1) (104.0, 278.0)
	Mean (SE)[a]	166.1 (5.8)	178.0 (6.1)
Week 12	Mean (SD) Range	165.4 (36.4) (79.0, 236.0)	169.3 (41.2) (87.0, 312.0)
	Mean (SE)[a]	165.4 (5.6)	169.3 (5.8)
Change from Baseline to Week 12	Mean (SD) Range	-0.7 (29.4) (-93.0, 63.0)	-8.7 (30.1) (-64.0, 74.0)
	Mean (SE)[a]	-0.7 (4.2)	-8.7 (4.4)
	Mean Diff. vs. Placebo (SE)[a]		**-8.0 (6.0)**
	p-value vs. Placebo[b]		**0.092**
% Change from Baseline to Week 12	Mean (SD) Range	1.7 (18.6) (-35.6, 61.2)	-3.9 (17.5) (-30.0, 50.3)
	Mean (SE)[a]	1.7 (2.5)	-3.9 (2.6)
	Mean Diff. vs. Placebo (SE)[a]		**-5.6 (3.6)**
	p-value vs. Placebo[b]		**0.077**

(b) (4)

on ranked data including effects for treatment, gender, and their interaction

Table 36: Studies 22388 and 24380 - Change and Percent Change from Baseline to Week 12 in Non-HDL Cholesterol (mg/dL) Integrated Overall by Treatment Group For Subjects Who Received LLAs vs. Those Who Did Not (Modified ITT Population) - Integrated ANOVA Performed by the Sponsor

		Modified ITT Subjects			
		On LLA		Not on LLA	
Time Point		Placebo n=48	Serostim 4 mg daily n=93	Placebo n=102	Serostim 4 mg daily n=207
Baseline	Mean (SD)	170.0 (42.2)	170.9 (45.5)	159.5 (41.9)	154.7 (41.1)
	Range	(81.0, 325.0)	(78.0, 311.0)	(79.0, 288.0)	(69.0, 269.0)
Week 12	Mean (SD)	171.4 (45.3)	145.5 (41.6)	158.8 (40.7)	146.5 (39.6)
	Range	(93.0, 274.0)	(64.0, 291.0)	(79.0, 363.0)	(51.0, 305.0)
Change from Baseline to Week 12	Mean (SD)	1.5 (30.5)	-25.4 (48.0)	-0.7 (28.4)	-8.3 (29.7)
	Range	(-81.0, 64.0)	(-169.0, 109.0)	(-93.0, 75.0)	(-136.0, 118.0)
	Mean Diff. vs. Placebo (SE)[a]	**-26.8 (6.1)**		**-7.5 (4.2)**	
	p-value[b]	**<0.001**		**0.027**	
% Change from Baseline to Week 12	Mean (SD)	1.9 (17.6)	-12.0 (24.2)	1.4 (18.6)	-3.6 (19.1)
	Range	(-40.1, 46.3)	(-58.7, 79.0)	(-36.2, 61.2)	(-58.4, 95.2)
	Mean Diff. vs. Placebo (SE)[a]	**-13.7 (3.6)**		**-4.8 (2.5)**	
	p-value[b]	**<0.001**		**0.027**	

(a) Least squares means from a three-way ANOVA model on raw data including effects for **study**, treatment, lipid lowering status, and the treatment by lipid lowering status interaction
(b) p-value from a three-way ANOVA model on ranked data including effects for **study**, treatment, lipid lowering status, and the treatment by lipid lowering status interaction

6.1.4.4.1.6.2 Brief Comment About Changes in Other Lipid Parameters

LDL Cholesterol: Treatment effects (vs. placebo) were not significant in Study 24380 and barely significant in Study 22388 (even with a proportionately weighted ANOVA model)

HDL Cholesterol: Treatment effects (vs. placebo) were not significant in Study 22388, and modestly significant treatment effect noted in Study 24380 disappeared when the analysis was reperformed with an equally weighted ANOVA model.

Total Cholesterol: Treatment effects (vs. placebo) were not significant in Study 24380. Treatment effects for both doses of Serostim (vs. placebo) were significant in Study 22388; however, a proportionately weighted ANOVA model was used by the sponsor.

6.1.4.4.1.7 Change in Lean Body Mass - Consequential Secondary Efficacy Endpoint

The mean differences in the change from baseline to Week 12 in LBM between the Serostim 4 mg QD group and the placebo group were significant in Study 24380 (**+3.2 kg; p<0.001**; see Table 37), Study 22388 (**+3.2 kg; p<0.001**; see Table 37), and in the integrated analysis (**+3.1 kg; p<0.001**; data not shown in a table). As expected, the mean differences in the percent change from baseline to Week 12 in LBM between these 2 treatment groups were also significant in Study 24380 (**+6.0%; p<0.001**; see Table 37), Study 22388 (**+6.3%; p<0.001**; see Table 37), and in the integrated analysis (**+5.9%; p<0.001**; see Table 37).

As seen in Table 37, **the mean difference in the change from baseline to Week 12 in LBM between the Serostim 4 mg QOD group and the placebo group was significant (+2.3 kg; p<0.001), but clearly smaller than the difference observed after treatment with Serostim 4 mg QD vs. placebo (+3.2 kg).**

In other words, there was a dose-response observed with respect to change from baseline to Week 12 in LBM.

Table 37: Studies 22388 and 24380 - Treatment Difference vs. Placebo for Change and Percent Change from Baseline to Week 12 in Lean Body Mass

Study	22388	22388	24380	22388 + 24380
Lean Body Mass	**Serostim 4 mg QOD**	**Serostim 4 mg QD**	**Serostim 4 mg QD**	**Serostim 4 mg QD**
Study 22388[a]	**+2.3 kg** (1.2, 3.5)[c] p<0.001 **+4.3%** (2.4, 6.3) p<0.001	**+3.2 kg** (2.0, 4.5)[c] p<0.001 **+6.3%** (4.2, 8.5) p<0.001	XX	XX
Study 24380[a]	XX	XX	**+3.2 kg** (2.2, 4.2)[d] p<0.001 **+6.0%** (4.3, 7.7) p<0.001	XX
Studies 22388 & 24380 Combined/ Integrated[a]	XX	XX	XX	**+3.1 kg**[b] p<0.001 **+5.9%**[b] p<0.001

(a) Ordinary least squares mean (CI) and p-values from ANOVA including effects for treatment, gender and treatment by gender interaction
(b) LSM Change from Baseline (SE) = 0.0 (0.3) for placebo and 3.1 (0.2) for Serostim 4 mg QD; LSM % Change from Baseline (SE) = 0.1 (0.5) for placebo and 6.0 (0.4) for Serostim 4 mg QD in the Integrated Analysis
(c) LSM Change from Baseline (SE) = 0.1 (0.4) & 2.5 (0.4) & 3.3 (0.5) for placebo & Serostim 4 mg QOD & Serostim 4 mg QD, respectively, in Study 22388
(d) LSM Change from Baseline (SE) = -0.1 (0.5) & 3.1 (0.2) for placebo & Serostim 4 mg QD, respectively, in Study 24380

6.1.4.4.1.8 Change in Belly Appearance Distress (BAD), Belly Size Evaluation (BSE) - Two Most Consequential Patient-Reported Outcomes as Secondary Efficacy Endpoints (Induction Phase - Weeks 0-12)

BAD and BSE results are presented in 3 different ways: 1) responder analyses were performed by the sponsor; 2) a (revised post-hoc) ANCOVA model was used by the sponsor to determine the differences in change from baseline to Week 12 in BAD and BSE scores after treatment with Serostim 4 mg QD and Serostim 4 mg QOD vs. placebo; and 3) CDF curves were constructed by the Division's Statistical Reviewer.*
*BPA results are not presented because the Division's SEALD consultant did not think it was appropriate to present the results of a parameter which was used as an anchor to determine the responder criteria for BAD and BSE.

6.1.4.4.1.8.1 Responder Analyses

The numerical product of the "minimum benefit" for the BPA at baseline (prior to any treatment) and the change score from baseline to Week 12 in BPA was used as an anchor in each study to calibrate/validate/interpolate the "minimum benefit" for BAD and BSE (using a regression line derived from blinded data). The "minimum benefits" for BAD and BSE were then used as responder criteria for responder analyses comparing treatment groups (see Sections 6.1.3.6.1.3 and 6.1.3.7.3). **It is important to note that the Division's SEALD consultant completely agreed with the above described derivation of responder criteria (even though it was not prespecified in the protocol).***
It should be noted that the "minimum benefit" for the BPA and the change score for the BPA was also generated based on the perceptions of the patient's treating physician; however, it was felt by the Agency's SEALD consultant that **patient-derived data (as described above) would be more appropriate** for these analyses.

The responder criteria obtained in this fashion were as follows:

BAD Study 22388: Responder criterion was +20 rounded off to +25 = 2 scale units
Study 24380: Responder criterion was +30 rounded off to +25 = 2 scale units
BSE Study 22388: Responder criterion was -39 rounded off to -50 = 2 scale units
Study 24380: Responder criterion was -44 rounded off to -50 = 2 scale units

<u>Therefore, in each instance, a subject would need to improve by at least 2 scale units to be designated a responder</u>. The Division's SEALD consultant felt <u>very strongly</u> that a change of 2 scale units was <u>mandatory</u> for a subject to be designated as a responder, and therefore was in total agreement with these criteria.

The results of the responder analyses are presented in Table 38. The numbers in Table 38 are raw means, and the p-values were determined using Fisher's Exact Test. **The differences in the proportion of subjects who were designated as responders for BAD and BSE after treatment with Serostim 4 mg QD vs. placebo for 12 weeks in Studies 23388 and 24380 were highly significant (only 1 p-value was >0.002)**.

A dose-response was apparent in that none of the differences in the proportion of subjects who were designated as responders for BAD and BSE after treatment with Serostim 4 mg QOD vs. placebo for 12 weeks in Study 22388 were significant.

Table 38: Studies 24380 and 22388 - Responder Analyses: Percentage of Subjects in Each Treatment Group Whose Change Score from Baseline in BAD, BSE and BPA Exceeded the Responder Criterion Derived from the Patient-Reported Smallest Acceptable Benefit in BPA at Baseline and the Change Score from Baseline in BPA; and Whose Change Score from Baseline in BPA was More Negative than the Difference Between the Current Look Belly Profile and the Smallest Acceptable Benefit Profile at Baseline

Parameter	Study	Placebo	Serostim 4 mg QOD	Serostim 4 mg QD
Belly Appearance Distress	22388	17.9%	**26.6% p=0.250***	**45.7% p<0.001***
	24380	11.9%	---	**32.9% p<0.001***
Belly Size Evaluation	22388	23.1%	**32.9% p=0.214***	**39.5% p=0.028***
	24380	23.9%	---	**43.1% p<0.001***
Belly Profile Assessment	22388	6.4%	**15.2% p=0.121***	**24.7% p=0.002***
	24380	6.3%	---	**24.0% p<0.001***

*Fisher's Exact Test (2-sided), as shown in the "Chi-Square Tests" tables in the sponsor's submission **was used to calculate the p-values (vs. placebo)**

6.1.4.4.1.8.2 Analysis of Change from Baseline to Week 12 for BAD and BSE

The mean differences in the change from baseline to Week 12 in BAD between the Serostim 4 mg QD group and the placebo group were significant in Study 24380 (**19.2 points; p<0.001**; see Table 39 and Figure 17) and Study 22388 (**9.9 points; p=0.041**; see Table 40 and Figure 18). **The mean differences in the change from baseline to Week 12 in BSE between the Serostim 4 mg QD group and the placebo group were also significant** in Study 24380 (**-41.6 points; p<0.001**; see Table 41 and Figure 19) and Study 22388 (**-26.4 points; p=0.016**; see Table 42 and Figure 20).

As seen in Tables 40 and 42, and Figures 18 and 20, **the mean differences in the change from baseline to Week 12 in BAD and BSE between the Serostim 4 mg QOD group and the placebo group in Study 22388 were not significant (3.5 points; p=0.480 and -12.3 points; p=0.260, respectively), and clearly smaller than the differences observed after treatment with Serostim 4 mg QD vs. placebo (9.9 points and -26.4 points).**

In other words, there was a dose-response observed with respect to change from baseline to Week 12 in BAD and BSE.

Of note, none of the treatment by gender interactions were significant (P>0.1) in any of these analyses - except for a minimally significant (p=0.077) treatment by gender interaction for the change score in the BSE analysis for Study 24380. A subgroup analysis by gender was felt not to be necessary.

Furthermore, the sponsor reported that increases in BAD correlated with decreases in VAT (the primary efficacy endpoint). Since the analyses were exploratory, the data are not shown.

Table 39: Study 24380 - Change from Baseline to Week 12 in Belly Appearance Distress by Treatment Group (Modified ITT Population w/ LOCF)

	Placebo n=77	Serostim 4 mg daily n=229
Baseline (SE)[a]	17.2 (4.1)	25.8 (2.3)
Week 12 (SE)[a]	23.6 (4.6)	42.8 (2.5)
Change from Baseline (SE)[a]	-0.5 (4.6)	18.7 (2.5)
Difference from Placebo for Change (CI)		**19.2 (8.9, 29.5) p<0.001**

(a) Ordinary LSM from ANCOVA model including effects for gender, treatment, and treatment by gender interaction with age as a universal covariate and Week 12 BAD score as covariate for the change score only

Table 40: Study 22388 - Change from Baseline to Week 12 in Belly Appearance Distress by Treatment Group (Modified ITT Population w/ LOCF)

	Placebo n=76	Serostim 4 mg QOD n=78	Serostim 4 mg daily n=79
Baseline (SE)[a]	13.4 (2.8)	14.3 (2.8)	13.4 (2.9)
Week 12 (SE)[a]	23.0 (3.4)	26.4 (3.4)	32.91 (3.5)
Change from Baseline (SE)[a]	4.8 (3.4)	8.2 (3.4)	14.72 (3.5)
Difference from Placebo for Change (CI)		3.5 (-6.0, 13.0) p=0.480	**9.9 (0.4, 19.5) p=0.041**

(a) Ordinary LSM from ANCOVA model including effects for gender, treatment, and treatment by gender interaction with age as a universal covariate and BSE score as covariate for the change score only

Table 41: Study 24380 - Change from Baseline to Week 12 in Belly Size Evaluation by Treatment Group (Modified ITT Population w/ LOCF)

	Placebo n=77	Serostim 4 mg daily n=230
Baseline (SE)[a]	44.7 (8.4)	61.1 (4.6)
Week 12 (SE)[a]	55.6 (8.8)	14.1 (4.9)
Change from Baseline (SE)[a]	1.6 (8.8)	-40.0 (4.9)
Difference from Placebo for Change (CI)		**-41.6 (-61.5, -21.7) p<0.001**

(a) Ordinary LSM from ANCOVA model including effects for gender, treatment, and treatment by gender interaction with age as a universal covariate and Week 12 BSE score as covariate for the change score only

Table 42: Study 22388 - Change from Baseline to Week 12 in Belly Size Evaluation by Treatment Group (Modified ITT Population w/ LOCF)

	Placebo n=77	Serostim 4 mg QOD n=78	Serostim 4 mg daily n=79
Baseline (SE)[a]	57.9 (6.5)	75.9 (6.5)	72.0 (6.5)
Week 12 (SE)[a]	54.9 (7.7)	42.5 (7.7)	28.5 (7.7)
Change from Baseline (SE)[a]	-10.2 (7.7)	-22.6 (7.7)	-36.6 (7.7)
Difference from Placebo for Change (CI)		-12.3 (-33.9, 9.2) 0.260	**-26.4 (-47.9, -4.9) p=0.016**

(a) Ordinary LSM from ANCOVA model including effects for gender, treatment, and treatment by gender interaction with age as a universal covariate and BSE score as covariate for the change score only

Figure 17: Study 24380 - Comparison of Mean Changes from Baseline to Week 12 in Belly Appearance Distress After Treatment with Serostim 4 mg QD vs. Placebo

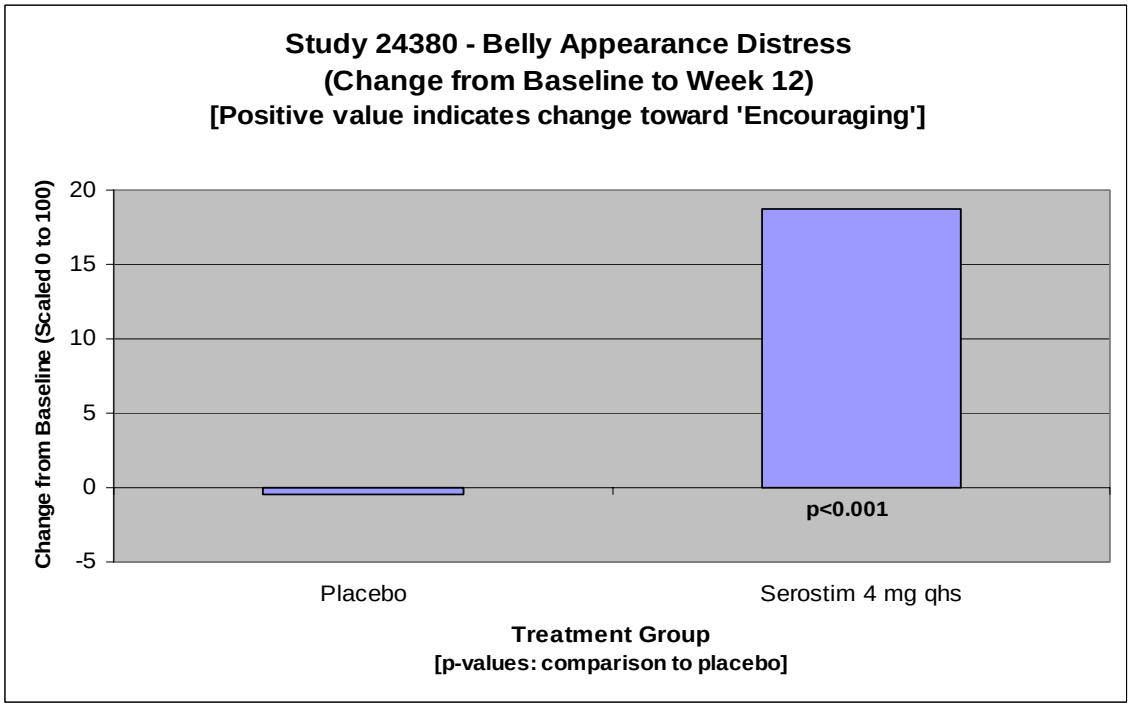
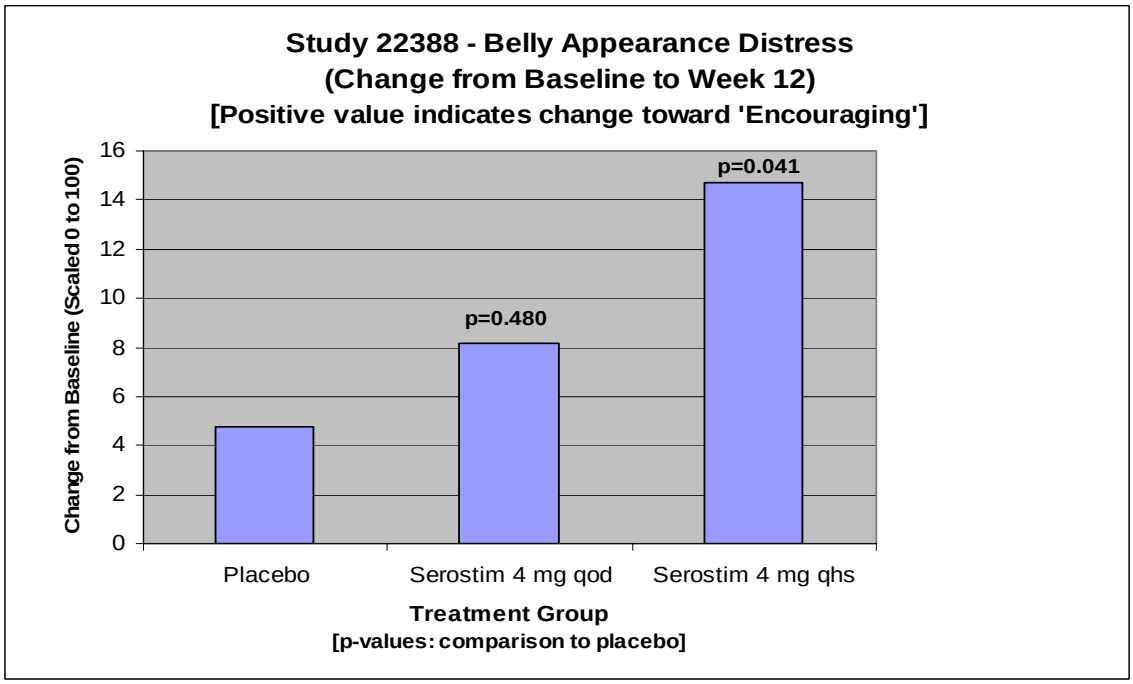
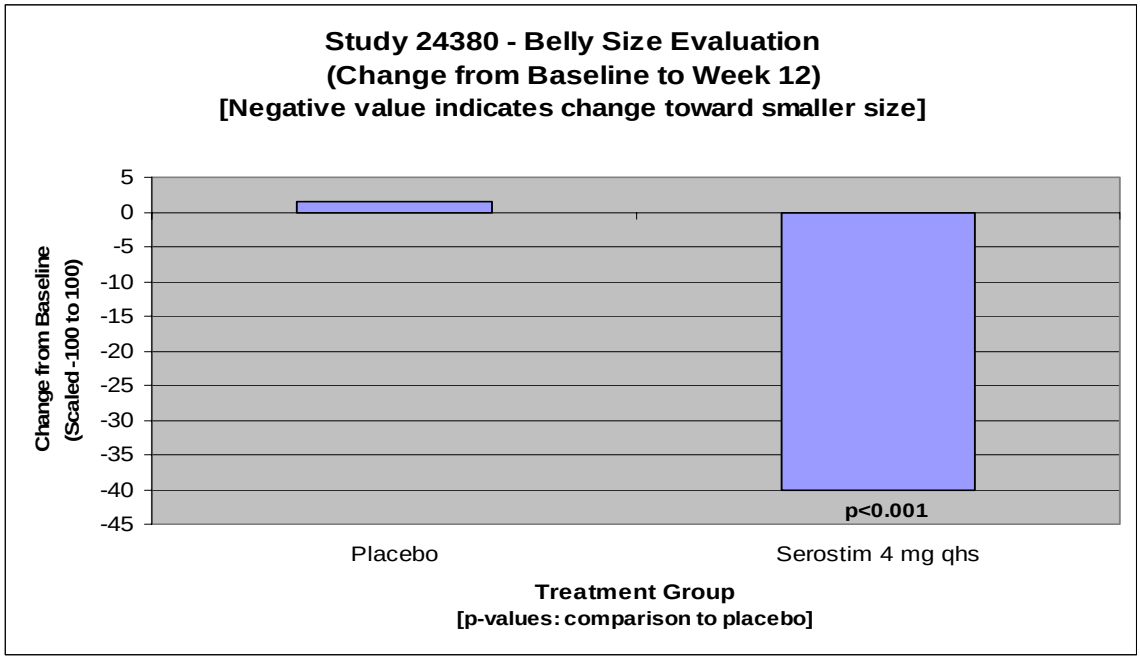


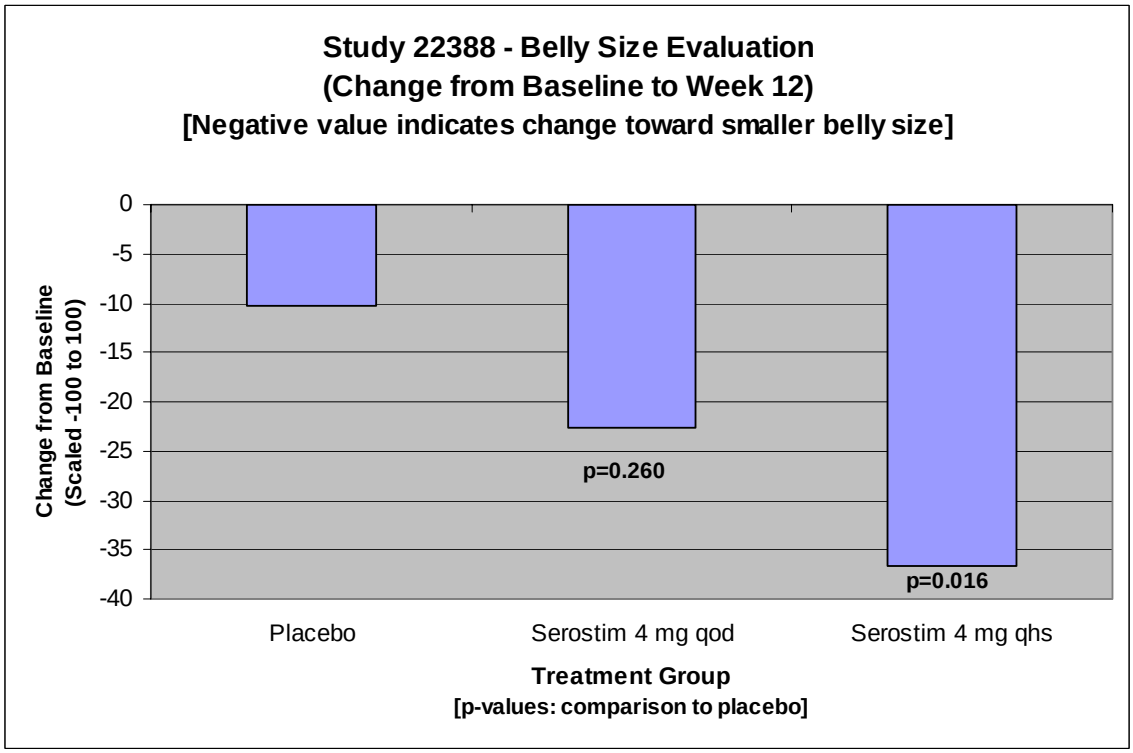
Figure 18: Study 22388 - Comparison of Mean Changes from Baseline to Week 12 in Belly Appearance Distress After Treatment with Serostim 4 mg QD and Serostim 4 mg QOD vs. Placebo



Figures 19: Study 24380 - Comparison of Mean Changes from Baseline to Week 12 in Belly Size Evaluation After Treatment with Serostim 4 mg QD vs. Placebo



Figures 20: Study 22388 - Comparison of Mean Changes from Baseline to Week 12 in Belly Size Evaluation After Treatment with Serostim 4 mg QD and Serostim 4 mg QOD vs. Placebo



6.1.4.4.1.8.2.1 Correlations of Changes from Baseline to Week 12 in BAD and BSE to Changes from Baseline to Week 12 in VAT and Trunk Fat

Of significant interest to this Medical Officer, the sponsor performed correlation analyses (?Spearman's test?) to assess the relationship between changes from baseline to Week 12 in BAD/BSE and changes from baseline to Week 12 in VAT (the primary efficacy endpoint) and trunk fat (1 of the most consequential non-PRO secondary efficacy endpoints). As seen in Table 43, **significant correlations (p=0.01) were observed between changes in BAD (as well as BSE) and changes in VAT and trunk fat**.

Table 43: ?Study 24380? – Correlations of Changes in BAD and BSE with Changes in VAT and Trunk Fat After Treatment with ?Serostim 4 mg QD? During the Induction Phase - Weeks 0-12

Correlations

			VAT Chg from BL to Week 12	Trunk Fat Chg from BL to Week 12	Trunk:Limb Fat Ratio Chg BL-Wk 12
Spearman's rho	Belly Size	Correlation Coefficient	.185**	.276**	.206**
		Sig. (2-tailed)	.000	.000	.000
		N	396	411	411
	Belly Appearance	Correlation Coefficient	-.246**	-.344**	-.251**
		Sig. (2-tailed)	.000	.000	.000
		N	396	411	411
	Body Size	Correlation Coefficient	.181**	.232**	.223**
		Sig. (2-tailed)	.000	.000	.000
		N	396	411	411
	Body Appearance	Correlation Coefficient	-.250**	-.306**	-.226**
		Sig. (2-tailed)	.000	.000	.000
		N	396	411	411

**. Correlation is significant at the 0.01 level (2-tailed).

6.1.4.4.1.8.3 Cumulative Distribution Functions for BAD and BSE During the Induction Phase (Weeks 0-12) of Studies 24380 and 22388

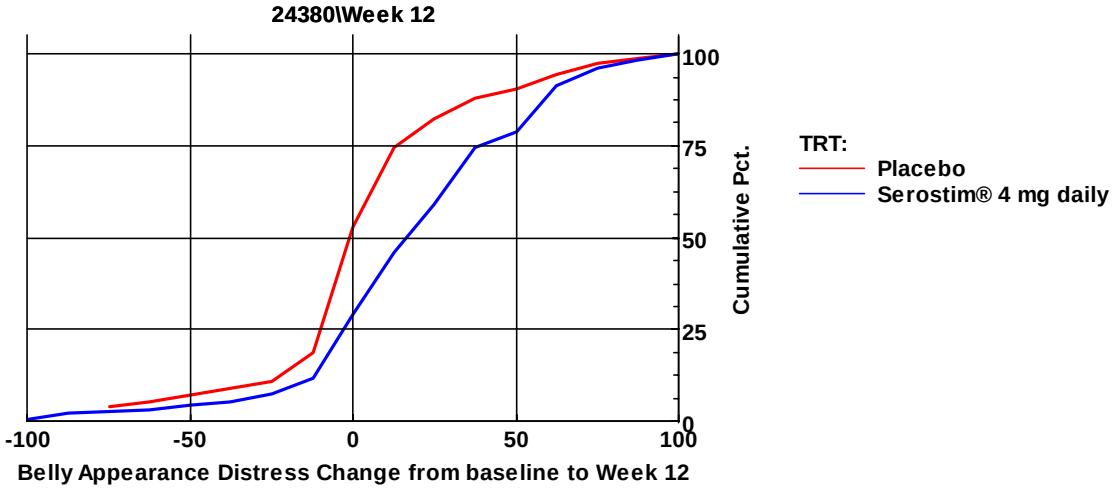
BAD (see Figures 21 and 22)

The **non-responder rates** (defined as the cumulative percentage of subjects with a change score <0) were **~25% and ~50%** for the Serostim 4 mg QD and placebo groups, respectively, in both studies.

The cumulative percentages of patients with a BAD change score **>25 (equal to 2 scale units)** were **~40% and ~20%** in the Serostim 4 mg QD and placebo groups, respectively, in Study 24380 (which crudely corresponds to **32.9% and 11.9%** in the responder analysis table [Table 38]).

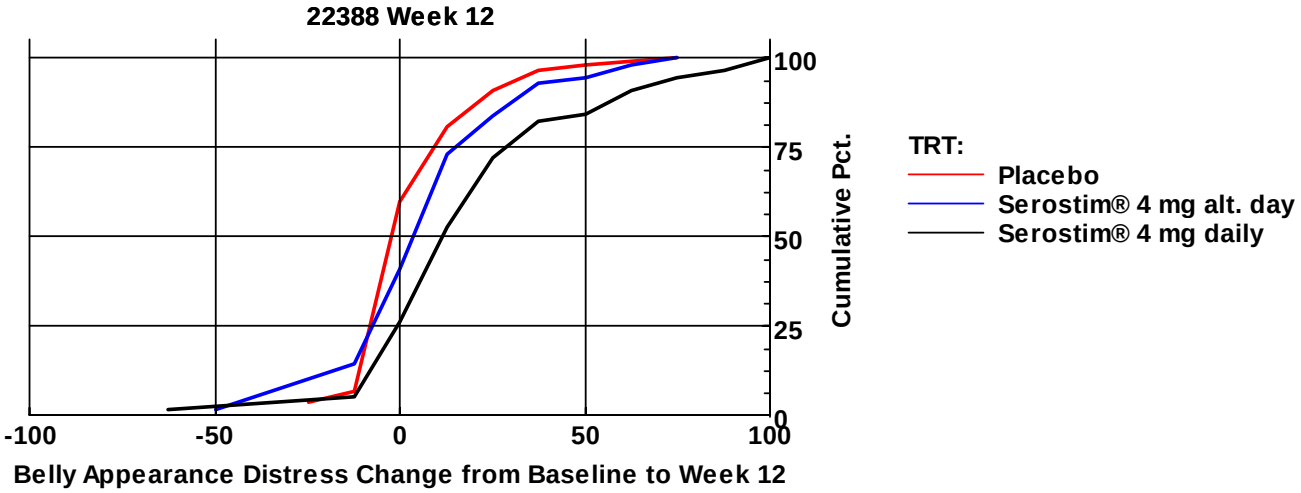
The cumulative percentages of patients with a BAD change score >25 (equal to 2 scale units) were **~30% and ~10%** in the Serostim 4 mg QD and placebo groups, respectively, in Study 22388 (very crudely corresponding to **45.7% and 17.9%** in the responder analysis table [Table 38]).

Figure 21: Study 24380 - Cumulative Distribution Function for Change from Baseline to Week 12 in BAD Score



More Distress **More Encouraging**

Figure 22: Study 22388 - Cumulative Distribution Function for Change from Baseline to Week 12 in BAD Score



More Distress **More Encouraging**

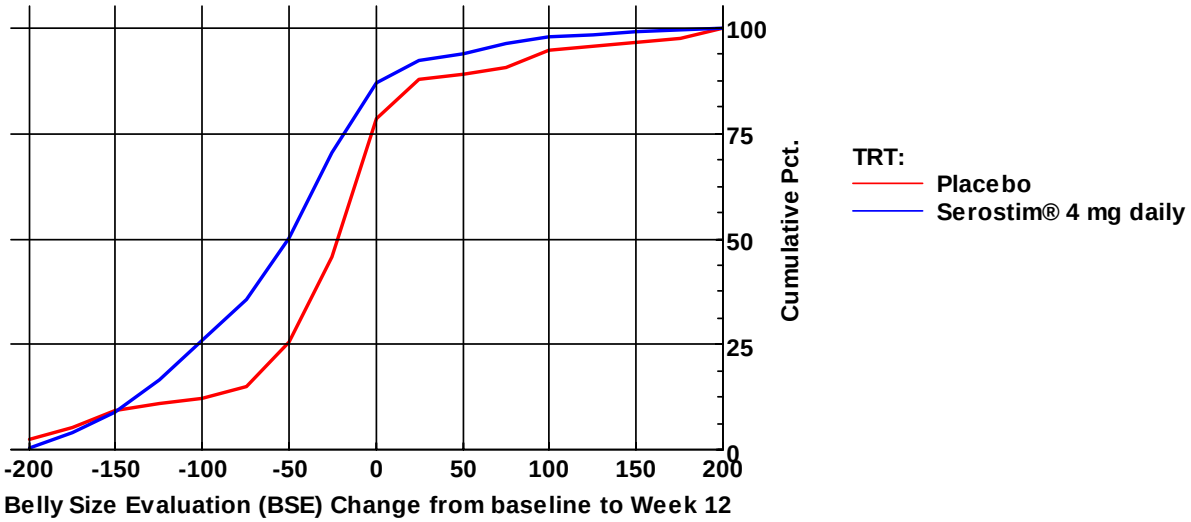
BSE (see Figures 23 and 24)

The **non-responder rates** (defined as the cumulative percentage of subjects with a change score >0) were **~12% and ~25%** for the Serostim 4 mg QD and placebo groups, respectively, in Study 24380, and ~9% and 12% for the Serostim 4 mg QD and placebo groups, respectively, in Study 22388.

The cumulative percentages of patients with a BAD change score **<-50 (equal to 2 scale units)** were **~45% and ~25%** in the Serostim 4 mg QD and placebo groups, respectively, in Study 24380 (corresponding **very well** to **43.1% and 23.9%** in the responder analysis table [Table 38]).

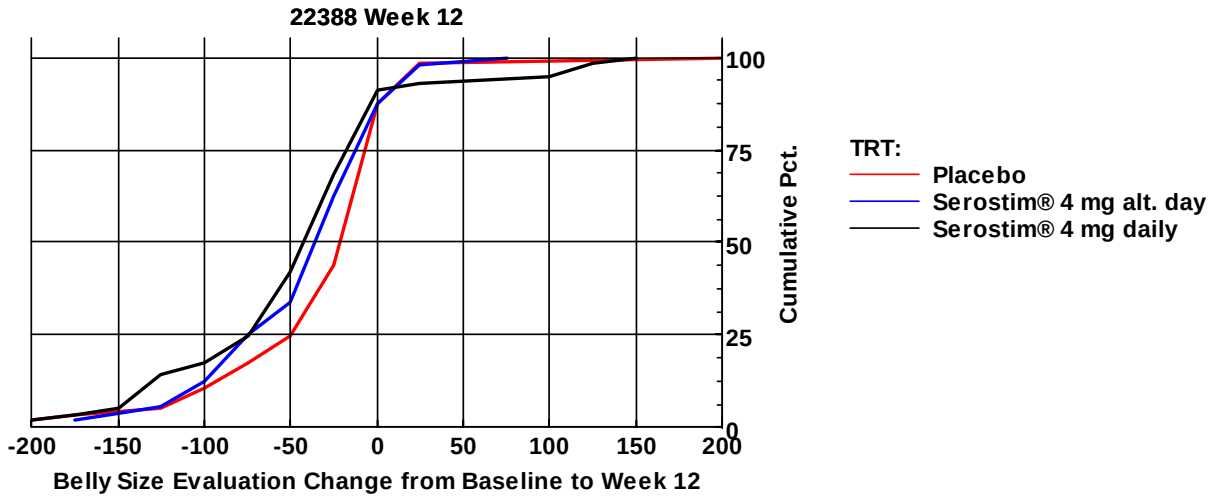
The cumulative percentages of patients with a BAD change score **<-50 (equal to 2 scale units)** were **~40% and ~25%** in the Serostim 4 mg QD and placebo groups, respectively, in Study 22388 (again corresponding **very well** to **39.5% and 23.1%** in the responder analysis table [Table 38]).

Figure 23 : Study 24380 - Cumulative Distribution Function for Change from Baseline to Week 12 in BSE Score



Belly Size Smaller **Belly Size Bigger**

Figure 24: Study 22388 - Cumulative Distribution Function for Change from Baseline to Week 12 in BSE Score



Belly Size Smaller Belly Size Bigger

6.1.4.4.2 Maintenance Phase Efficacy Results

6.1.4.4.2.1 Study 22388 (Weeks 12-24)

Pilot data that indicated that maintenance therapy is needed came from an open-label pilot study (53), and **data generated during Weeks 12-24 of Study 22388**. In order to evaluate the efficacy of a Serostim regimen for maintenance therapy in HARS, the subjects in Study 22388 who were initially treated with Serostim 4 mg QD for 12 weeks during the induction phase were rerandomized to receive either Serostim 4 mg QOD (n=34) or placebo (n=33) at the end of Week 12 (i.e., a blinded randomized withdrawal) for 12 weeks of maintenance therapy (see Figure 1 for design cartoon). During Study 22388, the reduction in VAT that had occurred from baseline to Week 12 after treatment with Serostim 4 mg QD was not sustained in the placebo group (p=0.001 at Week 12 [vs. baseline] and p=0.273 at Week 24 [vs. baseline]) **and, in fact, VAT reaccumulated, with a mean increase of 17.7 cm^2 between Weeks 12 and 24**. In contrast, a sustained decrease in VAT was observed in the Serostim 4 mg QOD group (p<0.001 at Weeks 12 and 24 [vs. baseline]). **These findings indicated that Serostim "maintenance" therapy warranted further study. Data is not shown for these preliminary results**.

6.1.4.4.2.2 Study 23056 (Weeks 12-36) (Equivalent to Weeks 36-60 of Studies 22388-23056 Combined)

The dosing regimen of Serostim selected for evaluation as a maintenance therapy in patients with HARS was determined from Study 23056 - a 36 week, open label, parallel group, multicenter, partially randomized extension trial proceeding from Study 22388 (see Figure 2 for design cartoon).

The Serostim maintenance therapies (1 mg QD vs. 2 mg QD) were administered for 24 weeks (**Weeks 36-60 of Studies 22388-23056 combined**) after a 12 week period (Weeks 24-36 of Studies 22388-23056 combined) during which subjects from Study 22388 were retreated with Serostim 4 mg QD or 2 mg QD (unless they had previously been switched to Serostim 1 mg QD due to toxicity) (see Figure 2 for design cartoon). Expressed another way, during the **24 week maintenance period of Study 23056** (Weeks 12-36 **equivalent to Weeks 36-60 of Studies 22388-23056 combined**), subjects were assigned to treatment with Serostim 1 mg QD vs. 2 mg QD after being treated with varying doses of Serostim for the previous 36 weeks (subjects who had experienced study drug toxicity during the first 36 weeks of the combined study were assigned only to the 1 mg maintenance group).

It was not possible to measure VAT by CT scan during the maintenance period of Study 23056 because it would have exposed subjects to excessive radiation in that they had already received CT scans at baseline, Week 12, and Week 24 in Study 22388. However, it was possible to assess change in trunk fat over the entire 60 week course of Studies 22388-23056 combined by DEXA scan (minimal radiation exposure - performed at baseline and Weeks 12, 24, 36, and 60 of the combined study).

As seen in Table 44, during Weeks 36-60 of Studies 22388-23056 combined, **the expected reaccumulation of trunk fat after maintenance treatment with Serostim 1 mg QD vs. Serostim 2 mg QD was very similar** (0.4 kg [8.1% increase] and 0.6 kg [8.1% increase], respectively). **While on maintenance therapy with either dose, subjects sustained a substantial amount of the trunk fat loss that they had achieved during the prior 36 week period**. In addition, both maintenance treatments succeeded in significantly maintaining reductions in non-HDL (and total) cholesterol (data not shown).

The Weeks 36-60 maintenance period of Studies 22388-23056 combined was not placebo controlled and patients were treated differently during Weeks 0-36; however, it should be noted that the subjects in the 2 maintenance groups of interest did receive equal amounts of Serostim in total during Weeks 0-36. **In any case, given the fact that Serostim 1 mg QD had essentially the same efficacy (and safety) profile as Serostim 2 mg QD during the 24 week maintenance period, Serostim 1 mg QD was chosen for further evaluation during the maintenance period in Study 24380** (see Section 6.1.4.4.2.3).

Table 44: Studies 22388-23056 Combined - Change During 60 Weeks of Serostim Exposure in Trunk Fat (kg) (Modified ITT Population)

Time Point		Serostim 1 mg daily n=64	Serostim 2 mg daily n=26
Baseline	Mean (SD)	9.5 (3.8)	9.8 (4.5)
Week 36	n Mean (SD)	8.0 (3.8)	7.9 (3.7)
Week 60	n Mean (SD)	8.4 (3.5)	8.5 (4.1)
Change from Week 36 to Week 60	**Mean (SD)** **p-value[b]** **p-value[a]**	**+0.4 (1.2)** **0.009** **---**	**+0.6 (1.1)** **0.009** **0.393**
% Change from Week 36 to Week 60	**Mean (SD)** **p-value[b]** **p-value[c]**	**+8.1 (19.1)** **0.003** **---**	**+8.1 (14.8)** **0.011** **0.713**
Change from Baseline to Week 60	Mean (SD) p-value[b] p-value[a]	-1.1 (2.2) <0.001 ---	-1.4 (2.2) 0.002 0.921

(a) From a two-way ANOVA model on ranked data including effects for treatment, gender and their interaction (Serostim 1 mg QD vs. Serostim 2 mg QD)
(b) From a Wilcoxon Signed-Rank test for the within group change
(c) From an ANCOVA model on ranked data including effects for treatment, gender and treatment by gender interaction with Week 36 trunk fat as the single covariate (Serostim 1 mg QD vs. Serostim 2 mg)

6.1.4.4.2.3 Study 24380 - Pivotal Placebo Controlled Maintenance Phase (Weeks 12-36) Efficacy Results

Study 24380 further evaluated the efficacy of Serostim 2 mg QOD (roughly equivalent to the 1 mg QD maintenance dosage chosen after completion of Study 23056 as described above) by comparing it to placebo with respect to changes in VAT and PRO parameters as well as trunk fat, non-HDL cholesterol and other body composition/lipid endpoints during a 24 week maintenance phase (Weeks 12-36).

Subjects treated with Serostim 4 mg QD during the induction phase of Study 24380 (Weeks 0-12) were rerandomized to Serostim 2 mg QOD vs. placebo during a 24 week maintenance phase (Weeks 12-36) (i.e., a blinded, randomized withdrawal). Trunk fat was measured by DEXA scan and VAT was measured by CT scan at Week 36, and compared to the values obtained at Week 12 (and baseline).

The primary efficacy analysis for the maintenance treatment period of Study 24380 (Weeks 12-36) was pre-specified as comparing the rates of "maintenance treatment failure" in the Serostim 2 mg QOD and placebo groups. The" maintenance failure rate" was pre-defined as the proportion of subjects in each group who lost VAT during the induction phase (Weeks 0-12), and who regained, during the maintenance phase (Weeks 12-36), >50% of the original amount of VAT lost. The secondary efficacy analyses were performed using ANOVA models comparing the changes from Week 12 to Week 36 in VAT, trunk fat, non-HDL cholesterol, PRO

parameters (and other body composition/lipid endpoints) in the Serostim 2 mg QOD group vs. the placebo group.

The results of these maintenance phase analyses are presented in Tables 45-50 below.

- As seen in Table 45, during Weeks 12-36, **~54% of subjects treated with placebo were "maintenance treatment failures", compared with ~40% of subjects treated with Serostim 2 mg QOD, i.e. conversely, during Weeks 12-36, ~60% of subjects treated with Serostim 2 mg QOD were "maintenance treatment successes" compared with ~46% of subjects treated with placebo**. On the other hand, as seen in Table 46, **a comparison of the change from Week 12 to Week 36 in VAT using an ANOVA model revealed no difference between the maintenance treatment regimens**, i.e. the amount of expected VAT reaccumulation in both groups was very similar (~23 cm^2 for each group).
- **A comparison of the change from Week 12 to Week 36 in trunk fat revealed significantly less reaccumulation after treatment with Serostim 2 mg QOD (+1.5 kg) compared with placebo (+2.1 kg), i.e. greater preservation of the amount of trunk fat originally lost during the induction phase** (Weeks 0-12) (see Table 47). However, an analysis of change in abdominal SAT did not confirm the trunk fat findings (data not shown).
- A comparison of the change from Week 12 to Week 36 in LBM revealed significantly less rebound decrease after treatment with Serostim 2 mg QOD (-1.8 kg) compared with placebo (-3.9 kg), i.e. **greater preservation of the amount of LBM originally gained during the induction phase** (Weeks 0-12) (see Table 48).
- A comparison of the change from Week 12 to Week 36 in non-HDL cholesterol revealed less rebound increase after treatment with Serostim 2 mg QOD (+5.0 mg/dL) compared with placebo (+11.0 mg/dL). However, the between-group difference was not significant (see Table 49).
- A comparison of the change from Week 12 to Week 36 in BAD score revealed less rebound decrease after treatment with Serostim 2 mg QOD (-8.0 points) compared with placebo (-15.3), i.e. greater preservation of the improvement in BAD originally achieved during the induction period. However, the between-group difference was not significant (see Table 50).

Overall, maintenance therapy, consisting of Serostim 2 mg QOD (which was administered for 24 weeks after completion of the 12 week induction period) was well tolerated and, in the case of trunk fat and LBM, significantly more effective than placebo in preserving the benefits observed after 12 weeks of induction therapy.

Table 45: Study 24380 - Failure Rate During the Maintenance Period, i.e. Proportion of Subjects Who Regained >50% of VAT Lost During Weeks 1 to 12 (Subjects in the Weeks 12-36 Modified ITT Population Who Received Serostim 4 mg Daily During Weeks 0-12 and Lost VAT)

Failure Rate[a]	Serostim 4 mg daily/ Placebo n=83	Serostim 4 mg QD/ Serostim 2 mg QOD n=75	p-value[b]
Regained >50% VAT Lost During Weeks 1 to 12			
Unknown[c]	16	13	
No, n (%)	**31 (46.3)**	**37 (59.7)**	**0.136**
Yes, n (%)	**36 (53.7)**	**25 (40.3)**	
95% CI for Proportion (%)	(41.1, 66.0)	(28.1, 53.6)	

(a) Proportion of subjects who regained, from Weeks 12 to 36, >50% of the VAT lost during Weeks 0 to 12
(b) From a CMH general association test adjusted for gender
(c) Subjects with unknown failure status were excluded from the analysis.

Table 46: Study 24380 - Change & Percent Change from Week 12 to Week 36 in VAT (cm^2) by Treatment Group (Modified ITT Population w/ LOCF)

	Serostim 4 mg QD/ Placebo n=73	Serostim 4 mg QD/ Serostim 2 mg QOD n=75
Baseline (SD)	134.8 (63.2)	135.6 (69.9)
Baseline (SE)[a]	113.3 (11.1)	116.7 (10.6)
Week 12 (SD)	103.2 (49.8)	96.7 (44.8)
Week 12 (SE)[a]	93.3 (8.7)	87.6 (8.3)
Week 36 (SD)	126.9 (64.7)	119.9 (58.3)
Week 36 (SE)[a]	110.1 (9.9)	103.2 (9.5)
Change from Week 12 to Week 36 (SD)	**23.7 (45.1)**	**23.3 (34.9)**
Change from Week 12 to Week 36 (SE)[b]	**16.8 (7.0)**	**15.5 (6.7)**
Raw Mean Difference from Placebo for Change (CI)	**---**	**-0.4 (-15.6, 14.8)**
Difference from Placebo for Change (CI)[b]	**---**	**-1.2 (-20.3, 17.8) p=0.898**
% Change from Week 12 to Week 36 (SD)	**40.2 (127.9)**	**44.0 (152.5)**
% Change from Week 12 to Week 36 (SE)[b]	**28.0 (21.6)**	**29.7 (20.6)**
Raw Mean Difference from Placebo for % Change (CI)	**---**	**3.8 (-43.3, 51.0)**
Difference from Placebo for % Change (CI)[b]	**---**	**1.8 (-57.1, 60.7) p=0.953**

(a) Ordinary LSM from ANOVA model including effects for gender, treatment and their interaction
(b) Ordinary LSM from ANCOVA model including effects for gender, treatment and their interaction with baseline VAT as covariate

Table 47: Study 24380 - Change & Percent Change from Week 12 to Week 36 in Trunk Fat (kg) by Treatment Group (Modified ITT Population w/ LOCF)

	Serostim 4 mg QD/ Placebo n=79	**Serostim 4 mg QD/ Serostim 2 mg QOD n=75**
Baseline (SD)	11.6 (5.2)	10.7 (4.2)
Baseline (SE)[a]	12.1 (0.8)	11.3 (0.8)
Week 12 (SD)	9.5 (5.2)	8.4 (4.1)
Week 12 (SE)[a]	10.0 (0.8)	9.3 (0.8)
Week 36 (SD)	11.6 (5.5)	9.8 (4.3)
Week 36 (SE)[a]	12.0 (0.9)	10.4 (0.8)
Change from Week 12 to Week 36 (SD)	**2.1 (1.8)**	**1.5 (1.5)**
Change from Week 12 to Week 36 (SE)[a]	**2.0 (0.3)**	**1.2 (0.3)**
Raw Mean Difference from Placebo for Change (CI)		**-0.6 (-1.3, -0.02)**
Difference from Placebo for Change (CI)[a]		**-0.8 (-1.6, -0.02) p=0.045**
% Change from Week 12 to Week 36 (SD)	**28.2 (25.8)**	**21.6 (22.4)**
% Change from Week 12 to Week 36 (SE)[a]	**24.9 (3.8)**	**17.0 (3.7)**
Raw Mean Difference from Placebo for % Change (CI)		**-6.6 (-14.9, 1.6)**
Difference from Placebo for % Change (CI)[a]		**-7.9 (-18.3, 2.6) p=0.139**

(a) Ordinary LSM from ANOVA model including effects for gender, treatment and their interaction

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Table 48: Study 24380 - Change & Percent Change from Week 12 to Week 36 in Lean Body Mass (kg) by Treatment Group (Modified ITT Population w/ LOCF)

	Serostim 4 mg QD/ Placebo n=79	Serostim 4 mg QD/ Serostim 2 mg QOD n=75
Baseline (SD)	62.1 (10.0)	61.6 (9.0)
Baseline (SE)[a]	54.9 (1.4)	55.2 (1.3)
Week 12 (SD)	65.6 (10.1)	65.4 (9.2)
Week 12 (SE)[a]	57.8 (1.3)	58.6 (1.3)
Week 36 (SD)	61.8 (9.7)	63.6 (9.4)
Week 36 (SE)[a]	54.6 (1.3)	56.8 (1.3)
Change from Week 12 to Week 36 (SD)	**-3.9 (2.9)**	**-1.8 (2.7)**
Change from Week 12 to Week 36 (SE)[a]	**-3.1 (0.5)**	**-1.8 (0.5)**
Raw Mean Difference from Placebo for Change (CI)		**2.0 (1.0, 3.1)**
Difference from Placebo for Change (CI)[a]		**1.4 (0.1, 2.7) p=0.039**
% Change from Week 12 to Week 36 (SD)	**-5.9 (4.1)**	**-2.8 (4.0)**
% Change from Week 12 to Week 36 (SE)[a]	**-5.4 (0.7)**	**-3.1 (0.7)**
Raw Mean Difference from Placebo for % Change (CI)		**3.0 (1.4, 4.6)**
Difference from Placebo for % Change (CI)[a]		**2.4 (0.3, 4.4) p=0.025**

(a) Ordinary LSM from ANOVA model including effects for gender, treatment and their interaction

Table 49: Study 24380 - Change & Percent Change from Week 12 to Week 36 in Non-HDL Cholesterol (mg/dL) by Treatment Group (Modified ITT Population w/ LOCF)

	Placebo n=80	**Serostim 2 mg QOD n=78**
Baseline (SD)	148.6 (39.0)	153.0 (40.9)
Baseline (SE)[a]	146.4 (6.6)	156.6 (6.6)
Week 12 (SD)	133.3 (33.8)	141.2 (39.6)
Week 12 (SE)[a]	135.8 (6.4)	147.1 (6.4)
Week 36 (SD)	144.3 (38.6)	146.2 (43.0)
Week 36 (SE)[a]	146.3 (6.6)	150.8 (6.6)
Change from Week 12 to Week 36 (SD)	**11.0 (29.6)**	**5.0 (34.6)**
Change from Week 12 to Week 36 (SE)[a]	**10.4 (5.9)**	**3.7 (6.0)**
Raw Mean Difference from Placebo for Change (CI)		**-6.0 (-19.2, 7.2)**
Difference from Placebo for Change (CI)[a]		**-6.8 (-23.3, 9.8) p=0.423**
% Change from Week 12 to Week 36 (SD)	**10.3 (23.3)**	**5.4 (23.9)**
% Change from Week 12 to Week 36 (SE)[a]	**10.1 (4.0)**	**4.8 (4.0)**
Raw Mean Difference from Placebo for % Change (CI)		**-4.9 (-13.8, 4.1)**
Difference from Placebo for % Change (CI)[a]		**-5.3 (-16.5, 6.0) p=0.356**

(a) Ordinary LSM from ANOVA model including effects for gender, treatment and their interaction

Table 50: Study 24380 - Change from Week 12 to Week 36 in Belly Appearance Distress by Treatment Group (Modified ITT Population w/ LOCF)

	Placebo n=92/91	Serostim 2 mg QOD n=89
Week 12 (SD)	47.4 (29.2)	49.0 (24.4)
Week 12 (SE)[a]	48.3 (4.4)	44.5 (4.2)
Week 36 (SD)	31.3 (29.6)	40.8 (27.1)
Week 36 (SE)[a]	35.13 (4.5)	41.81 (4.3)
Change from Week 12 to Week 36 (SD)	**-15.3 (28.1)**	**-8.0 (27.1)**
Change from Week 12 to Week 36 (SE)[a]	**-12.3 (4.0)**	**-6.9 (3.8)**
Raw Mean Difference from Placebo for Change (CI)	**---**	**---**
Difference from Placebo for Change (CI)[a]	**---**	**5.4 (-5.5, 16.3) p=0.328**

a) Ordinary LSM from ANCOVA model including effects for gender, treatment, and treatment by gender interaction with age as a universal covariate and Week 12 BAD score as covariate for the change score only

6.1.6 Efficacy Summary/Discussion/Conclusions

6.1.6.1 Efficacy Summary of Results/Selective Discussion

6.1.6.1.1 Induction Phase: Weeks 0-12 of Studies 24380 and 22388

6.1.6.1.1.1 Primary Efficacy Endpoint: Change in VAT

- **The mean <u>differences</u> in the change and percent change from baseline to Week 12 in VAT between the Serostim 4 mg QD group and the placebo group were significant** in Study 24380 (**-17.0 cm^2; p=0.005**; **-17.2%; p=0.0005**), Study 22388 (**-18.2 cm^2; p=0.031**; **-14.0%; p=0.022**), and in the integrated analysis (**-18.1 cm^2; p<0.001**; **-15.0%; p<0.001**).
- CDF curves show a clear separation of the subjects in the Serostim 4 mg QD and placebo groups. With respect to change and percent change from baseline to Week 12 in VAT, the cumulative percentages of patients who were **non-responders** (defined as a response >0) **were ~50% for the placebo group vs. ~10-25% for the Serostim 4 mg QD groups** in Studies 24380 and 22388. Furthermore, if one selects a within-group change of **-25 cm^2** (a number more negative than the mean between-group differences of -17-18 cm^2) **as a cutpoint**, the cumulative percentages of patients **with changes more negative than -25 cm^2 were ~60% for the Serostim 4 mg QD groups vs. ~25-30% for the placebo groups** in Studies 24380 and 22388. Finally, if one selects a within-group percent change of **-15%** (a number approximating the robust, mean between-group differences noted in the preceding bullet - **and which clearly exceeds the -5-10% change thought to be the minimally significant difference prior to the pivotal studies) as a cutpoint**, the cumulative percentages of patients **with changes more negative than -15% were ~60-70% for the Serostim 4 mg QD groups vs. ~25% for the placebo groups** in Studies 24380 and 22388.
- **The mean <u>differences</u> in the change and percent change from baseline to Week 12 in VAT between the Serostim 4 mg QOD group and the placebo group (-19.7 cm^2 and -16.7%) were very similar to those observed between the Serostim 4 mg QD group and the placebo group (-18.2 cm^2 and -14.0%)**. This is **confirmed by the CDF curves** for Study 22388 wherein the **"plots"** for the Serostim 4 mg QD group and the Serostim 4 mg QOD group **were identical** and overlap each other. **<u>In other words, there was no dose-response observed with respect to change from baseline to Week 12 in VAT</u>**.
- **The treatment by baseline VAT interaction was quantitatively significant (p=0.0002) for change from baseline to Week 12 in VAT for Study 24380. As baseline VAT decreased, the reduction from baseline to Week 12 in VAT decreased in the Serostim 4 mg QD group**, and **the difference in VAT reduction** from baseline to Week 12 between the Serostim 4 mg QD treatment group and the placebo group **significantly increased as the baseline VAT increased**. **In other words, a lower baseline VAT predicts a smaller treatment effect (Serostim 4 mg QD vs. placebo)**. This has previously been reported in patients with HARS and the non-HIV infected population (13, 58-59).

- **The treatment by gender interactions were highly significant (p=0.0006)** and minimally significant p=0.1) in Studies 24380 and 22388, respectively, **for the Serostim 4 mg QD treatment group vs. the placebo group in the analyses of the entire population**. **Mean VAT levels at baseline in female treatment groups (105 cm^2 and 85 cm^2 in Studies 22388 and 24380, respectively) were clearly smaller than in the male treatment groups (156 cm^2 and 143 cm^2 in Studies 22388 and 24380, respectively)**. This has previously reported by several authors in patients with HARS (13, 60-61) as well as the obese (and non-obese) HIV-negative population (59-61). In this regard, Kotler et al reported mean VAT levels of **~56 cm^2 and ~73 cm^2** in non-HIV infected women and men, respectively, whose BMIs were roughly comparable to the BMIs of patients enrolled in Studies 22388 and 24380 (60).

    - **The treatment effects (Serostim 4 mg QD vs. placebo) for the change and percent change from baseline to Week 12 in VAT in males were significant in both studies, and very similar to the treatment effects derived from the analyses of <u>all</u> patients**. This is not surprising in that **<u>~85% of the patients</u>** in the modified ITT population treated with Serostim 4 mg QD vs. placebo in each study **<u>were male</u>**.
    - **<u>On the other hand, the treatment effects (Serostim 4 mg QD vs. placebo) for the change and percent change from baseline to Week 12 in VAT in females were not significant, i.e. the responses of women treated with Serostim 4 mg QD and placebo were similar in both studies</u>**.
    - **The CDF curves** for change from baseline to Week 12 in VAT by gender **support the ANCOVA findings described above**. In both studies, ~10% of men treated with Serostim 4 mg QD vs. ~50% of men treated with placebo were non-responders, which mirrors the non-responder rates for the entire population. **In contrast, ~50% of the women treated with Serostim 4 mg QD <u>or</u> placebo in Study 24380, and ~40% of the women treated with Serostim 4 mg QD <u>or</u> placebo in Study 22388 were non-responders**. The response curves for women treated with Serostim 4 mg QD and placebo were essentially identical in both studies.
    - **<u>In summary, the treatment of women with Serostim 4 mg QD (or 4 mg QOD) vs. placebo during the induction phases of Studies 24380 and 22388 did not result in significant treatment effects/differences</u>**. The lack of response in women may partially be explained by the fact that **estrogen** (especially orally administered hormone replacement therapy, but also endogenous estrogen in a menstruating women) diminishes the response to rhGH (i.e., generation of IGF I). This has been demonstrated in numerous publications reporting the treatment of adult GHD (see reference 45 - a Clinical Practice Guideline issued by the Endocrine Society in 2006). However, in that ~5 times as much rhGH was administered to the women with HARS in these pivotal studies as is typically administered to adult GHD women (~50 µg/kg in an 80 kg woman with HARS receiving Serostim 4 mg QD vs. ~10 µg/kg in a typical adult GHD woman), this Medical Officer has doubts about the role estrogen, i.e. the effect of very large,

pharmacologic amounts of rhGH should have "trumped" any estrogen-mediated resistance to rhGH. Another possible explanation relates to the fact that the **lower baseline VAT levels in women compared with men** (see first paragraph of this bullet) **predicts a lesser VAT reduction in response to Serostim/rhGH** (see last bullet on previous page). **Finally, only ~15% of the subjects enrolled in each of the pivotal studies were women, and the studies may have been underpowered to detect a significant treatment effect**.

6.1.6.1.1.2 Change in Non-PRO Consequential Secondary Efficacy Endpoints (summarized in Table 50 below)

- The mean **differences** in the change from baseline to Week 12 in **trunk fat**, **abdominal SAT**, total body fat, LBM, non-HDL cholesterol (Study 24380 only), dorsocervical fat pad (integrated analysis only) between the Serostim 4 mg QD group and the placebo group **were all significant** (by ANCOVA with baseline score as covariate).
- **In contrast to the VAT results, a dose response is evident** when the differences in the change from baseline to Week 12 in **trunk fat**, **abdominal SAT**, **total body fat and LBM after treatment with Serostim 4 mg QOD vs. placebo are compared with the differences observed after treatment with Serostim 4 mg QD vs. placebo**, i.e. in the case of trunk fat and LBM, the same high degree of significance ($p<0.001$) for both doses of Serostim vs. placebo, but a smaller treatment difference; in the case of abdominal SAT, a smaller, non-significant treatment difference after Serostim 4 mg QOD vs. placebo; in the case of total fat mass, a smaller, less significant treatment difference after Serostim 4 mg QOD. **The importance of these observations will be expanded upon in this Medical Officer's Efficacy Conclusions**.
- In contrast to the VAT results, in the case of every one of these variables, the treatment by gender interactions were not significant in Studies 24380 and 22388 for the Serostim 4 mg QD treatment group vs. the placebo group in the analyses of the entire population. **The importance of these observations will also be expanded upon in this Medical Officer's Efficacy Conclusions**.

Table 51: HARS Studies 22388 and 24380 Induction Phase - Summary of Change from Baseline to Week 12 and Difference from Placebo in Various Secondary Body Composition and Metabolic Endpoints by Treatment Group (Modified ITT Population w/ LOCF)

	Study 22388			Study 24380	
Variable as LSM (SE) above Diff. from Placebo as LSM (CI)	**Placebo**	**Serostim 4 mg QOD**	**Serostim 4 mg QD**	**Placebo**	**Serostim 4 mg QD**
Trunk Fat (kg)	0.2 (0.2)	**-1.1 (0.3)** **-1.3[a]**	**-2.0 (0.3)** **-2.2[a]**	0.3 (0.3)	**-2.0 (0.2)** **-2.3[a]**
Abdominal Subcutaneous Adipose Tissue (cm^2)	-1.7 (6.1)	**-12.1 (7.3)** **-10.4[c]**	**-28.6 (6.1)** **-26.9[b]**	-0.9 (5.6)	**-18.0 (3.0)** **-17.0[b,d]**
Total Body Fat (kg)	0.3 (0.4)	**-1.5 (0.4)** **-1.7[b]**	**-2.5 (0.5)** **-2.8[a]**	0.6 (0.4)	**-2.4 (0.2)** **-3.0[a]**
Lean Body Mass (kg)	0.1 (0.4)	**2.5 (0.4)** **2.3[a]**	**3.3 (0.5)** **3.2[a]**	-0.1 (0.5)	**3.1 (0.2)** **3.2[a,]**
Non-HDL Cholesterol (mg/dL)	1.2 (6.1)	-11.4 (6.1) -12.5[c]	-11.2 (6.1) -12.4[c]	4.6 (6.2)	**-10.4 (3.3)** **-15.0[b,e]**
Dorsocervical Fat Pad (cm^2)	-8.6 (10.8)	-8.0 (9.2) 0.6[c]	-40.0 (15.7) -31.4[c]	-19.8 (14.3)	**-32.0 (7.5)** **-12.1[c,g]**

(a) p<0.001 vs. placebo by ANOVA (n=8)
(b) p-value vs. placebo by ANOVA >0.001 but <0.05 (n=4): (0.008 and 0.002 for Serostim 4 mg QD treatment effect for abdominal SAT in Studies 24380 & 22388, resp.; 0.003 for Serostim 4 mg QOD treatment effect for total body fat in Study 22388; 0.034 for Serostim 4 mg QD treatment effect for non-HDL cholesterol in Study 24380
(c) Non-significant vs. placebo (n=6): all 3 treatment effects for dorsocervical fat pad, both non-HDL cholesterol treatment effects in Study 22388, and abdominal SAT treatment effect for Serostim 4 mg QOD in Study 22388
(d) In integrated analysis, treatment effect was –20.8 (p<0.001)
(e) In integrated analysis, treatment effect was -13.1 (p=0.002)
(f) In integrated analysis, treatment effect was -15.6 (p=0.05)

6.1.6.1.1.3 Change in Most Consequential PRO Secondary Efficacy Endpoints

- The mean **differences** in the change from baseline to Week 12 in **BAD and BSE** between the Serostim 4 mg QD group and the placebo group **were all significant** (by ANCOVA with baseline score as covariate).
- **Once again, in contrast to the VAT results, and concordant with the abdominal SAT/trunk fat results, a dose-response is evident** when the differences in the change from baseline to Week 12 in **BAD and BSE after treatment with Serostim 4 mg QOD vs. placebo are compared with the significant differences observed after treatment with Serostim 4 mg QD vs. placebo**, i.e. there are smaller, non-significant treatment

differences after treatment with Serostim 4 mg QOD vs. placebo. **The importance of these observations will also be expanded upon in this Medical Officer's Efficacy Conclusions**.

- Once again, in contrast to the VAT results, in the case of every one of these variables, the treatment by gender interactions were not significant in Studies 24380 and 22388 for the Serostim 4 mg QD treatment group vs. the placebo group in the analyses of the entire population. **The importance of these observations will also be expanded upon in this Medical Officer's Efficacy Conclusions**.
- The sponsor demonstrated a **significant correlation** between changes from baseline to Week 12 in **BAD (as well as BSE)** with changes from baseline to Week 12 in VAT and **trunk fat** after treatment with Serostim 4 mg QD in Study 24380.
- The **responder analyses** performed by the sponsor are **supportive of the findings of the ANCOVAs**. The differences in the proportion of subjects who were designated as responders for BAD and BSE after treatment with Serostim 4 mg QD vs. placebo for 12 weeks in Studies 23388 and 24380 were highly significant. With regard to BAD and BSE, ~30-45% and ~40% of the subjects treated with Serostim 4 mg QD, respectively, compared with ~12-18% and ~23% of the subjects treated with placebo, respectively, were designated as responders across the 2 studies. **Once again, a dose response was apparent in that none of the differences in the proportion of subjects who were designated as responders for BAD and BSE after treatment with Serostim 4 mg QOD vs. placebo in Study 22388 for 12 weeks were significant**.
- The CDF curves reflecting the change from baseline to Week 12 in BAD after treatment with Serostim 4 mg QD vs. placebo demonstrate non-responder rates of **~25% and ~50%** for the Serostim 4 mg QD and placebo groups, respectively, in both studies. The cumulative percentages of patients with a BAD change score **>25 (equal to 2 scale units)** were **~30-40% and ~10-20%** in the Serostim 4 mg QD and placebo groups, respectively, across the 2 studies. The CDF curves reflecting the change from baseline to Week 12 in BSE after treatment with Serostim 4 mg QD vs. placebo demonstrate non-responder rates of **~12% and ~25%** for the Serostim 4 mg QD and placebo groups, respectively, in Study 24380. The cumulative percentages of patients with a BSE change score **<-50 (equal to 2 scale units)** were **~40-45% and ~25%** in the Serostim 4 mg QD and placebo groups, respectively, across the 2 studies (which were amazingly concordant with the percentages displayed in the responder analysis table !

6.1.6.1.2 Maintenance Phase: Weeks 12-36 of Study 24380

6.1.6.1.2.1 Background Information

Study 22388: Weeks 12-24

During Study 22388, the reduction in VAT that had occurred from baseline to Week 12 after treatment with Serostim 4 mg QD was not sustained in subjects rerandomized to placebo during Weeks 12-24 **and, in fact, VAT reaccumulated, with a mean increase of 17.7 cm^2 between Weeks 12 and 24**. In contrast, a sustained decrease in VAT was observed in the subjects

rerandomized to Serostim 4 mg QOD. **These findings indicated that Serostim maintenance therapy warranted further study.**

Studies 22388-23056 Combined: Weeks 36-60 (Equivalent to Weeks 12-36 of Study 23056)

During the 24 week maintenance period of Study 23056, subjects were assigned to treatment with Serostim 1 mg QD vs. 2 mg QD after being treated with varying doses of Serostim for the previous 36 weeks. During the maintenance period, the expected reaccumulation of trunk fat after treatment with Serostim 1 mg QD vs. Serostim 2 mg QD was very similar, and subjects sustained a substantial amount of the trunk fat loss that they had achieved during the prior 36 week period. Given the fact that Serostim 1 mg QD had essentially the same efficacy (and safety) profile as Serostim 2 mg QD during the 24 week maintenance period, Serostim 1 mg QD was chosen for further evaluation during the maintenance period in Study 24380.

6.1.6.1.2.2 Study 24380: Weeks 12-36 – Pivotal Placebo Controlled Maintenance Phase

Study 24380 further evaluated the efficacy of Serostim 2 mg QOD (roughly equivalent to the 1 mg QD maintenance dosage chosen after completion of Study 23056 as described above). Subjects treated with Serostim 4 mg QD during the induction phase of Study 24380 (Weeks 0-12) were rerandomized to Serostim 2 mg QOD vs. placebo during a 24 week maintenance phase (Weeks 12-36). During Weeks 12-36, ~54% of subjects treated with placebo were "maintenance treatment failures", compared to ~40% of subjects treated with Serostim 2 mg QOD (maintenance failure had been defined per protocol as regaining, during the maintenance period, >50% of the VAT lost during the 12 week induction period). On the other hand, as seen in Table 52, a comparison of the change from Week 12 to Week 36 in VAT revealed that the amount of expected VAT reaccumulation in both groups was very similar (~23 cm^2 for each group). On the other hand, as also seen in Table 52, a comparison of the the changes from Week 12 to Week 36 revealed less reaccumulation of trunk fat (p=0.045) and non-HDL cholesterol, and less deterioration in LBM (p=0.039) and BAD point score after treatment with Serostim 2 mg QOD (vs. placebo).

Table 52: HARS Study 1 Maintenance Phase: Change from Week 12 to Week 36 in Various Secondary Body Composition, Metabolic, and Patient Reported Outcome Endpoints by Treatment Group (Modified ITT Population w/ LOCF)

Variable as Mean (SD)	Serostim 4 mg QD/Placebo	Serostim 4 mg QD/ Serostim 2 mg QOD
Visceral Adipose Tissue (cm^2)	23.7 (45.1)	23.3 (34.9)
Trunk Fat (kg)	2.1 (1.8)	1.5 (1.5)*
Lean Body Mass (kg)	-3.9 (2.9)	-1.8 (2.7)*
Non-HDL Cholesterol (mg/dL)	11 (29.6)	5 (34.6)
Belly Appearance Distress (points)	-15.3 (28.1)	-8.0 (27.1)

***p<0.05 (vs. placebo; ANOVA)**

6.1.6.1.3 Other Miscellaneous Results of Interest

- Mean baseline VAT levels in Study 24380 (85 cm^2 in females and 143 cm^2 in males) (**enrolled in 2004**) were clearly smaller than the mean baseline VAT levels in Study 22388 (105 cm^2 in females and 156 cm^2 in males) (**enrolled in 2001**). The **explanation** for the baseline differences in **VAT** across the studies probably relates to the fact that the patients enrolled in Study 24380 **were being treated more often with newer generation antiretroviral medications** which have been reported to result in less VAT accumulation (42-43). The **explanation** for the baseline differences in **lipid levels** across the studies also probably relates to the fact that the patients enrolled in Study 24380 **were being treated more often with newer generation, more "lipid-friendly" antiretroviral medications** (42-43, 56). Nonetheless, despite treatment with newer generation antiretroviral agents, HARS remains associated with a number of clinically significant metabolic abnormalities and an increased risk of atherosclerosis and myocardial infarction (57). Furthermore, the **greater mean baseline VAT level** in Study 22388 (which many believe contributes significantly to the dyslipidemia seen in HARS patients) in and of itself **may partially explain the greater mean baseline lipid levels** in Study 22388. **None of these differences in baseline parameters across the 2 studies were considered significant enough to preclude the performance of integrated analyses**. **However, since there were differences in important baseline parameters by study, all statistical models used by the sponsor in the efficacy analyses of the pooled/integrated data included an effect parameter for study**.
- The sponsor presented subgroup analyses for subjects in Study 22388 receiving or not receiving concomitant LLA treatment which suggest that Serostim (rhGH) and LLAs may act synergistically in lowering levels of non-HDL cholesterol in patients with HARS, i.e. a significant treatment effect for Serostim 4 mg QOD (vs. placebo) was only observed in patients receiving concomitant therapy with LLAs.

6.1.6.2 Efficacy Conclusions

A. Regarding the approval of Serostim 4 mg QD (as proposed by the sponsor) vs. Serostim 4 mg QOD as a 12 week induction dose:

On the one hand, Serostim 4 mg QD and Serostim 4 mg QOD appear to be equally efficacious in reducing VAT (and potentially reducing long-term cardiovascular risk), and the safety profile for Serostim 4 mg QD is clearly more adverse than the safety profile for Serostim 4 mg QOD (see Safety Conclusions/Recommendations ahead). On its face, this suggests that the smaller dose should be approved for the induction phase.

However, there is a global dose response with regard to the differences in change from baseline to Week 12 in multiple consequential non-PRO and PRO secondary efficacy endpoints (i.e., **trunk fat, abdominal SAT, BAD/BSE**, total fat mass and LBM). **The dose response for trunk fat/abdominal SAT and BAD/BSE are especially important** because it is reasonable to presume that **they are linked** both intuitively and with respect to the fact that the sponsor was able to demonstrate a **statistically significant correlation between improvements in BAD scores (as well as BSE scores) and decreases in trunk fat** (as well as VAT). In other words, **the more substantial decreases in trunk fat and abdominal SAT after treatment with Serostim 4 mg QD (compared with Serostim 4 mg QOD) may have resulted in the more substantial improvements in BAD/BSE when the same comparison is made**, i.e. the greater reductions in trunk fat/abdominal SAT (even absent a greater reduction in VAT) after treatment with the larger dose would appear to be at least part of the reason why the patient's perception of his/her belly size and his/her distress associated with belly size improves to a greater extent. **This may have major clinical implications in that patients with greater improvements in BAD/BSE may be even less inclined to discontinue or be non-compliant with lifesaving antiretroviral therapy** (please refer back to the earlier references indicating that, currently, many patients with HARS do in fact discontinue or are non-compliant with their HAART regimens because of the emotional distress/stigmatization associated with their body/belly dysmorphia)

Furthermore, the more adverse safety profile observed with the full dose is tolerable and acceptable if it is only administered during the 12 week induction period, and certain caveats regarding use of Serostim 4 mg QD are added, i.e. cut back to Serostim 4 mg QOD if significant rhGH-related adverse events should occur, start with Serostim 4 mg QOD in patients considered to be at special risk for rhGH-related adverse effects (see Safety Conclusions and Recommendations ahead).

B. Regarding the approval of Serostim 4 mg QD for men and women (as proposed by the sponsor) vs. approval for men alone:

One the one hand, as summarized in detail in this Medical Officer's Summary of Results, women treated with either dose of Serostim do not demonstrate a difference in the change from baseline to Week 12 in VAT. As discussed previously, this may relate to estrogen-mediated resistance to

rhGH and/or to the fact that the clearly lower baseline VAT levels in women compared to men predicts a lesser response. On its face, this suggests that the indication should be limited to men.

However, globally speaking, the differences in change from baseline to Week 12 in multiple consequential non-PRO and PRO secondary efficacy endpoints including trunk fat, abdominal SAT, and BAD/BSE are very similar in men and women. Therefore, precisely the same argument can be made for approving Serostim 4 mg QD for women - as was made above with reference to approving Serostim 4 mg QD as the induction dose. Furthermore, **only ~15% of the subjects enrolled in each of the pivotal studies were women, and the studies may have been underpowered to detect a significant treatment effect.**

C. Regarding the approval of Serostim 2 mg QOD as a 24 week maintenance dose (as proposed by the sponsor):

On the one hand, as summarized in this Medical Officer's Summary of Results, during the 24 week maintenance phase of Study 24380, VAT reaccumulated to the same extent after treatment with Serostim 2 mg QOD or placebo (by ANOVA). On the other hand, 1) the Division had previously indicated to the sponsor that if >50% of the subjects who lost VAT during the induction period regained, during the maintenance period, <50% of the VAT originally lost, that would be considered a "maintenance success". In fact, ~60% of subjects treated with Serostim 2 mg QOD met that criteria (vs. 46% in the placebo group); and 2) there was significantly less reaccumulation of trunk fat and deterioration of LBM after treatment with Serostim 2 mg QOD (vs. placebo). The lesser amount of non-HDL cholesterol reaccumulation and deterioration of the BAD point score after treatment with Serostim 2 mg QOD (vs. placebo) were not statistically significant.

6.1.6.4 Efficacy Recommendations

- **<u>This Medical Officer recommends approval of Serostim 4 mg QD as the induction dose (as requested by the sponsor)</u>. The detailed rationale behind this decision can be found in the Efficacy Conclusions section. The more adverse safety profile observed with the full Serostim 4 mg QD is tolerable and acceptable if it is only administered during the 12 week induction period, and certain caveats regarding the use of Serostim 4 mg QD are added/labeled, i.e. <u>cut back to Serostim 4 mg QOD if significant rhGH-related adverse events should occur, start with Serostim 4 mg QOD in patients considered to be at special risk for rhGH-related adverse effects (see Safety Conclusions and Recommendations ahead)</u>.**

- **<u>This Medical Officer recommends approval of Serostim 4 mg QD in women as well as men (as requested by the sponsor)</u>. Again, the detailed rationale behind this decision can be found in the Efficacy Conclusions section. This recommendation comes with certain caveats/conditions as well:**

    - **<u>The CLINICAL STUDIES section of the PI should clearly indicate that women did not demonstrate a significant reduction in VAT after treatment</u>**

with Serostim 4 mg QD (vs. placebo), but did respond as well as men with regard to reduction in trunk fat, abdominal SAT, total body fat, and non-HDL cholesterol, increase in LBM, and improvement in BAD and BSE scores. A small table containing descriptive statistics depicting the VAT response by gender should be included as well in the CLINICAL STUDIES section as well.

- (b) (4)
- **3) The sponsor should be firmly requested to make a formal Phase IV commitment to conduct an adequately powered similar study in women as soon as feasible.**

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The electronic submitted Summary of Safety, the individual study reports for Studies 22388, 23056, and 24380, as well as the electronically submitted Safety Update were thoroughly reviewed by this Medical Officer.

7.1.0 Exposure

Patient exposure during the 3 main studies are summarized in Table 53 below. 122 subjects treated for 12-18 weeks and 64 subjects treated for 30-36 weeks received the largest amount of Serostim/rhGH (>36 grams)

Table 53: Studies 22388, 23056 and 24380 - Subject Total Weeks and Amount of Exposure (mg) to Serostim*

Duration of Treatment (weeks)	All Subjects Receiving Serostim		
	Number of Subjects	Total Time of Treatment (Subject-weeks)	Total Amount of Serostim Received (mg)
0-6	62	234.1	5446.5
>6 to 12	122	1306.1	29817.6
>12 to 18	**122**	1611.3	**36774.1**
>18 to 24	26	596.6	9053.5
>24 to 30	15	402.6	6953.6
>30 to 36	**64**	2236.9	**30838.7**
>36 to 42	28	1038.0	13504.0
>42 to 48	28	1304.9	16765.5
>48 to 54	25	1229.3	17056.0
>54 to 60	34	2005.7	24831.2
>60	23	1423.4	19017.1

*Also includes subjects from Study 21747 – a pilot study which was discontinued prematurely after minimal patient exposure

7.1.1 Deaths

There were 5 deaths during these studies – aspiration following alcohol abuse, pneumonia in a patient with lung cancer, myocardial infarction, cardiorespiratory arrest secondary to a drug overdose, and unknown cause. None of the deaths were thought to be related to Serostim administration.

7.1.2 Other Serious Adverse Events (SAEs)

Across the studies, 49 SAEs were reported by 39 subjects. The most common organ systems involved were infections, gastrointestinal, cardiac and neoplasm of some kind. None were thought to be related to Serostim.

7.1.3 Discontinuations Due to Adverse Events (AEs)

Across Studies 22388-23056 and 24380, 565 subjects received study drug. Of these 565 subjects, 217 (38.4%) were discontinued at some point in their treatment history. Of the 565 subjects who were discontinued, 109 (19.3%) were discontinued due to AEs. Of these 109 subjects, 94 were receiving Serostim: **Serostim 4 mg QD (n=65 [69.1%]); Serostim 4 mg QOD (n=13 [13.8%]); Serostim 2 mg QD (n=2 [2.1%]); Serostim 2 mg QOD (n=6 [6.4%]); and Serostim 1 mg QD (n=8 [8.5%]).**

Twenty two subjects (22/565 [3.9%]) discontinued because of an elevated serum glucose (see Table X in Section 7.1.7.3.1.3).

7.1.3.1 Integrated Analysis of the Induction Phase (Weeks 0-12) in Studies 22388 and 24380 - Serostim 4 mg QD vs. Placebo (also AE withdrawal data with regard to induction with Serostim 4 mg QOD in Study 22388)

As seen in Table 54, a greater percentage of subjects in the Serostim 4 mg QD treatment group withdrew due to AEs compared to the placebo group (**13.2% [43/326] versus 1.2% [2/162]**). Twenty of the 43 subjects who withdrew discontinued due to 2 or more AEs. Many of these AEs have long been known to be associated with rhGH treatment. **The most common AEs that led to study withdrawal during the integrated induction phases included: peripheral edema (11 subjects), "hyperglycemia", "blood glucose increased" (8 subjects) (see Table X in Section 7.1.7.3.1.3), arthralgia (8 subjects), hypoesthesia (5 subjects), and pain in the extremities (5 subjects).**

Table 54: Studies 22388 and 24380 - Discontinuations Due to AEs During Weeks 0-12 After Treatment with Serostim 4 mg QD or Placebo (Excluding 80 Serostim 4 mg QOD Patients)

Study 22388		Study 24380		All Subjects	
Placebo (n=78) n (%)	Serostim 4 mg daily (n=82) n (%)	Placebo (n=81) n (%)	Serostim 4 mg daily (n=244) n (%)	Placebo (n=159) n (%)	Serostim 4 mg daily (n=326) n (%)
0	9 (11.0)	2 (2.5)	34 (13.9)	2 (1.3)	43 (13.2)

As seen in Table 55, in Study 22388, **5.1% (4/79)** of subjects induced with **Serostim 4 mg QOD** withdrew from the study due to AEs (including hyperglycemia, carpal tunnel syndrome, edema and hypertriglyceridemia). An additional patient withdrew just after completing the 12 week induction period due to hyperglycemia as well. During the same study (as seen in Table 54 on the left hand side), **11% (9/82)** of subjects induced with **Serostim 4 mg QD** withdrew due to

mostly rhGH-related AEs including edema, arthralgia, carpal tunnel syndrome and hyperglycemia (X 3).

Table 55: Studies 22388 and 24380 - Discontinuations Due to AEs During Weeks 0-12 After Treatment with Serostim 4 mg QD, Serostim 4 mg QOD or Placebo

Placebo (n=159) n (%)	Serostim 4 mg QOD (n=80) n (%)	Serostim 4 mg daily (n=326) n (%)
2 (1.3)	4 (5.0)*	43 (13.2)

7.1.3.1.1 Induction Periods During Other Portions of Studies 22388 and 24380

During Weeks 12-24 in Study 22388, **17.6% (13/74**) of subjects receiving **Serostim 4 mg QD** (after originally receiving placebo for 12 weeks) withdrew from the study due to AEs.

During Weeks 24-36 in Study 24380, 7 subjects receiving Serostim 4 mg QD (after originally receiving placebo for 24 weeks) withdrew from the study due to AEs. Two of them were withdrawn because of hyperglycemia (see Table X in Section 7..1.7.3.1.3).

7.1.3.2 Pivotal Placebo Controlled Maintenance Phase (Weeks 12-36 of Study 24380)

During Weeks 12-36 of Study 24380, 7 vs. 6 subjects receiving placebo vs. Serostim 2 mg QOD, respectively, discontinued due to an AE, **i.e. no real difference was seen**. One of the Serostim patients discontinued because of hyperglycemia.

7.1.4 Dose Modifications (Hold or Reduce) to Adverse Events

Table 56 depicts the AEs which led to study drug modification (hold or reduce) during Weeks 0-12 in Studies 22388 and 24380. The most common reasons for drug modification were, as expected, glucose intolerance, myalgia/arthralgia, paraesthesia/carpal tunnel syndrome/nerve compression and edema (in descending order of frequency). **It is evident that a dose response exists for each and every rhGH-related AE**. Using glucose intolerance as an example, the percentages of subjects requiring **dose modification** for **glucose intolerance issues** were **2.5%, 11.3% and 16.6%** in the placebo, Serostim 4 mg QOD and Serostim 4 mg QD groups, respectively. In Tables 57 and 58, this dose response is once again clearly demonstrated. With regard to dose reduction for **any** reason, the percentages of subjects **requiring dose reduction** in the placebo, Serostim 4 mg QOD and Serostim 4 mg QD groups were **1.3%, 18.8% and 25.5%**, respectively.

Table 56: Studies 22388 and 24380: AEs Resulting in Study Drug Modification During Weeks 0-12

	Placebo n=159 **Subjects n (%)**	Serostim 4 mg QOD n=80 **Subjects n (%)**	Serostim 4 mg QD n=326 **Subjects n (%)**
All Glucose Issues	**4 (2.5)**	**9 (11.3)**	**54 (16.6)**
Blood glucose increased	3 (1.9)	2 (2.5)	37 (11.3)
Hyperglycemia	1 (0.6)	7 (8.8)	14 (4.3)
Blood glucose abnormal	0	0	2 (0.6)
Blood glucose	0	0	1 (0.3)
All Arthralgia/Myalgia	**0**	**6 (7.5)**	**39 (12.0)**
Arthralgia	0	3 (3.8)	19 (5.8)
Pain in extremity	0	2 (2.5)	7 (2.1)
Myalgia	0	0	6 (1.8)
Musculoskeletal stiffness	0	1 (1.3)	2 (0.6)
Polymyalgia	0	0	3 (0.9)
Arthritis	0	0	2 (0.6)
All Nerve Compression	**0**	**2 (2.5)**	**21 (6.4)**
Hypoaesthesia	0	1 (1.3)	9 (2.8)
Paraesthesia	0	1 (1.3)	7 (2.1)
Carpal tunnel syndrome	0	0	4 (1.2)
All edema	**0**	**3 (3.6)**	**21 (6.4)**
Oedema peripheral	0	2 (2.5)	18 (5.5)
Fluid retention	0	1 (1.3)	3 (0.9)

Table 57: Studies 22388 and 24380 - Summary of Actions on Study Drug During Weeks 0-12 After Treatment with Serostim 4 mg QD or Placebo (Excluding 80 Serostim 4 mg QOD Patients)

		Study 22388		**Study 24380**		**All Subjects**	
Reason for Dose Change	**Action on Study Drug**	**Placebo (n=78) n (%)**	**Serostim 4 mg daily (n=82) n (%)**	**Placebo (n=81) n (%)**	**Serostim 4 mg daily (n=244) n (%)**	**Placebo (n=159) n (%)**	**Serostim 4 mg daily (n=326) n (%)**
Adverse Event	**Held**	**2 (2.6)**	**15 (18.3)**	**2 (2.5)**	**20 (8.2)**	**4 (2.5)**	**35 (10.7)**
	Reduced	**1 (1.3)**	**25 (30.5)**	**1 (1.2)**	**58 (23.8)**	**2 (1.3)**	**83 (25.5)**
	Discontinued	**0**	**9 (11.0)**	**2 (2.5)**	**34 (13.9)**	**2 (1.3)**	**43 (13.2)**
Subject Non-Compliance	Held	37 (47.4)	45 (54.9)	39 (48.1)	121 (49.6)	76 (47.8)	166 (50.9)

	Reduced	0	0	0	0	0	0
	Discontinued	0	1 (1.2)	0	1 (0.4)	0	2 (0.6)

Table 58: Studies 22388 and 24380 - Summary of Actions on Study Drug During Weeks 0-12 After Treatment with Serostim 4 mg QD, Serostim 4 mg QOD or Placebo

Reason for Dose Change	Action on Study Drug	Placebo (n=159) n (%)	Serostim 4 mg QOD (n=80) n (%)	Serostim 4 mg daily (n=326) n (%)
Adverse Event	**Held**	**4 (2.5)**	**5 (6.3)**	**35 (10.7)**
	Reduced	**2 (1.3)**	**15 (18.8)**	**83 (25.5)**
	Discontinued	**2 (1.3)**	**4 (5.0)**	**43 (13.2)**
Subject Non-Compliance	Held	76 (47.8)	31 (38.8)	166 (50.9)
	Reduced	0	1 (1.3)	0
	Discontinued	0	1 (1.3)	2 (0.6)

7.1.5 Common Adverse Events

7.1.5.3 Incidence of Common Adverse Events

Table 59 displays the incidence of treatment emergent AEs with **>5% incidence** in either of the 2 **active** treatment groups for Studies 22388 and 24380 combined. Once again we see the same AEs that resulted in the vast majority of study discontinuations and dose modifications - edema, arthralgia, hypoesthesia, glucose intolerance in descending order of frequency. In addition, once again, there is a clearly evident dose response. The incidence of **edema** was **3.8%, 18.8% and 45.4%** in the placebo, Serostim 4 mg QOD and Serostim 4 mg QD groups, respectively.

Table 59: Controlled HARS Trials 22388 and 24380 - Adverse Events with >5% Incidence in Either Active Treatment Group

System Organ Class	Placebo Patients (n=159) %	Serostim 4 mg QOD[1] Patients (n=80) %	Serostim 4 mg QD Patients (n=326) %
Musculoskeletal and connective tissue disorders			
Arthralgia	**11.9**	**27.8**	**37.1**
Pain in extremity	**3.8**	**5.0**	**19.3**
Myalgia	**3.8**	**2.5**	**12.6**
Musculoskeletal stiffness	**1.9**	**3.8**	**8.0**
Joint stiffness	**1.3**	**3.8**	**7.7**
Joint swelling	0.6	5.0	6.1
General disorders and administration site conditions			
Edema peripheral	**3.8**	**18.8**	**45.4**
Fatigue	1.9	6.3	8.9
Nervous system disorders			
Hypoesthesia	**0.6**	**8.8**	**15.0**
Headache	3.1	3.8	14.1
Paraesthesia	**2.5**	**12.5**	**11.0**
Investigations (Laboratory Evaluations)			
Blood glucose increased	**2.5**	**3.8**	**13.8**
Metabolism and nutrition disorders			
Hyperglycemia	**0.6**	**8.8**	**7.1**
Fluid retention	**0.6**	**2.5**	**5.2**
Gastrointestinal disorders			
Nausea	2.5	1.3	6.1
Psychiatric disorders			
Insomnia	1.9	7.5	8.3
Infections and infestations			
Upper respiratory tract infection	5.0	10.0	5.2

[1]Study 22388 only

7.1.7 Laboratory Findings

7.1.7.1 Overview of Laboratory Testing in the Development Program

This Medical Officer's review of laboratory findings will focus on changes in **glycemic parameters, IGF I/IGF I SDS levels, viral load and CD4 helper lymphocyte counts.** A brief review of other standard safety laboratory tests revealed no significant changes from baseline, and no outliers of note.

7.1.7.2 Measures of Glucose Tolerance - In Particular Fasting Blood Glucose (FBG)

This Medical Officer will focus on changes in FBG levels. **Importantly, mean changes in hemoglobin A1C levels were minimal (0.3% in Study 24380 at the end of the induction phase!)**. Not surprisingly, mean fasting and 2 hour post-prandial insulin levels did indeed increase significantly after treatment with Serostim, but the vast majority of the time, increases in

insulin were not accompanied by glucose intolerance. Furthermore, the change in 2 hour post-prandial blood glucose levels followed the same pattern as FBG levels.

7.1.7.2.1 Difference in the Change from Baseline to Week 12 in FBG for Studies 22388 and 24380 Combined After Treatment with Serostim 4 mg QD vs. Placebo, and for Study 22388 Alone (as well as descriptive statistics for Study 22388)

Table 60 demonstrates that the difference in the change from baseline to Week 12 in FBG after treatment with Serostim 4 mg QD vs. placebo was statistically significant (5.7 mg/dL). **However, clinically speaking, the mean FBG level remained within the normal range at Week 12**. The integrated analysis in Table 62 confirms a statistically significant treatment effect (Serostim 4 mg QD vs. placebo) of ~6 mg/dL. Table 60 also demonstrates, not surprisingly, that the difference in the change from baseline to Week 12 in FBG after treatment with Serostim 4 mg QOD vs. placebo was smaller and not significant. Table 61 from Study 22388 shows that mean FBG levels "bump up" 2 weeks after the initiation of either dose of Serostim (with a dose response), but are back down to normal by Week 12.

Table 60: Study 22388 – Change from Baseline to Week 12 in FBG (mg/dL) (Modified ITT Patients)

Time Point		Placebo	Serostim 4 mg QOD	Serostim 4 mg daily
Baseline	n	69	71	67
	Mean[2] (SE)	92.0 (1.3)	96.7 (1.3)	92.3 (1.3)
Week 12	n	69	71	67
	Mean[2] (SE)	93.7 (1.7)	102.6 (1.6)	99.7 (1.7)
Change from Baseline to Week 12	n	69	71	67
	Mean[2] (SE)	1.7 (1.6)	5.9 (1.6)	7.4 (1.7)
Treatment Comparison versus Placebo				
Baseline	Overall p-value[1]	0.097		
Change from Baseline to Week 12	Mean difference (SE)[2]		4.1 (2.3)	5.7 (2.3)
	p-value[2]		0.055	0.002

(1) Ordinary least squares means and p-value from a two-way ANOVA model including effects for sex, treatment and their interaction
(2) Proportionally weighted least squares means using the same model as (1)

Table 61: Study 22388 - Descriptive Statistics for FBG (Weeks 0-12)

		Placebo			Serostim 4 mg QOD			Serostim 4 mg		
Glucose		Baseline	Week 2	Week 12	Baseline	Week 2	Week 12	Baseline	Week 2	Week 12
	n	77	43	59	79	44	54	82	48	55
	Mean (SD)	92.7 (9.9)	93.1 (11.6)	94.3 (11.5)	97.4 (10.1)	105.6 (14.4)	102.8 (16.0)	93.5 (10.7)	118.5 (47.7)	101.2 (15.0)
	Range	(66, 115)	(71, 135)	(68, 122)	(70, 129)	(79, 137)	(75, 144)	(65, 119)	(74, 404)	(63, 142)

Table 62: Studies 22388 and 24380 Combined - Change from Baseline to Week 12 in FBG (mg/dL) After Treatment with Serostim 4 mg QD vs. Placebo (Modified ITT Population)

Time Point		Study 22388		Study 24380		All Subjects	
		Placebo	Serostim 4 mg daily	Placebo	Serostim 4 mg daily	Placebo	Serostim 4 mg daily
Baseline	n	78	82	78	243	156	325
	Mean (SD)	92.8 (9.8)	92.9 (12.0)	93.8 (14.0)	94.7 (17.9)	93.3 (12.0)	94.2 (16.6)
	Range	(66.0, 117.0)	(62.0, 131.0)	(69.0, 168.0)	(55.0, 255.0)	(66.0, 168.0)	(55.0, 255.0)
Week 12	n	78	82	78	243	156	325
	Mean (SD)	93.6 (10.4)	102.4 (20.5)	95.6 (12.4)	100.7 (17.4)	94.6 (11.4)	101.1 (18.2)
	Range	(67.0, 115.0)	(66.0, 229.0)	(75.0, 152.0)	(60.0, 225.0)	(67.0, 152.0)	(60.0, 229.0)
Change from Baseline to Week 12	n	78	82	78	243	156	325
	Mean (SD)	0.8 (9.9)	9.5 (21.5)	1.8 (15.3)	6.0 (20.8)	1.3 (12.9)	6.9 (21.0)
	Range	(-20.0, 30.0)	(-42.0, 145.0)	(-68.0, 60.0)	(-146.0, 123.0)	(-68.0, 60.0)	(-146.0, 145.0)
	p-value[(b)]	0.477	<0.001	0.117	<0.001	0.119	<0.001
	Mean[(a)]diff. (SE)	---		---		6.0 (1.9)	
	p-value[(c)]	---		---		<0.001	

(a) (b) (4) (b) (4)

(b) p-value from a Wilcoxon Signed Rank test on the change from baseline to Week 12
(c) p-value from a three-way ANOVA model on ranked data including effects for study, treatment, sex, and the treatment by sex interaction
(d) p-value from a three-way ANOVA model on raw data including effects for study, treatment, sex, and the treatment by sex interaction

7.1.7.2.2 Shift Tables for Changes in FBG During Weeks 0-12 in Study 22388, and Weeks 0-12, 12-36 and 0-36 in Study 24380

Tables 63 and 64 were created by the sponsor for this Medical Officer at my request. The basic thought was to demonstrate how many patients with a normal FBG at baseline (<100 mg/dL) shifted into the impaired fasting glucose (IFG) range (100-126 mg/dL) or the high FBG range (>126 mg/dL) after treatment with Serostim 4 mg QD and Serostim 4 mg QOD vs. placebo at various timepoints.

Table 63 in fact demonstrates **a dose response**, i.e. after 12 weeks, the percentages of subjects who began Study 22388 with a normal FBG and then shifted into the IFG or high FBG range at Week 12 were 21.8% and 2.6% in the placebo group, respectively, 32.5% and 3.8% in the Serostim 4 mg QOD group, respectively, and 39.0% and 8.5% in the Serostim 4 mg QD group, respectively.

Table 63: FBG: Shift from Baseline to Week 12 (Safety Population from Study 22388)

Start to End Timepoints	Start Value Status[a]	Placebo (n=78)				
		Peak Value Status[b]				
		Normal	IFG	High FG	Missing	Total
		n (%)	n (%)	n (%)	n (%)	n (%)
Baseline to Week 12	Normal	36 (46.2)	**17 (21.8)**	**2 (2.6)**	0	55 (70.5)
	IFG	5 (6.4)	15 (19.2)	1 (1.3)	0	21 (26.9)
	High FG	2 (2.6)	0	0	0	2 (2.6)
	Missing	0	0	0	0	0
	Total	43 (55.1)	32 (41.0)	3 (3.8)	0	78 (100.0)
Start to End Timepoints	**Start Value Status[a]**	**Serostim 4 mg QOD (n=80)**				
		Peak Value Status[b]				
		Normal	**IFG**	**High FG**	**Missing**	**Total**
		n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Baseline to Week 12	Normal	14 (17.5)	**26 (32.5)**	**3 (3.8)**	0	43 (53.8)
	IFG	3 (3.8)	21 (26.3)	11 (13.8)	1 (1.3)	36 (45.0)
	High FG	0	0	1 (1.3)	0	1 (1.3)
	Missing	0	0	0	0	0
	Total	17 (21.3)	47 (58.8)	15 (18.8)	1 (1.3)	80 (100.0)
Start to End Timepoints	**Start Value Status[a]**	**Serostim 4 mg QD (n=82)**				
		Peak Value Status[b]				
		Normal	**IFG**	**High FG**	**Missing**	**Total**
		n (%)	**n (%)**	**n (%)**	**n (%)**	**N (%)**
Baseline to Week 12	Normal	14 (17.1)	**32 (39.0)**	**7 (8.5)**	0	53 (64.6)
	IFG	1 (1.2)	15 (18.3)	12 (14.6)	0	28 (34.1)
	High FG	0	0	1 (1.2)	0	1 (1.2)
	Missing	0	0	0	0	0
	Total	15 (18.3)	47 (57.3)	20 (24.4)	0	82 (100.0)

(a) Normal=Maximum screening and baseline FBG value is <=100 mg/dL; IFG=Maximum screening and baseline FBG value is >100 and <=126 mg/dL; High FBG=Maximum screening and baseline FBG value is >126 mg/dL
(b) Normal=Maximum FBG value in the period is <=100 mg/dL; IFG=Maximum FBG value in the period is >100 and <=126 mg/dL; High FBG=Maximum FBG value in the period is >126 mg/dL

Table 64 demonstrates that after 12 weeks of treatment with Serostim 4 mg QD vs. placebo, the percentages of subjects who began the study with a normal FBG and then shifted into the IFG or high FBG range at Week 12 were **28.4% and 1.2%** in the placebo group, respectively, and **42.2% and 7.0%** in the Serostim 4 mg QD group, respectively - very similar to shift at Week 12 in Study 22388 for the Serostim 4 mg QD dose. Table 64 also demonstrates that after 24 weeks of maintenance treatment with Serostim 2 mg QOD vs. placebo, the percentages of subjects who began the maintenance period with a normal FBG and then shifted into the IFG or high FBG range at Week 36 were **21.5% and 1.1%** in the placebo group, respectively, and **43.5% and 4.3%** in the Serostim 2 mg QOD group, respectively. These findings indicate that the proportion of subjects who shifted to the IFG range after 12 weeks of induction treatment with Serostim 4 mg QD is equivalent to the proportion of subjects who shifted to the IFG range after 24 weeks of maintenance treatment with Serostim 2 mg QOD, i.e. there was no drop-off. **On the other hand, there was a drop-off in the proportion of patients who shifted to the high FBG range (from 7.0% to 4.3%) - indicating that maintenance treatment with Serostim 2 mg QOD results in somewhat less glucose intolerance than induction treatment with Serostim 4 mg QD**.

Table 64: Fasting Glucose Glycemic Status: Shift from Baseline to Week 12, Baseline to Week 36, Week 12 to Week 36 (Population: Safety Subjects from 24380)

Start to End Timepoints	Start Value Status[a]	Placebo (n=81)					Serostim 4 mg daily (n=244)				
		Peak Value Status[b]					Peak Value Status[b]				
		Normal	IFG	High FG	Miss.	Total	Normal	IFG	High FG	Miss.	Total
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Baseline to Week 12	**Normal**	**33 (40.7)**	**23 (28.4)**	**1 (1.2)**	2 (2.5)	59 (72.8)	**35 (14.3)**	**103 (42.2)**	**17 (7.0)**	0	155 (63.5)
	IFG	3 (3.7)	15 (18.5)	1 (1.2)	0	19 (23.5)	2 (0.8)	56 (23.0)	25 (10.2)	1 (0.4)	84 (34.4)
	High FG	1 (1.2)	1 (1.2)	0	1 (1.2)	3 (3.7)	1 (0.4)	3 (1.2)	1 (0.4)	0	5 (2.0)
	Missing	0	0	0	0	0	0	0	0	0	0
	Total	37 (45.7)	39 (48.1)	2 (2.5)	3 (3.7)	**81 (100)**	38 (15.6)	162 (66.4)	43 (17.6)	1 (0.4)	**244 (100)**
		Serostim 4 mg daily/Placebo/Placebo (n=93)					**Serostim 4 mg daily/Serostim 2 mg QOD/2 mg QOD (n=92)**				
		Peak Value Status[b]					**Peak Value Status[b]**				
	Start Value Status[a]	**Normal**	**IFG**	**High FG**	**Miss.**	**Total**	**Normal**	**IFG**	**High FG**	**Miss.**	**Total**
		n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**N (%)**	**n (%)**
Baseline to Week 36	Normal	11 (11.8)	42 (45.2)	6 (6.5)	0	59 (63.4)	7 (7.6)	46 (50.0)	10 (10.9)	0	63 (68.5)
	IFG	0	20 (21.5)	12 (12.9)	0	32 (34.4)	0	20 (21.7)	6 (6.5)	0	26 (28.3)
	High FG	1 (1.1)	1 (1.1)	0	0	2 (2.2)	0	2 (2.2)	1 (1.1)	0	3 (3.3)
	Missing	0	0	0	0	0	0	0	0	0	0
	Total	12 (12.9)	63 (67.7)	18 (19.4)	0	93 (100)	7 (7.6)	68 (73.9)	17 (18.5)	0	92 (100.0)

(a) Normal=Maximum screening and baseline FBG value is <=100 mg/dL; IFG=Maximum screening and baseline FBG value is >100 and <=126 mg/dL; High FBG=Maximum screening and baseline FBG value is >126 mg/dL

(b) Normal=Maximum FBG value in the period is <=100 mg/dL; IFG=Maximum FBG value in the period is >100 and <=126 mg/dL; High FBG=Maximum FBG value in the period is >126 mg/dL

Table 64 Continued: Fasting Glucose Glycemic Status: Shift from Baseline to Week 12, Baseline to Week 36, Week 12 to Week 36 (Population: Safety Subjects from 24380)

Start to End Timepoints	Start Value Status[a]	Serostim 4 mg daily/Placebo/Placebo (n=93)					Serostim 4 mg daily/2 mg QOD/2 mg QOD (n=92)				
		Peak Value Status[b]					Peak Value Status[b]				
		Normal	IFG	High FG	Miss.	Total	Normal	IFG	High FG	Miss.	Total
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n\(%)	n (%)
Week 12 to Week 36	Normal	**38 (40.9)**	**20 (21.5)**	**1 (1.1)**	0	59 (63.4)	**18 (19.6)**	**40 (43.5)**	**4 (4.3)**	1 (1.1)	63 (68.5)
	IFG	5 (5.4)	26 (28.0)	1 (1.1)	0	32 (34.4)	2 (2.2)	22 (23.9)	1 (1.1)	1 (1.1)	26 (28.3)
	High FG	2 (2.2)	0	0	0	2 (2.2)	0	3 (3.3)	0	0	3 (3.3)
	Missing	0	0	0	0	0	0	0	0	0	0
	Total	45 (48.4)	46 (49.5)	2 (2.2)	0	93 (100.0)	20 (21.7)	65 (70.7)	5 (5.4)	2 (2.2)	92 (100)

(a) Normal=Maximum screening and baseline FBG value is <=100 mg/dL; IFG=Maximum screening and baseline FBG value is >100 and <=126 mg/dL; High FBG=Maximum screening and baseline FBG value is >126 mg/dL
(b) Normal=Maximum FBG value in the period is <=100 mg/dL; IFG=Maximum FBG value in the period is >100 and <=126 mg/dL; High FBG=Maximum FBG value in the period is >126 mg/dL
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7.1.7.2.3 Glycemic AEs Leading to Study Discontinuation

With the able assistance of the sponsor, this Medical Officer was able to construct Table 65 which reflects a significant amount of information about 23 patients who were discontinued at any time during any of the studies because of glucose intolerance. A review of the table clearly indicates that the most common dosing regimen that led to sufficient glucose intolerance to require study discontinuation was, not surprisingly, Serostim 4 mg QD - accounting for 13 of the 23 glucose intolerance-mediated withdrawals (56%). Three patients treated with Serostim 1 mg QD and 1 patient treated with the planned maintenance dose (Serostim 2 mg QOD) also were discontinued. None of these patients apparently were hospitalized or treated with antidiabetic medications. It is unclear to me how many of them had sustained follow-up to ensure that their glucose tolerance returned to normal off Serostim.
With regard to the 2 patients who manifested the highest blood sugars: 1) Patient #3100005 (Study 24380) had a pre-study FBG level of 95 mg/dL and 12 days after Serostim 4 mg QD was started, his FBG increased to 386 mg/dL. Serostim was discontinued and 1 month later his FBG was back to 96 mg/dL; 2) Patient #4280009 (Study 22388) had a pre-study FBG level of 89 mg/dL and 21 days after Serostim 4 mg QD was started, his FBG increased to 404 mg/dL. He was immediately discontinued from the study; the narrative describes him as having had **ketoacidosis**. It is beyond my comprehension how he was not admitted and treated at that time. The only other information in the narrative indicates a random post-termination blood glucose of 224 mg/dL 1 week later. The patient was then lost to followup. **This patient may well have developed diabetes mellitus**.

Table 65: Subjects Who Discontinued at Any Time from Any Study due to Glucose Intolerance

Study	Subject No.	Treatment Period (weeks)	Treatment Group	Treatment at Time of Withdrawal	Days on Assoc. Trt	FBG (mg/dL) triggering reduction/ withdrawal	Narrative Location
22388	**0050007**	**0-12**	**4 mg DD**	**unconfirmed[1]**	**22**	**132**	CSR 22388 Addend 1, pg 16
	3280042	**0-12**	**4 mg DD**	**4 mg AD[1]**	**31/28**	**230[1]/143**	CSR 22388 Addend 1, pg 22
	4280009	**0-12**	**4 mg DD**	**4 mg DD**	**21**	**404**	CSR 22388 Addend 1, pg 15
	4280008	**0-12**	**4 mg AD**	**4 mg AD**			CRF only
	0210009	12-24	Placebo/4 mg DD	4 mg AD[1]	14/15	223[1]/138	CSR 22388 Addend 1, pg 12
	3010005	12-24	Placebo/4 mg DD	4 mg DD			CRF only
	5220015	12-24	4 mg DD/4 mg AD	4 mg AD			CRF only
	5220023	12-24	4 mg DD/4 mg AD	4 mg AD[1, 2]	29/67	146[1]/133	CSR 22388 Addend 1, pg 23
	0200015	12-24	4 mg AD/4 mg AD	4 mg AD			CRF only
	3100010	12-24	4 mg AD/4 mg AD	4 mg AD			CRF only
	3280029	12-24	4 mg DD/Placebo	Placebo			CRF only
23056	1570023	0-12	1 mg DD[3]	1 mg DD	14	163	CSR 23056 pg 439-440
	3190001	0-12	1 mg DD[4]	1 mg DD	~14	146	CSR 22388 Addend 1, pg 36
	0180001	12-36	2 mg DD/1 mg DD[5]	1 mg DD	~14/48	130[1]/154	CSR 22388 Addend 1, pg 25
24380	**0070012**	**0-12**	**4 mg DD**	**4 mg DD**			CRF only
	3010005	**0-12**	**4 mg DD**	**4 mg AD[1]**	**16/13**	**126[1]/170**	CSR 24380 Addend 1, pg 20
	3280015	**0-12**	**4 mg DD**	**4 mg AD[1]**	**20/8**	**127[1]/139**	CSR 24380 Addend 1, pg 22
	5270017	**0-12**	**4 mg DD**	**4 mg AD[1]**	**15/8**	**204[1]/156**	CSR 24380 Addend 1, pg 10
	5270022	**0-12**	**4 mg DD**	**4 mg AD[1]**	**15/9**	**165[1]/141**	CSR 24380 Addend 1, pg 11
	3100005	**0-12**	**4 mg DD**	**4 mg DD**	**12**	**386 (Baseline FBG = 95)**	CSR 24380 pg 1205
	3010004	12-36	Placebo/4 mg DD	4 mg DD			CRF only
	5270029	12-36	Placebo/4 mg DD	4 mg AD[1]	~14/15	180[1]/131	CSR 24380 Addend 1, pg 28
	0240015	12-36	4 mg DD/2 mg AD	2 mg AD			CRF only

DD = daily dose; AD = alternate days; [1]dose reduction followed by drug discontinuation; [2]withdrew between treatment periods; [3]received Serostim 4 mg AD for 24 weeks in Study 22388; [4]received Serostim 4 mg DD for ~10.5 weeks followed by placebo for ~12 weeks in Study 22388; [5]received Serostim 4 mg AD for 24 weeks in Study 22388, then no study drug for 1 month, then Serostim 2 mg DD for ~5 weeks and Serostim 1 mg DD for ~7 weeks in Study 23056

7.1.7.2.4 Additional Information Regarding Serostim Treatment and Glycemic Parameters

- In the group that received Serostim 4 mg QD for 12 weeks followed by maintenance therapy with Serostim 2 mg QOD for 24 weeks in Study 24380 (the "Induction-Maintenance" group), mean FBG (as well as 2 hour post-prandial blood glucose level, fasting insulin, and insulin AUC) all returned to levels insignificantly different from baseline during the maintenance period. Mean hemoglobin A1C significantly increased by a clinically meaningless 0.1%
- Not surprisingly, most peak FBG levels occurred within 2-4 weeks of Serostim initiation; as therapy continued, FBG levels typically decreased and, in most cases, normalized by the end of treatment (see Table 61 from Study 22388).
- Most peak FBG levels were in the 100-126 mg/dL IFG range, usually transient, but occasionally sustained. Except for the 23 patients who were discontinued with persistent FBG >126 mg/dL (see Table 23), peak FBG levels exceeding 126 mg/dL were almost exclusively transient.

7.1.7.3 Change in IGF I/IGF I SDS

This Medical Officer has decided to focus only on the changes in serum IGF I SDS - which more readily allows comparisons across age and gender. I am under the impression that the sponsor used a central laboratory for IGF I determinations - so that serum IGF I values could be calculated easily and accurately.

As seen in Table 66, the difference in the change from baseline to Week 12 in serum IGF I SDS after treatment with Serostim 4 mg QD vs. placebo in an integrated analysis of both studies was highly significant and enormously substantial (+5.7 units; $p<0.001$). Figure 25 displays the proportion of patients with serum IGF I SDS >+2 at baseline and Week 12 for Studies 22388 and 24380 combined in stacked bar graphs. At baseline, it appears that the proportion of subjects with serum IGF I SDS levels is ~10-20%, while after treatment with either dose of Serostim, that percentage becomes 80-90%. Figure 26 displays the same information at baseline, Week 12 and Week 36 for subjects in Study 24380. The baseline and Week 12 proportions confirm the findings from Figure 25. At Week 36, in patients rerandomized to placebo at Week 12, the proportion of subjects with serum IGF I levels >+2 had returned to baseline/normal (e.g., ~5%). On the other hand, almost 50% of the patients randomized to Serostim 2 mg QOD at Week 12 still had very serum IGF I levels >+2.

Table 66: Studies 22388 and 24380 - Change from Baseline to Week 12 in Serum IGF-I SDS After Treatment with Serostim 4 mg QD vs. Placebo (Modified ITT Population)

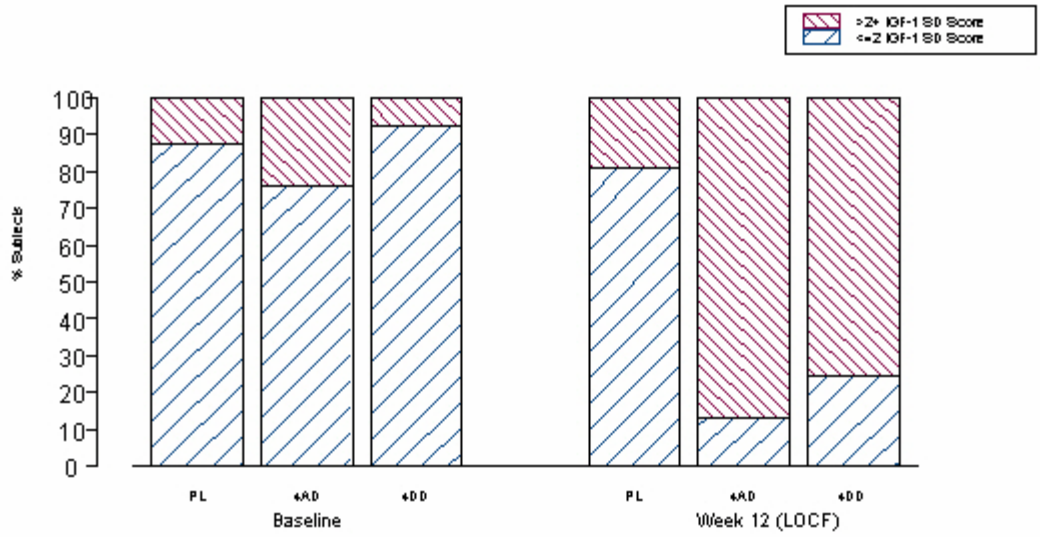
Time Point		Study 22388		Study 24380		All Subjects	
		Placebo n=72	Serostim 4 mg daily n=70	Placebo n=73	Serostim 4 mg daily n=220	Placebo n=145	Serostim 4 mg daily n=290
Baseline	Mean (SD)	1.0 (1.1)	0.9 (1.8)	-0.2 (1.3)	-0.3 (1.3)	0.4 (1.4)	0.0 (1.6)
	Range	(-1.4, 4.0)	(-1.9, 11.9)	(-2.5, 4.8)	(-3.0, 5.8)	(-2.5, 4.8)	(-3.0, 11.9)
Week 12	Mean (SD)	1.3 (1.4)	7.5 (5.7)	0.3 (1.6)	5.6 (4.7)	0.8 (1.6)	6.1 (5.0)
	Range	(-1.5, 5.5)	(0.0, 29.2)	(-2.6, 6.7)	(-1.8, 23.1)	(-2.6, 6.7)	(-1.8, 29.2)
Change from Baseline to Week 12	Mean (SD)	0.3 (1.0)	6.6 (4.8)	0.5 (1.6)	5.9 (4.5)	0.4 (1.3)	6.1 (4.6)
	Range	(-2.9, 3.4)	(-1.4, 24.3)	(-2.3, 7.7)	(-2.4, 22.6)	(-2.9, 7.7)	(-2.4, 24.3)
	p-value (b)	0.026	<0.001	0.008	<0.001	<0.001	<0.001
	Mean Diff. From Placebo (SE) (a)	---		---		5.7 (0.4)	
	p-value (c)	---		---		<0.001	

(a) (b) (4)

(b) p-value from a Wilcoxon Signed Rank test on the change from baseline to Week 12.
(c) p-value from a three-way ANOVA model on ranked data including effects for study, treatment, sex, and the treatment by sex interaction.

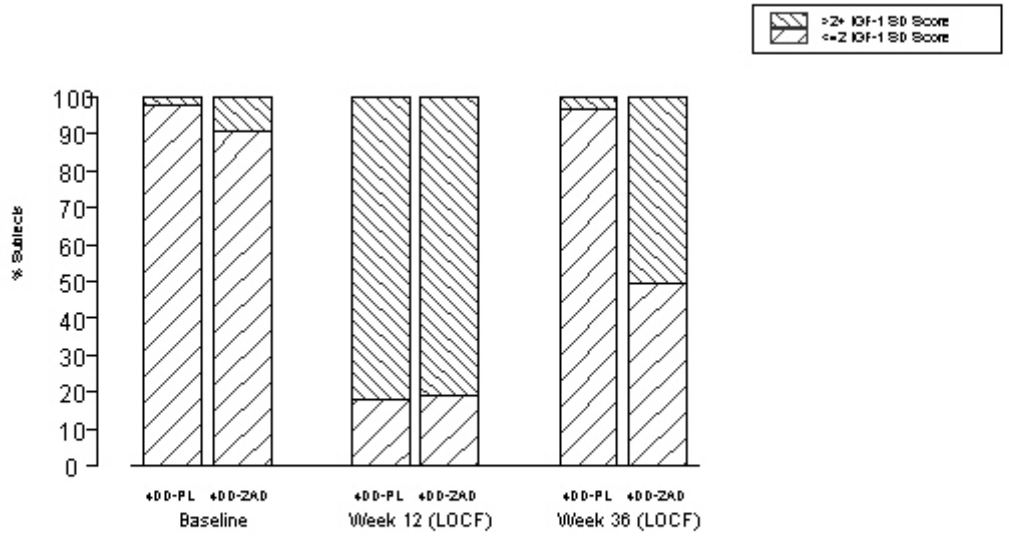
Figure 25: Studies 22388 and 24380 Combined - Proportion of Subjects with IGF I SDS >2+ at Baseline and Week 12 After Treatment with Serostim 4 mg QD and Serostim 4 mg QOD vs. Placebo (Safety/ITT Population)

FDA Request, Figure 1
Proportion of Subjects with IGF-1 SD Scores > 2+
Population: Weeks 1-12 Safety Subjects from 22388 and 24380 with Baseline and Followup



4DD=Serostim® 4 mg daily (n= 290); 4AD=Serostim® 4 mg alt. daily (n= 75); PL=Placebo (n= 145)

Figure 26: Study 24380 - Proportion of Subjects with IGF I SDS >2+ at Baseline, Week 12 After Treatment with Serostim 4 mg QD vs. Placebo and Week 36 After Treatment with Serostim 2 mg QOD vs. Placebo



4DD-2AD=Serostim® 4 mg daily/Serostim® 2 mg alt. days/Serostim® 2 mg alt. days (n= 85);
4DD-PL=Serostim® 4 mg daily/Placebo (n= 88)

7.1.7.4 Measures of HIV Activity

7.1.7.4.1 HIV Viral Load

Two hundred fifty-six (256) subjects in the Serostim 4 mg QD treatment group and 127 subjects in the placebo group had HIV-1 RNA levels ≤400 copies/mL at baseline. Of these subjects, 85.2% (218/256) in the Serostim 4 mg QD group and 84.2% (107/127) in the placebo group maintained an HIV-1 RNA level of ≤400 copies/mL at Week 12. Data not shown.

7.1.7.4.2 CD4+ T Helper Lymphocyte Cell Quantitation

As expected, there was no significant difference between the Serostim 4 mg QD vs. placebo treatment groups in the change or percent change from baseline to Week 12 in CD4+ count. Data not show

7.1.10 Immunogenicity

Although it was measured ~12 weeks in the pivotal studies, no patients were reported in any of the studies with positive anti-rhGH antibodies.

7.1.17 Postmarketing Experience

There is extensive experience with an even larger dose of Serostim (0.1 mg/kg [up to a maximum of 6 mg QD]) for the treatment of patients with HIV-associated wasting or cachexia (the sponsor's currently approved [approved in 8/96] and only indication for Serostim). During the first 5 years of so after this approval (when HIV-associated wasting was much more prevalent than it is currently in the United States), the administration of this remarkably pharmacologic amount of rhGH (10-20 times the amount usually prescribed for adults with GHD and1 ½ times the 4 mg QD dose that the sponsor is currently seeking approval for to treat patients with HARS), resulted in very frequent and sometimes severe AEs. Not surprisingly glucose intolerance-related and fluid retention-related AEs (i.e., edema, arthralgia, myalgia, carpal tunnel syndrome, etc) were the most common AEs reported via AERS and other mechanisms. As a result, several years ago, the frequency of glucose intolerance-related events including new onset diabetes mellitus and diabetic ketoacidosis led to a language upgrade in the PRECAUTIONS and ADVERSE REACTIONS sections of the Serostim package insert. I am not sure, but I believe that the frequency of these AE reports has diminished in more recent years with the advent and much more routine use of HAART resulting in a much decreased prevalence of HIV-associated wasting.

7.2.9 Additional Submissions, Including Safety Update

A brief review of the Safety Update submitted on 9/28/06 reveals no findings of note. Following the conclusion of the maintenance phase of Study 24380, subjects were allowed to enroll in Study 25373 and receive open label reinduction therapy with Serostim 4 mg QD for 12 weeks. The quality and the frequency of the AEs reported are no different from that reported during the original placebo-controlled induction phases in Studies 24380 and 22388.

7.3.1 Safety Summary of Results/Discussion/Conclusions

- The AEs that occurred during these trials were the longstanding well known AEs associated with rhGH treatment (especially with large doses) - glucose intolerance and fluid retention-related AEs such as edema, arthralgia, myalgia, carpal tunnel syndrome/hypoesthesia/paresthesias.
- The safety profile of Serostim 4 mg QD was clearly and emphatically different from and more "adverse" than the safety profile of Serostim 4 mg QOD. This safety-related dose response manifested itself over and over including the following:
  --when the data from Studies 22388 and 24380 are integrated for Weeks 0-12, the proportions of subjects who discontinued due to an AE were 1.3%, 5%, and 13.2% in the placebo, Serostim 4 mg QOD and Serostim 4 mg QD groups, respectively
  ---Amongst the 94 subjects discontinued during the entire drug development program due to an AE, 69% were being treated with Serostim 4 mg QD and ~14% were being treated with Serostim 4 mg QOD
  ---when the data from Studies 22388 and 24380 are integrated for Weeks 0-12, and AEs with a >5% incidence in any active treatment arm are tabulated, there is a clearcut dose response with respect to each and every rhGH-related AE, i.e. the incidence of edema was 3.8%, 18.8% and 45.4% in subjects treated with placebo, Serostim 4 mg QOD and Serostim 4 mg QD, respectively
  ---when the data from Studies 22388 and 24380 are integrated for Weeks 0-12, 1.3%, 18.8% and 25.5% of subjects treated with placebo, Serostim 4 mg QOD and Serostim 4 mg QD, respectively, required some type of dose modification due to an AE
- With regard to glucose intolerance-related issues specifically which are clearly expected given that very large amounts of rhGH are being administered to a cohort of HARS patients who already are insulin resistant and possibly glucose intolerant at baseline:
  ---23 patients were discontinued during drug development en toto because of hyperglycemia (and 13/23 were being treated with Serostim 4 mg QD)
  ---one of these 23 patients may well have developed overt diabetes mellitus;
  ---none of these patients were allegedly hospitalized or treated with antihyperglycemic medications and post-study FBG levels were documented as normal in some of them off Serostim, but follow-up data is not available for all of them
  ---peak FBGs on-study were typically between 100-126 mg/dL, usually transient, but occasionally sustained; peak FBGs >126 mg/dL were most often transient – except of course in the 23 patients who were discontinued because of unacceptable hyperglycemia
  ---many patients demonstrated FBG increases 2-4 weeks after starting Serostim, but, over time, mean FBG levels returned to normal without discontinuing the drug
  ---it is well documented that the difference in the change from baseline to Week 12 in FBG after 12 weeks of treatment with Serostim 4 mg QD vs. placebo is ~6 mg/dL; however, the Week 12 FBG level is still usually <100 mg/dL
  ---in patients treated with Serostim 4 mg QD as induction therapy for 12 weeks followed by 24 weeks of Serostim 2 mg QOD as maintenance therapy, all glucose/insulin parameters of interest become insignificantly different from pre-treatment values by Week 36

- With respect to changes in serum IGF I SDS
  ---the difference in the change from baseline to Week 12 after treatment with Serostim 4 mg QD vs. placebo is highly significant and quite robust (+5.7)
  ---both Serostim 4 mg QD and Serostim 4 mg QOD increased the proportion of subjects with serum IGF I SDS >+2 from <10% to >80% after 12 weeks of treatment
  ---when subjects are rerandomized to placebo for 24 weeks after 12 weeks of induction therapy, IGF I SDS return to baseline; however, if patients were rerandomized to Serostim 2 mg QOD as maintenance therapy for 24 weeks, a substantial proportion (~50%) of them still had serum IGF I levels >+2 at Week 36. The oncogenic potential of this phenomena remains unknown and controversial. Some authors believe the that the concomitant increase in serum IGFBP-3 after treatment with rhGH is in fact cancer-protective.
- There were no changes from baseline in HIV-1 RNA copies or CD4+ lymphocyte counts after treatment

7.7.4 Safety Recommendations

- **The more adverse safety profile observed with Serostim 4 mg QD is tolerable and acceptable if it is only administered during the 12 week induction period, and certain caveats regarding the use of Serostim 4 mg QD are added/labeled, i.e. <u>cut back to Serostim 4 mg QOD if significant rhGH-related adverse events should occur, start with Serostim 4 mg QOD in patients considered to be at special risk for rhGH-related adverse effects, especially glucose intolerance</u>**

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

See Executive Summary.

8.3 Special Populations

See Executive Summary.

8.4 Pediatrics

There are no ongoing trials evaluating the use of Serostim for pediatric patients with HARS. I am unaware of the exact prevalence of HARS in the pediatric population, but I believe that it occurs very infrequently.

8.7 Postmarketing Risk Management Plan

See Safety Conclusions/Recommendations in the Executive Summary.

9 OVERALL ASSESSMENT

See Executive Summary. It would be repetitious and add to an already very long review if I completed this section.

9.4 Labeling Review

16 Pages Draft Labeling Withheld in Full Immediately Following This Page as B4 (CCI/TS)

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/s/

Robert Perlstein
7/12/2007 11:11:42 AM
MEDICAL OFFICER

Mary Parks
7/12/2007 06:30:16 PM
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see Director's memo

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020604Orig1s040

CHEMISTRY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
OFFICE OF NEW DRUG QUALITY ASSESSMENT

POST-MARKETING EVALUATION
CMC ASSESSMENT FORM

APPLICANT: EMD SERONO	**NDA NUMBER: 020604**	**DOC TYPE: SE1**	**SEQ NUMBER: 040**	**SUBMISSION TYPE: ORIGINAL**
PROPRIETARY NAME: SEROSTIM (SOMATROPIN) FOR INJECTION 6MG		**ESTABLISHED NAME: SOMATROPIN**		
DOSAGE FORM: INJ	**STRENGTH/POTENCY: 4,5,6 MG & 6-MG/0.5-ML**		**PHARMACOLOGICAL CATEGORY:**	
LETTER DATE: 6/12/2006	**STAMP DATE: 6/14/2006**	**PDUFA GOAL DATE: 4/14/2007**	**SUBMISSION (CHECK ONE) FIRM: PA FINAL: PA**	
DIVISION IV BRANCH: VII	**OND DIVISION: 510**	**MANAGED BY: OND**	**PAL: Brown**	
			MEDIA SUBMISSION: Electronic	
SUPPLEMENT PROVIDES FOR: the reduction of abnormal trunk fat, including visceral adipose tissue, and associated body image distress in patients infected with HIV being treated concomitantly with antiretroviral therapy.				
BUNDLED: No				
CHANGE CATEGORY: Efficacy Supplement				
LABELING INVOLVED: Yes - PI only	**PAT: No**	**COMPARABILITY PROTOCOL: No**	**PHASE 4 COMMITMENT:**	
REVIEW PATH: 3 - Moderate Risk - Minimal Review				
CONSULTS:				

JUSTIFICATION/COMMENTS: 4/11/2007 - BROWNJA

1. The applicant has requested a categorical exclusion from the requirements to prepare an Environmental Assessment under 21 CFR §25.31(a) for Serostim. This supplement meets the requirements of a categorical exclusion under 21 CFR §25.31(a) because it will not increase the use of the drug. The applicant's request for a categorical exclusion is granted.

2. There are two CMC labeling changes in the 06-Feb-2007 submission.
   a. STABILITY AND STORAGE: [redacted] (b) (4)

   b. HOW SUPPLIED: The revised labeling states that ***"Serostim® can be administered using (1) a standard sterile, disposable syringe and needle, (2) a compatible Serostim® needle-free injection device or (3) a compatible Serostim® needle injection device. For proper use, refer to the Instructions for Use provided with the administration device."*** The labeling review by the PM for NDA 19-764/S-030 includes the same change and is repeated in this supplement. The how supplied is revised to be more generic with respect to the device so that when new devices are approved by CDRH, labeling doesn't need to be revised. This change is implemented NDA 19-764/S-030 was approved on 16-Jan-2007 and the labeling change is also acceptable in this supplement.

[redacted] (b) (4)

(b) (4) 3. From a CMC standpoint, this supplement can be approved.
PAL ACTION: From a CMC standpoint, this supplement can be approved.
BRANCH CHIEF: James Vidra

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/s/

Janice Brown
4/11/2007 11:37:44 AM
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Jim Vidra
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020604Orig1s040

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number:	20-604 SE1-040
Drug Name:	Serostim [somatropin (rDNA origin)] (mammalian cell-derived recombinant human growth hormone, r-hGH)for injection
Indication(s):	Reduction of abnormal trunk fat, including visceral adipose tissue, and associated body image distress in patients infected with the human immunodeficiency virus (HIV) being treated concomitantly with antiretroviral therapy
Applicant:	Serono
Date(s):	July 6, 2007 (3 month extension, amendment dated 7/14/2007)
Review Priority:	Standard
Biometrics Division:	DB2
Statistical Reviewer:	Lee-Ping Pian, Ph.D.
Concurring Reviewers:	Todd Sahlroot, PhD, Statistical Team Leader.
Medical Division:	Division of Metabolism and Endocrinology Products (DMEP)
Clinical Team:	Robert Perlstein, M.D.
	Mary Parks, M.D. Division Director
Project Manager:	Kati Johnson

Keywords: New Drug Application (NDA) review, clinical studies, Patient Reported Outcome (PRO)

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1. EXECUTIVE SUMMARY

This supplemental NDA included a 24-week dose finding study (22388) and a 36-week phase 3 study (24380) comparing Serostim to placebo in the treatment of Human Immunodeficiency Virus-associated Adipose Redistribution Syndrome (HARS).

At the end-of-phase 2 meeting on May 22, 2002, the sponsor and the Agency reached agreement concerning: 1) the overall protocol design of the phase 3 study (24380); 2) the CT-derived Visceral Adipose Tissue (VAT) as the primary endpoint and DEXA-derived truncal fat (secondary endpoint) after the 12-week induction period as the primary objectives of the study; and 3) it was essential that Serono demonstrate sustained efficacy during the six-month maintenance phase as well to obtain registration for this indication.

1.1 Conclusions and Recommendations

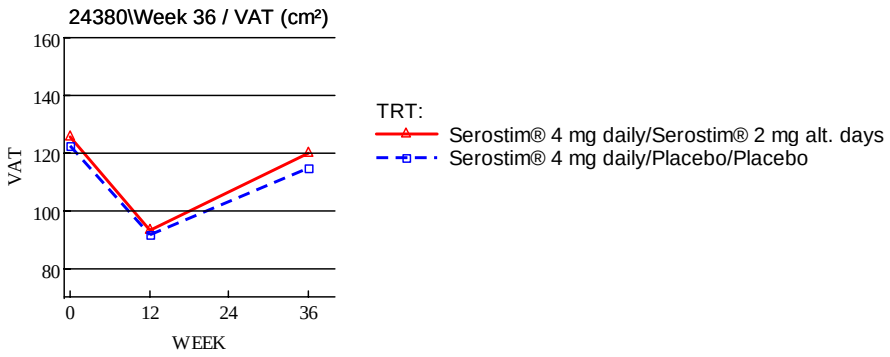
For the 12-week induction phase of both studies, Serostim 4 mg daily (QD) was statistically significantly better than placebo in VAT change from baseline to week 12. The 4 mg alternate day (QOD) dose, which was studied only in the dose finding study, was also significantly better than placebo in VAT change from baseline to week 12. Least-square (LS) mean treatment differences and 2-sided 95% confidence intervals between Serostim 4 mg daily and placebo in mean VAT change from baseline were -17 cm^2 [-29, -5] in Study 24380 and -18 cm^2 [-35, -2] in Study 22388. The -20 cm^2 [-38, -2] LS mean difference between Serostim 4 mg QOD and placebo in Study 22388 was similar to the LS mean treatment difference between Serostim 4 mg QD and placebo in that study.

Randomizations in both studies were stratified by gender. Treatment-by-gender interactions comparing Serostim 4 mg QD and placebo were statistically significant at the 10% level in both studies. VAT LS mean treatment differences were +4 cm^2 in females and -38 cm^2 in males in Study 24380, and -4 cm^2 in females and -32 cm^2 in males in Study 22388.

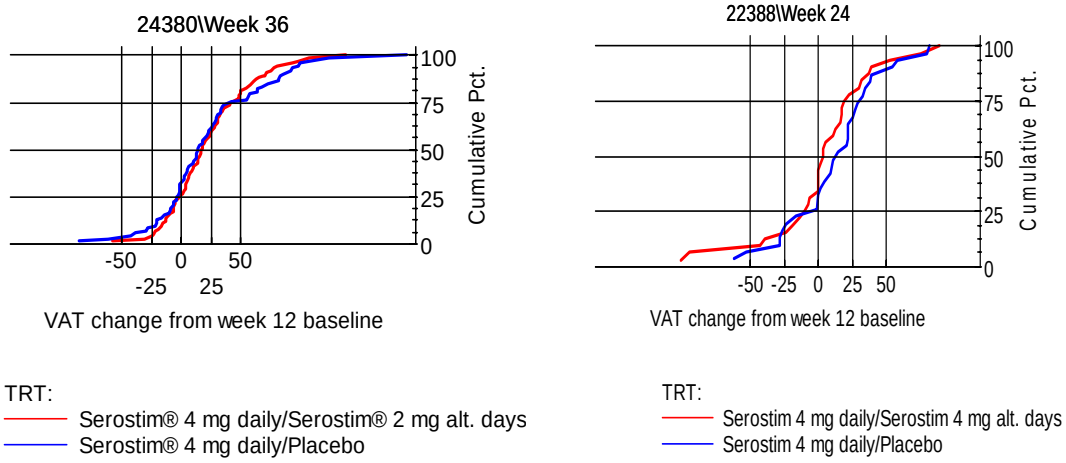
Serostim 4 mg QD and QOD and were significantly different from placebo in truncal fat mean change from baseline to week 12 in both studies. The mean difference between Serostim 4 mg daily and placebo in Study 24380 was -2.4 kg. The treatment-by-gender interactions comparing 4 mg and placebo were not significant in either study.

Both studies re-randomized patients at Week 12 to maintenance doses for 24 weeks in Study 24380 and 12 weeks in Study 22388. Patients in Study 24380 initially randomized to Serostim 4 mg QD were re-randomized to maintenance doses of Serostim 2 mg QOD or placebo. Patients in Study 22388 initially randomized to Serostim 4 mg QD were re-randomized to maintenance doses of Serostim 4 mg QOD or placebo.

In Study 24380, the two groups had similar changes in VAT change from Weeks 12 to 36. Mean VAT changes were +23.7 cm^2 for Serostim 2 mg QOD (n=73) and +23.3 cm^2 (n=75) for placebo. In Study 22388, mean VAT changes from Weeks 12 to 24 were +4 cm^2 for 4 mg QOD (n=32) and +13 cm^2 for placebo (n=31). The Figure below depicts median VAT values from week 1 (baseline) to weeks 12 and 36 for the two treatment sequences in Study 24380.



The following Figures depict cumulative distributions for VAT changes from Week 12 to Week 36 in Study 24380 and to From Week 12 to Week 24 in Study 22388.



In conclusion, Serostim 4 mg QD and QOD were statistically significantly superior to placebo and similar to each other in VAT reduction for the 12-week induction periods. Serostim did not reduce VAT in female HARS patients. Serostim 2 mg QOD failed to demonstrate sustained efficacy in the maintenance phase of Study 24380. Results from the dose finding study suggest that a higher dose (Serostim 4 mg QOD) may be required for maintenance of efficacy produced by Serostim 4 mg QD during induction.

1.2 Brief Overview of Clinical Studies

The dose finding study randomized patients in a 1:1:1 ratio to 4 mg serostim daily (high dose group), 4 mg serostim on alternating days with placebo (low dose group) and placebo daily in the first 12-week period. In 12 additional weeks patients on Serostim high dose were re-randomized in a 1:1 ratio to daily placebo (high dose/placebo group), or to Serostim maximum 4mg and placebo alternate days (high dose/low dose group). Patients initially on Serostim low dose remained on that regimen (low dose/low dose group). Patients initially on placebo received Serostim maximum 4mg/day (placebo/high dose group). After 24 weeks of the study, patients were offered to enroll into the maintenance period in a separate study protocol 23056.

Study 24380 randomized patients in a 3:1 ratio to 4 mg serostim daily and placebo in period 1 (12 weeks). In period 2 (weeks 12 to 36), patients who received Serostim were re randomized in a 1:1 ratio to placebo or Serostim 2 mg alternate days (AD). Patients who received placebo in period 1 were continued on placebo for weeks 12-24 and then received Serostim 4 mg daily for weeks 24-36.

The primary efficacy variable was the change from baseline to week 12 in absolute area of VAT as measured by cross-sectional CT scan at the level of the L4-5 inter-vertebral disk.

1.3 Statistical Issues and Findings

Clinically, the sponsor expected gender to be a significant factor related to response; therefore, gender was a stratification factor in all randomizations. The targeted gender stratification was 25% females and 75% males.

As expected, treatment-by-gender interaction for the primary efficacy variable, VAT change from baseline to week 12, was highly significant ($p<0.01$). Furthermore, difference between treatment and placebo was only in males (-38 cm^2) and not in females (+4 cm^2) (Table & Figure). This is a special case of a ‘quantitative’ interaction known as ‘effect concentration’. The VAT analysis therefore, should be presented by gender for treatment difference and a corresponding confidence interval. The sponsor’s overall estimate weighted by number of patients was only a representative of the male response since the majority of patients were males.

2. INTRODUCTION

2.1 Overview

Serostim [somatropin (rDNA origin) for injection] (NDA 20-604) was approved on August 23, 1996 for the treatment of AIDs wasting or cachexia. The new proposed indication for this supplement is for the treatment of HIV-associated adipose redistribution syndrome (HARS). The submission included 2 randomized, placebo-controlled studies for the treatment of HARS. Study 22388 was a 3-parallel group, dose-finding, phase 2/3 study in 240 patients conducted during 2001 to 2002. Study 24380 was a 2-parallel group Phase 3 study in 325 patients for treatment and maintenance of HARS conducted during 2004-2005.

2.2 Data Sources

The electronic common technical document (eCTD) is located at: \\CDSESUB1\EVSPROD\NDA020604\0000

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

Study 24380

Study 24380 was a multi-center, randomized, double-blind, placebo-controlled, parallel group study in the treatment and maintenance of HIV-associated adipose redistribution syndrome (HARS).

The 36-week phase 3 study had a treatment (12 weeks) period and a maintenance (24 weeks) period. Patients were randomized at period one in a 3 to 1 ratio to serostim 4 mg or placebo once daily for 12 weeks. At week 12, patients randomized at period 1 to serostim 4 mg daily were re-randomized in a 1 to 1 ratio to receive placebo or serostim 2 mg on alternate days for 24 weeks (weeks 12 to 36). Patients initially randomized to placebo daily were not re randomized but received placebo on alternate days from weeks 12 to week 24. From weeks 24 to 36, Serostim 4 mg daily was provided for those placebo patients.

The protocol indicated that 'the purpose of this trial is to confirm or disconfirm our earlier findings on the effect of Serostim (4 mg daily versus placebo for 12 weeks) on VAT in HARS patients (Protocol 22388). This trial will also observe the effect of 2 mg alternate day Serostim or placebo on VAT as a maintenance therapy for HARS during Weeks 12-36. In addition, this trial will investigate other efficacy parameters such as changes in metabolic profile; subject reported quality of life (QoL), and the safety of the therapy. In the present Serono protocol (Study 24380), the primary endpoint at Week 12 will be change in VAT at the L4-L5 level as assessed by cross-sectional Computed Tomography (CT) scan in patients on r-hGH as compared to placebo. The primary endpoint of the maintenance phase (Weeks 12-36) of this protocol will be the proportion of subjects who regain >50% of the VAT that was lost during Weeks 0-12, as measured at Week 36. CT (and DXA) scans will be performed at baseline and at Weeks 12 and 36.'

A total of 537 patients were screened and 326 were randomized. Of the 211 patients who were screen failures, the majority (56%) were due to glucose abnormality (FG>110 mg/dL and/or 2 hr glucose>140 mg/dL).

Of the 322 patients who had a post-baseline assessment, 243 were in the Serostim group and 79 were in the placebo group. More Serostim patients than placebo patients (18% vs. 6%) did not complete the 12-week treatment period (Table 1).

For study withdrawals, the percentages were 24.2% for Serostim and 9.9% for placebo. More patients in the Serostim group than in the placebo group withdrew due to adverse event (13.9% vs. 2.5%) (Table 2).

Table 1 Patient disposition – study 24380

	Placebo n(%)	**r-hGH 4 mg daily n(%)**	**Total n(%)**
Randomized	**81**	**245**	326 (60.7%)
Did Not Receive Study Drug	0	1 (0.4%)	1 (0.3%)
Subject Decision	0	1 (100.0%)	1 (100.0%)
Received Study Drug (Safety)	**81 (100.0%)**	**244 (99.6%)**	325 (99.7%)
Without Post-Baseline Assessment - Subject Decision	2 (2.5%)	1 (0.4%)	3 (0.9%)
With Post-Baseline Assessment (Modified ITT)	**79 (97.5%)**	**243 (99.6%)**	322 (99.1%)
Did Not Complete Week 12	5 (6.3%)	43 (17.7%)	48 (14.9%)
Completed Week 12	74 (93.7%)	200 (82.3%)	274 (85.1%)
Withdrew after Week 12	1 (1.4%)	15 (7.5%)	16 (5.8%)
Continued into Period II	73 (98.6%)	185 (92.5%)	258 (94.2%)

Table 2 Summary of patient withdrawals during weeks 1 to 12 – study 24380

	Placebo n=81	r-hGH 4 mg daily n=244	Total n(%)
Safety Patients Withdrawn During Period I	8 (9.9%)	59 (24.2%)	67 (20.6%)
Adverse Event	2 (2.5%)	34 (13.9%)	36 (11.1%)
Protocol Violation	0	4 (1.6%)	4 (1.2%)
Lost to Follow-up	1 (1.2%)	4 (1.6%)	5 (1.5%)
Patient Decision	3 (3.7%)	11 (4.5%)	14 (4.3%)
Administrative Reasons	0	2 (0.8%)	2 (0.6%)
Other	2 (2.5%)	4 (1.6%)	6 (1.8%)

In period 2, 84% of patients completed week 36 for the two re-randomized groups (4mg/placebo and 4mg/2 mg alternate days) and 76% completed in the placebo/placebo/4mg group (Table 3). The adverse event rates for the 3 groups were 7.5%, 6.5% and 13.7%, respectively (Table 4).

Table 3 Patient disposition during weeks 12 to 36 (treatment period II)

Disposition	**GH 4mg daily/ Placebo/Placebo n (%)**	**GH 4mg daily/ GH 2mg alt. days/ GH 2mg alt. days n (%)**	**Placebo/Placebo/ GH 4mg daily n (%)**	**Total n (%)**
ITT in Weeks 1-12 n	122	121	79	322
Randomized into Weeks 12-36	95 (77.9%)	95 (78.5%)	74 (93.7%)	264 (82.0%)
Did Not Receive Study Drug	2 (2.1%)	3 (3.2%)	1 (1.4%)	6 (2.3%)
Adverse Event	1 (50.0%)	0	0	1 (16.7%)
Protocol Violation	0	2 (66.7%)	0	2 (33.3%)
Lost to Follow-up	1 (50.0%)	1 (33.3%)	0	2 (33.3%)
Other	0	0	1 (100.0%)	1 (16.7%)
Received Study Drug (Safety)	93 (97.9%)	92 (96.8%)	73 (98.6%)	258 (97.7%)
Without Post-Week 12 Assessment	0	1 (1.1%)	1 (1.4%)	2 (0.8%)
Lost to Follow-up	0	0	1 (100.0%)	1 (50.0%)
Subject Decision	0	1 (100.0%)	0	1 (50.0%)
W/Post-Week 12 Assessment (Modified ITT Weeks 12-36)	93 (100.0%)	91 (98.9%)	72 (98.6%)	256 (99.2%)
Did Not Complete Week 36	15 (16.1%)	15 (16.5%)	17 (23.6%)	47 (18.4%)
Completed Week 36	78 (83.9%)	76 (83.5%)	55 (76.4%)	209 (81.6%)

Table 4 Summary of patient withdrawals during weeks 12 to 36 – study 24380

	GH 4mg daily/ Placebo/Placebo n (%)	GH 4mg daily/ GH 2mg alt. days/ GH 2mg alt. days n (%)	Placebo/Placebo/ GH 4mg daily n (%)	Total n (%)
n	93	91	72	256
Withdrawals During Weeks 12-36	15 (16.1%)	16 (17.4%)	18 (24.7%)	49 (19.0%)
Adverse Event	7 (7.5%)	6 (6.5%)	10 (13.7%)	23 (8.9%)
Protocol Violation	2 (2.2%)	1 (1.1%)	1 (1.4%)	4 (1.6%)
Lost to Follow-up	0	4 (4.3%)	2 (2.7%)	6 (2.3%)
Subject Decision	5 (5.4%)	4 (4.3%)	4 (5.5%)	13 (5.0%)
Death	1 (1.1%)	0	0	1 (0.4%)
Administrative Reasons	0	0	1 (1.4%)	1 (0.4%)
Other	0	1 (1.1%)	0	1 (0.4%)

Demographics:

The majority of patients were white (75%) males (85%). The mean age of patients was about 45 years. The mean (± SD) weight, height, and BMI of study patients were 83.5 (± 12.6) kg, 174.7 (± 9.5) cm, and 27.3 (± 3.9) kg/m^2, respectively (Table 5).

Table 5 Patient Demographics

Characteristic	Placebo (n=79)	Serostim® 4 mg daily (n=243)	All Subjects (n=322)	p-value(a)
Age (yrs)				
n	79	243	322	0.365
Mean (SD)	45.5 (7.5)	44.5 (7.0)	44.8 (7.1)	

Characteristic	Placebo (n=79)	Serostim® 4 mg daily (n=243)	All Subjects (n=322)	p-value(a)
Median	45.0	44.0	44.0	
Range	(31.0, 62.0)	(21.0, 62.0)	(21.0, 62.0)	
Sex at Birth, n (%)				
Male	68 (86.1)	207 (85.2)	275 (85.4)	0.846
Female	11 (13.9)	36 (14.8)	47 (14.6)	
Race, n (%)				
White	60 (75.9)	181 (74.5)	241 (74.8)	0.824
Black	8 (10.1)	22 (9.1)	30 (9.3)	
Asian	0	0	0	
Hispanic	11 (13.9)	38 (15.6)	49 (15.2)	
Other	0	2 (0.8)	2 (0.6)	
Weight (kg)				
n	79	243	322	0.163
Mean (SD)	85.8 (12.5)	82.7 (12.6)	83.5 (12.6)	
Median	85.9	81.6	82.4	
Range	(48.8, 117.9)	(52.6, 130.0)	(48.8, 130.0)	
Height (cm)				
n	79	243	322	0.438
Mean (SD)	175.9 (8.8)	174.4 (9.7)	174.7 (9.5)	
Median	175.3	174.0	175.3	
Range	(152.4, 195.6)	(138.0, 198.1)	(138.0, 198.1)	
Body Mass Index (kg/m²)				
n	79	243	322	0.629
Mean (SD)	27.8 (4.4)	27.2 (3.7)	27.3 (3.9)	
Median	27.1	26.6	26.7	
Range	(21.0, 50.8)	(20.0, 41.7)	(20.0, 50.8)	

1.1.1 Efficacy Weeks 1 to 12:

The primary efficacy parameter was the change from baseline to Week 12 in absolute area of VAT as measured by cross-sectional CT scan at the level of the L4-5 inter-vertebral disk. Major secondary efficacy endpoints included the changes from baseline to Week 12 in trunk fat, patient reported outcomes (PROs) of body image distress, and non-high density lipoprotein (non-HDL) cholesterol.

Primary - VAT change from baseline to week 12

Patient treated with Serostim 4 mg daily was statistically significantly better than placebo-treated patients in VAT change from baseline and VAT percent change from baseline to week 12 (Table 6). Figure 1 displays cumulative distribution of VAT change from baseline.

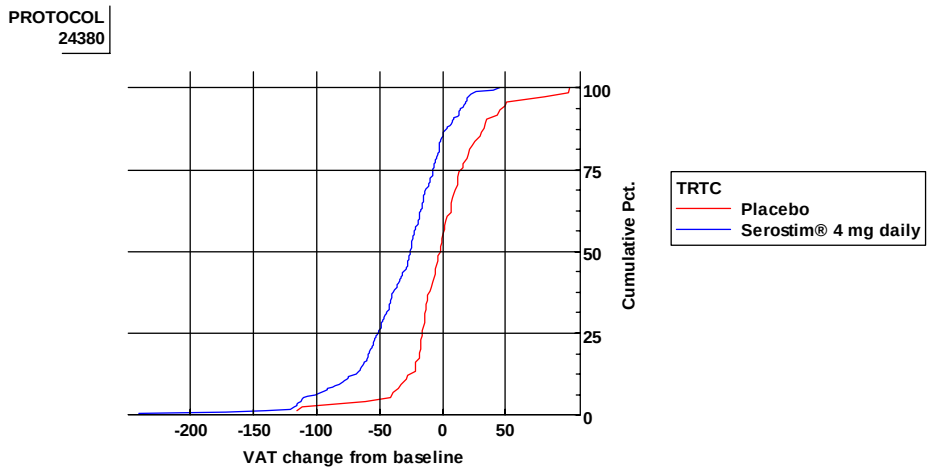
Table 6 Analysis of VAT change and VAT % change from baseline – LOCF ITT

Least Square Mean (LSM)	Placebo N=74	Serostim® 4 mg daily N=210
Baseline (SE)1	109.87 (10.64)	115.86 (5.82)
Week 12 (SE)2	123.93 (5.33)	106.93 (2.94)
Change from baseline (SE)2	-11.69 (5.33)	-28.69 (2.94)

Least Square Mean (LSM)	Placebo N=74	Serostim® 4 mg daily N=210
Difference from placebo [CL] for change		**-17 [-28.84, -5.16] P=0.005**
% change from baseline (SE)2	1.5% (4.35)	-15.7% (2.40)
Difference from placebo [CI] for % change		**-17.21% [26.87, -7.55] P=0.0005**

1 ANOVA model with gender, treatment and their interaction
2 ANCOVA model for gender, treatment, their interaction and baseline VAT as covariate

Figure 1 Cumulative distribution of VAT change from baseline to week 12



Treatment-by-gender interaction was highly significant (p=0.0006). Table 7 and figure 2 display descriptive statistics by gender. Mean VAT at baseline in female patients were smaller than male patients. VAT change from baseline was similar in female placebo and female Serostim 4 mg daily patients. The ANCOVA results were presented by gender in Table 8 and 9.

Table 7 VAT descriptive statistics by gender

TRT	Gender	N	Baseline VAT		Week 12 VAT		Change from baseline	
			Mean	StdDev	Mean	StdDev	Mean	StdDev
Placebo	Female	12	77.06	(49.81)	69.78	(20.44)	-7.29	(43.98)
Serostim® 4 mg daily	Female	36	87.37	(33.55)	80.55	(30.42)	-6.82	(19.41)
Placebo	Male	69	142.68	(53.82)	144.23	(57.59)	1.54	(33.27)
Serostim® 4 mg daily	Male	208	144.35	(65.49)	107.32	(49.46)	-37.03	(38.61)

Figure 2 Cumulative distribution of VAT change from baseline to week 12 by gender

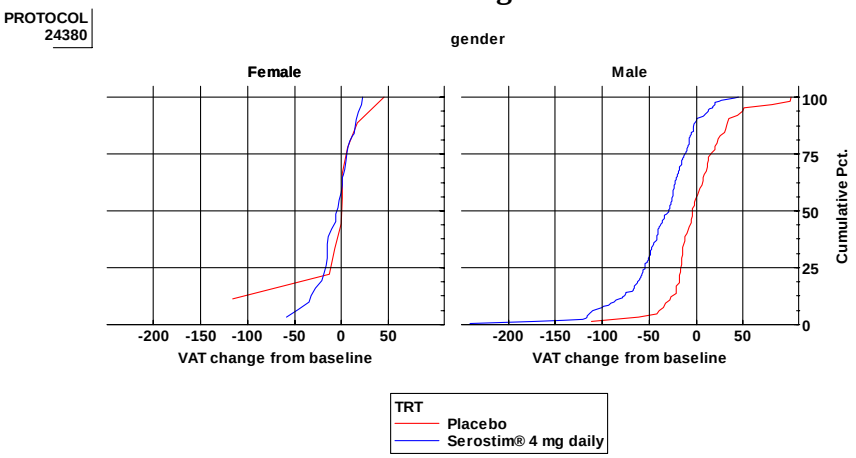


Table 8 ANCOVA analysis by gender for VAT change from baseline

Treatment	Gender	N	LSMean	S.E.	Difference from placebo	upper	lower
Placebo	Female	9	-27.34	(10.04)			
Serostim® 4 mg d	Female	31	-23.34	(5.51)	4.00	[-18.12,	26.11]
Placebo	Male	65	3.96	(3.68)			
Serostim® 4 mg d	Male	179	-34.04	(2.23)	-38.00	[-46.45	-29.54]

ANCOVA model: treatment, gender and treatment-by-gender interaction as fixed effects and baseline VAT as covariate

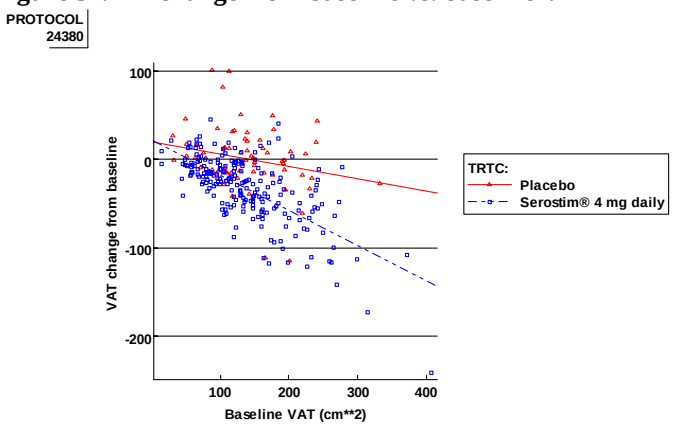
Table 9 ANCOVA analysis by gender for VAT % change from baseline

Treatment	Gender	N	LSMean	S.E.	Difference from placebo	upper	lower
Placebo	Female	9	-1.1	(8.19)			
Serostim® 4 mg d	Female	31	-9.3	(4.50)	-8.2	[-26.25	9.84]
Placebo	Male	65	4.1	(3.01)			
Serostim® 4 mg d	Male	179	-22.11	(1.82)	-26.22	[-33.11	-19.32]

ANCOVA model: treatment, gender and treatment-by-gender interaction as fixed effects and baseline VAT as covariate

Treatment-by-baseline interaction was significant (p=0.0002) in VAT change from baseline. Figure 3 displays the linear regression lines for the two treatment groups. The difference between the 2 treatment groups increased in VAT reduction from baseline as the baseline increased; however, the interaction was quantitative in nature.

Figure 3 VAT change from baseline vs. baseline VAT



Secondary Efficacy Variable: Trunk Fat

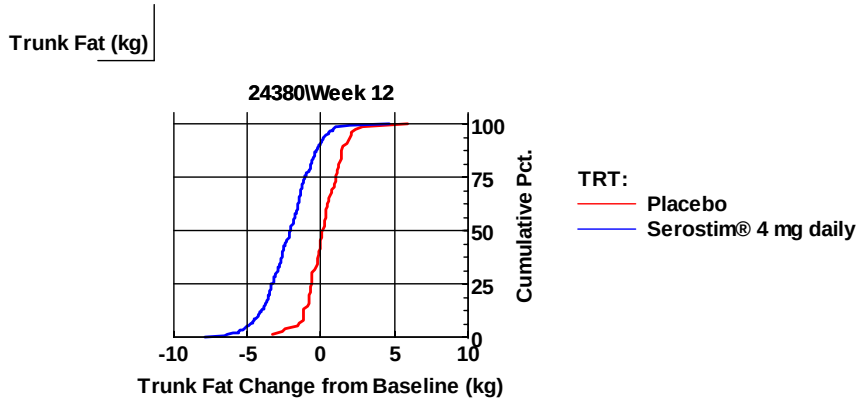
The -2.5 kg least squared mean difference between Serostim 4 mg daily group and placebo group in truncal fat change from baseline to week 12 was statistically significant (p<0.01) (Table 10). Treatment-by-gender interaction was not significant for truncal fat (p=0. 69). Figure 4 displays the cumulative distribution of truncal fat change from baseline.

Table 10 Analysis on Trunk Fat change from baseline (kg) - LOCF ITT

	Placebo	Serostim® 4 mg daily
	N=75	N=213
Baseline (SD)	12.00 (4.47)	11.72 (4.91)
Week 12 (SD)	12.21 (4.89)	9.56 (4.94)
LSM change from baseline (SE)	+0.44 (0.21)	-1.96 (0.14)
LSM Difference from placebo [CL]		-2.40 [-2.82, -1.98]

ANCOVA: treatment and gender as fixed effects and baseline Trunk Fat as covariable

Figure 4 Cumulative distribution of change from baseline Trunk Fat (kg)



Study 2388

Two hundred and forty-five (245) patients were randomized, and 240 received at least one dose of study drug. Of these 240 patients, one did not have a post-baseline visit and was thus excluded from the ITT population (Table 11). Two hundred and twenty-two (222) patients completed a Week 12 visit. The proportion of patients who withdrew without a Week 12 visit was greater for the Serostim high dose group (12.2%) compared to the placebo and Serostim low dose group (3.8% and 5.0%, respectively). Two hundred and fourteen (214) patients were enrolled into the Week 12-24 period. Two hundred and eight (208) patients received study drug in the Week 12-24 week period and 179 patients had a Week 24 visit (Table 12).

Table 11 Patient disposition

Disposition	Placebo	Serostim 4 mg alt days	Serostim 4 mg daily	All
Randomized	81	82	82	245
Patients Received Study Drug	78	80	82	240

Disposition	Placebo	Serostim 4 mg alt days	Serostim 4 mg daily	All
Received study drug	78(100.0%)	79(98.8%)	82(100.0%)	239(99.6%)
Completed Week 12	75(96.2%)	75(93.8%)	72(87.8%)	222(92.5%)
Without a major protocol violation (evaluable)	56(71.8%)	57(71.3%)	58(70.7%)	171(71.3%)
With a major protocol violation	19(24.4%)	18(22.5%)	14(17.1%)	51(21.3%)
Withdrew without week 12 visit	3(3.8%)	4(5.0%)	10(12.2%)	17(7.1%)

Table 12 Patient disposition during weeks 12-24

	P/4mg D	4mg AD/4mg AD	4mg D/P	4mgD/4mg AD	Total
Week 12 ITT population	78	79	41	41	239
Randomized in 12-24 week	75 (96.2%)	72 (91.1%)	33 (80.5%)	34 (82.9%)	214 (89.5%)
Received study drug in 12-24 week	74 (94.9%)	69 (87.3%)	32 (78.0%)	33 (80.5%)	208 (87.0%)
With a post 12 week visit (ITT)	74	69	32	33	208
With a week 24 visit	58 (78.4%)	63 (91.3%)	29 (90.6%)	29 (87.9%)	179 (86.1%)
Without a major protocol violation/evaluable in 0-12 week (evaluable)	37 (50.0%)	43 (62.3%)	24 (75.0%)	22 (66.7%)	126 (60.6%)
Non evaluable in 0-12 week only	21 (28.4%)	20 (29.0%)	5 (15.6%)	7 (21.2%)	53 (25.5%)
Major protocol violation & non-evaluable in 0-12 week	7 (9.5%)	7 (10.1%)	1 (3.1%)	1 (3.0%)	16 (7.7%)
Non-evaluable in 0-12 week only	9 (12.2%)	10 (14.5%)	2 (6.3%)	5 (15.2%)	26 (12.5%)
Major protocol violation & non-evaluable in 0-12 week	5 (6.8%)	3 (4.3%)	2 (6.3%)	1 (3.0%)	11 (5.3%)
Withdrew without week 24 visit	16 (21.6%)	6 (8.7%)	3 (9.4%)	4 (12.1%)	29 (13.9%)

D: daily, AD: alternate day, P:placebo, 4 mg: Serostim 4 mg

Table 13 presents the primary reason for withdrawal from the study during the initial Week 12 treatment period. The proportion of patients who withdrew without a Week 12 visit was greater for the high dose group (12.2%) compared to the placebo and low dose groups (3.8% placebo and 5.0%, respectively). The study withdrawal rate was greater for the high dose group compared to both low dose and placebo (20.7% versus 10.1 % and 3.8%, respectively), due to a larger percentage of patients who withdrew because of adverse events (11% versus 5.1% and 0%, respectively).

Table 13 Summary of patient withdrawals during weeks 0-12

	Placebo n=78	Serostim 4 mg alt.days n=79	Serostim 4 mg daily n=82	Total
Withdrawals	3 (3.8%)	8 (10.1%)	17 (20.7%)	28 (11.7%)
Adverse event	0	4 (5.1%)	9 (11.0%)	13 (5.4%)
Protocol violation	2 (2.6%)	0	0	2 (0.8%)

	Placebo n=78	Serostim 4 mg alt.days n=79	Serostim 4 mg daily n=82	Total
Lost to follow-up	1 (1.3%)	1 (1.3%)	3 (3.7%)	5 (2.1%)
Patient decision	0	2 (2.5%)	4 (4.9%)	6 (2.5%)
Adminstrative reason	0	1 (1.3%)	0	1 (0.4%)
Other	0	0	1 (1.2%)	1 (0.4%)

The proportion of patients who withdrew without a Week 24 visit was greater for the placebo/high dose group (21.6%) compared to the low dose/low dose group (8.7%) and low dose/placebo and high dose/low dose groups (9.4% and 12.1%, respectively). Similar to the results of the initial Week 12, the high dose group in the Week 12-24 had a higher rate of withdrawal compared to the other three treatment groups (Table 14). The study withdrawal rate was greater for the placebo/high dose group compared to low dose/low dose, high dose/placebo and high dose/low dose (21.6% versus 8.7%, 9.4% and 12.1%, respectively), due to a larger percentage of patients who withdrew because of adverse events (17.6% versus 5.8%, 9.4% and 12.1%, respectively). Overall, of the 29 patients who withdrew during the Week 12-24 period 24 (83%) withdrew from the study because of adverse events.

Table 14 Summary of patient withdrawals during weeks 12-24

Reason of withdrawal	P/4mg daily	4mg AD/4mg AD	4mg D/P	4mgD/4mg AD	Total
Patients withdrawn during 12-24 weeks	16 (21.6%)	6 (8.7%)	3 (9.4%)	4 (12.1%)	29 (13.9%)
Adverse event	13 (17.6%)	4 (5.8%)	3 (9.4%)	4 (12.1%)	24 (11.5%)
Protocol violation	0	2 (2.9%)	0	0	2 (1.0%)
Lost to follow-up	1 (1.4%)	0	0	0	1 (0.5%)
Patient decision	1 (1.4%)	0	0	0	1 (0.5%)
Death	1 (1.4%)	0	0	0	1 (0.5%)

Primary Efficacy Variable - VAT change from baseline to week 12

Table 15 displays ANCOVA results for the ITT population with LOCF for missing data. Both Serostim doses were significantly better than placebo in VAT change from baseline.

Table 15 Analysis of VAT change and % change from baseline – LOCF ITT

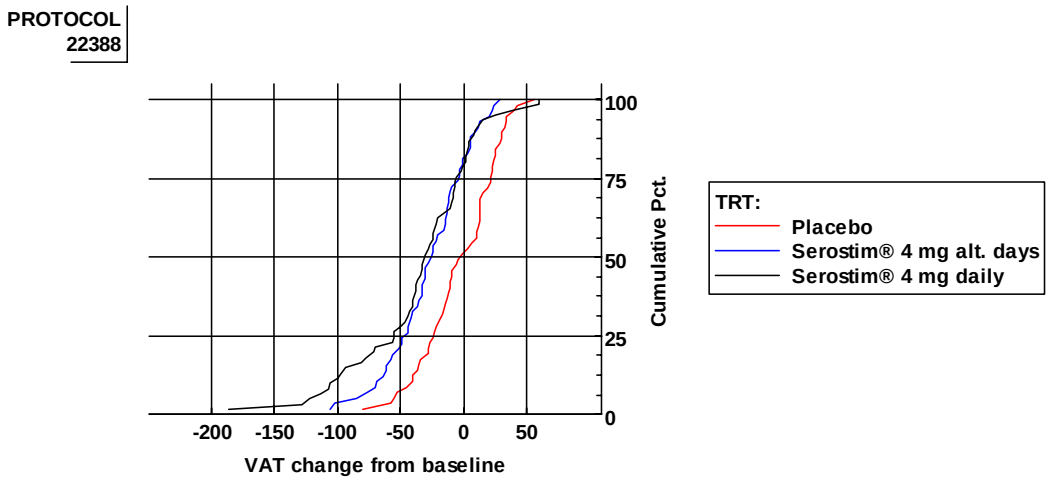
TRT	Placebo	Serostim® 4 mg QOD	Serostim® 4 mg daily
	N=57	N=58	N=61
Baseline (SE)1	136.33 (11.62)	120.88 (12.23)	135.44 (11.16)
Week 12 (SE)1	128.46 (10.61)	106.40 (12.59)	113.64 (10.54)
Change from baseline (SE)2	-8.63 (5.98)	-28.38 (7.10)	-26.87 (5.93)
Difference from placebo [CL]		**-19.74 [-37.96, -1.53] P=0.03**	**-18.24 [-34.79, -1.69] P=0.03**
% Change from baseline (SE)2	-2.36% (4.29)	-19.09% (5.09)	-16.31% (4.25)

TRT	Placebo	Serostim® 4 mg QOD	Serostim® 4 mg daily
% Difference from placebo [CL]		**-16.73% [-29.80, -3.67] P=0.01**	**-13.95% [-25.82, -2.08] P=0.02**

1 ANOVA model with gender, treatment and their interaction
2 ANCOVA model for gender, treatment, their interaction and baseline VAT as covariate

Figure 5 displays the cumulative distribution of VAT change from baseline.

Figure 5 Cumulative distribution of VAT change from baseline to week 12



Treatment-by-gender interaction was significant (p=0.1) for placebo and Serostim 4 mg daily group. Table 16 displays descriptive statistics by gender. Figure 6 displays the cumulative distribution of VAT change from baseline by gender. For female patients VAT changes from baseline were similar in Serostim 4 mg daily group and placebo group. Tables 17 and 18 display the ANCOVA results for VAT change and percent change, respectively.

Table 16 VAT descriptive statistics by gender

TRT	Gender	N	Baseline VAT		Week 12 VAT		Change from baseline	
			Mean	StdDev	Mean	StdDev	Mean	StdDev
Placebo	Female	10	118.5	(29.84)	110.46	(41.87)	-8.04	(31.28)
Serostim® 4 mg alt. days	Female	11	94	(44.19)	94.94	(30.25)	-19.79	(18.53)
Serostim® 4 mg daily	Female	11	103.89	(37.42)	98.67	(39.45)	-9.66	(17.45)
Placebo	Male	68	154.15	(76.52)	143.21	(62.84)	-1.52	(29.13)
Serostim® 4 mg alt. days	Male	69	147.75	(57.42)	119.63	(49.02)	-27.78	(31.86)
Serostim® 4 mg daily	Male	71	166.98	(68.32)	127.05	(64.80)	-38.57	(48.20)

Figure 6 Cumulative distribution of VAT change from baseline to week 12 by gender

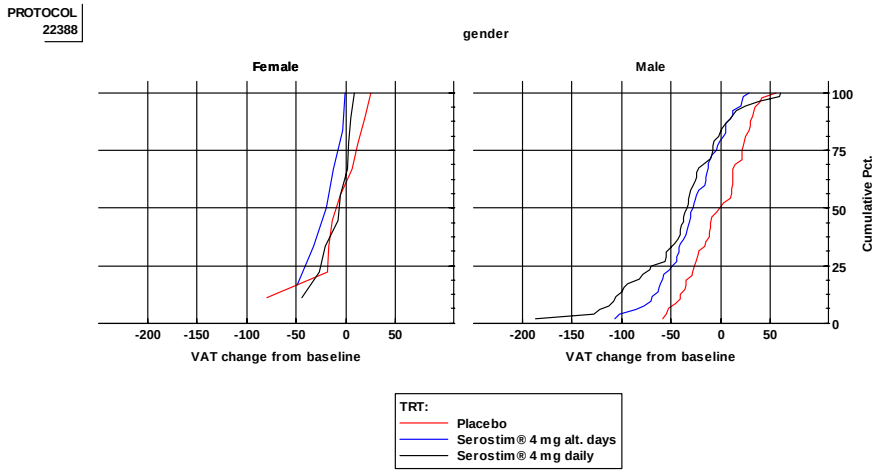


Table 17 ANCOVA analysis by gender for VAT change from baseline

Treatment	Gender	n	Estimate	StdErr	Difference From Plb	95% C.I. [upper, lower]	
Placebo	Female	9	-15.47	(10.98)			
Serostim® 4 mg alt days	Female	6	-28.88	(13.44)	-13.41	[-47.47	20.65]
Serostim® 4 mg daily	Female	9	-19.56	(11.03)	-4.09	[-34.56	26.38]
Placebo	Male	48	-1.79	(4.73)			
Serostim® 4 mg alt days	Male	52	-27.87	(4.54)	-26.08	[-39.01	-13.14]
Serostim® 4 mg daily	Male	52	-34.18	(4.59)	-32.39	[-45.41	-19.37]

ANCOVA model: treatment, gender and treatment-by-gender interaction as fixed effects and baseline VAT as covariate

Table 18 ANCOVA analysis by gender for VAT % change from baseline

Treatment	Gender	n	Estimate	StdErr	Difference From Plb	95% C.I. [upper, lower]	
Placebo	Female	9	-10.06	(7.87)			
Serostim® 4 mg alt days	Female	6	-21.22	(9.64)	-11.16	[-35.59	13.26]
Serostim® 4 mg daily	Female	9	-14.67	(7.91)	-4.61	[-26.46	17.24]
Placebo	Male	48	5.34	(3.39)			
Serostim® 4 mg alt days	Male	52	-16.97	(3.26)	-22.31	[-31.58	-13.03]
Serostim® 4 mg daily	Male	52	-17.95	(3.29)	-23.29	[-32.62	-13.95]

ANCOVA model: treatment, gender and treatment-by-gender interaction as fixed effects and baseline VAT as covariate

Secondary Efficacy Variable – Trunk Fat

Trunk Fat change from baseline to week 12 was statistically significant ($p<0.01$) between Serostim doses and placebo ($p<0.01$). Treatment-by-gender interaction was not significant ($p=0.75$). The LSM differences between Serostim and placebo in change from baseline were -1.50 kg and -2.46 kg for Serostim 4 mg QOD and Serostim 4 mg, respectively (Table 19).

Table 19 Summary of Trunk Fat change from baseline analysis – LOCF ITT

TRT	Placebo	Serostim® 4 mg QOD	Serostim® 4 mg daily
	N=63	N=60	N=59
Baseline (SD	11.26 (4.89)	10.06 (3.69)	10.10 (3.96)
Week 12 (SD	11.43 (4.97)	8.82 (3.69)	7.88 (3.78)
LSM change from baseline (SE)	+0.41 (0.21)	-1.09 (0.21)	-2.05 (0.22)
LSM difference from placebo [CL]		-1.50 [-2.00, -1.00]	-2.46 [-2.96, -1.97]

Maintenance Period

Week 12 to 36 VAT – Study 24380

The primary endpoint during the maintenance phase was the proportion of patients at Week 36 who regained >50% of the VAT that was lost during weeks 0-12. This analysis was therefore performed only on those patients who lost VAT during the induction period. The proportions on this endpoint were 61% (37/61) for Serostim 2 mg QOD and 48% (31/65) for placebo. The treatment difference was not statistically significant (p=0.2).

Table 20 displays descriptive statistics in VAT change from Week 12 to 36. Figure 7 displays the cumulative distribution functions for VAT change from Week 12 to 36 for the three treatment sequences. Mean VAT increases were similar for the 2 re-randomized groups.

Table 20 Descriptive statistics of maintenance VAT (week 12-week 36)

	4mg Daily/2mg Alt. Day n=75		4mg Daily/Placebo n=73		Pla/Pla/4mg Daily n=56	
	Mean	(SD)	Mean	(SD)	Mean	(SD)
VAT at Baseline (Week 0)	135.65	(69.93)	134.76	(63.21)	127.62	(58.99)
VAT at Week 12 LOCF	96.68	(44.77)	103.22	(49.81)	130.72	(59.15)
VAT at Week 36 LOCF	119.93	(58.29)	126.89	(64.67)	105.25	(44.14)
VAT Chg LOCF 12 - LOCF 36	**23.25**	**(34.91)**	**23.67**	**(45.08)**	**-25.47**	**(38.48)**

Figure 7 Cumulative distribution of VAT change from Week 12 to Week 36

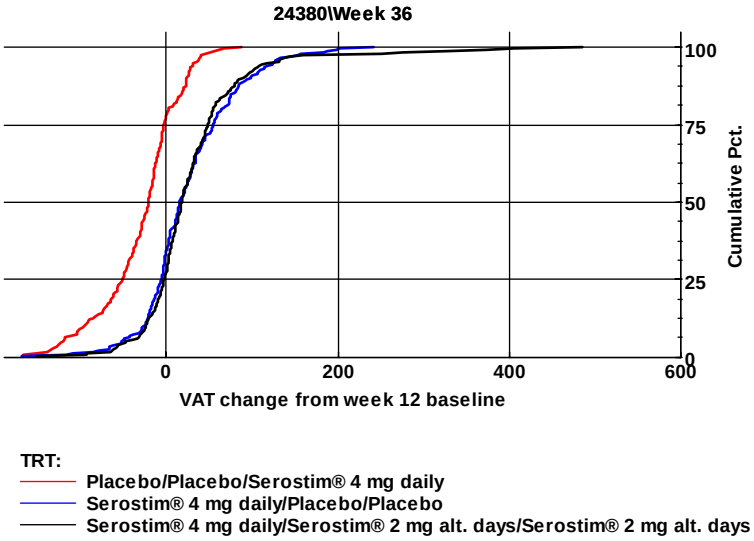


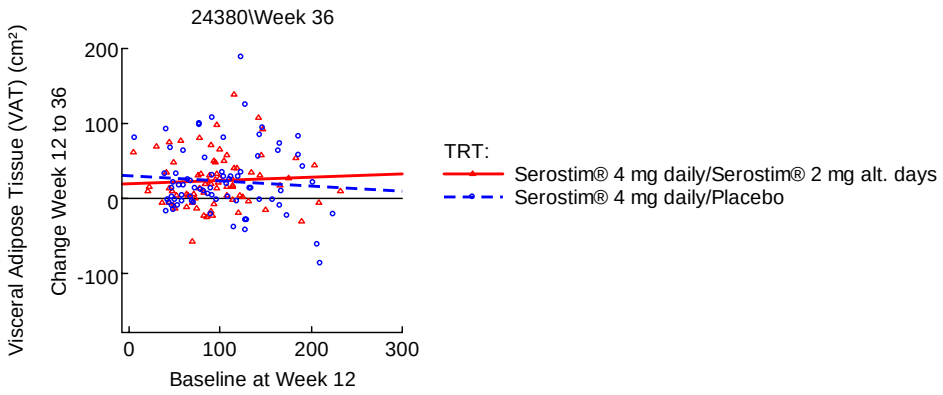
Table 21 presents descriptive statistics by gender for VAT variables.

Table 21 VAT descriptive statistics by gender Week 12 to Week 36

	Gender	n	Week 12 VAT		Week 36 VAT		Change week 12-36	
Treatment			Mean	(SD)	Mean	(SD)	Mean	(SD)
Plb/Plb/4 mg daily	Female	8	69	(21.71)	71.07	(17.86)	2.07	(16.04)
Plb/Plb/4 mg daily	Male	48	141	(57.16)	110.95	(44.73)	-30.06	(39.30)
4 mg daily/Plb/Plb	Female	9	80.24	(44.36)	87.88	(52.89)	7.64	(40.05)
4 mg daily/Plb/Plb	Male	64	106.45	(49.99)	132.37	(64.63)	25.92	(45.58)
4 mg daily/2 mg alt. days/2 mg alt. days	Female	10	75.29	(19.88)	80.32	(39.97)	5.02	(37.45)
4 mg daily/2 mg alt. days/2 mg alt. days	Male	65	99.97	(46.69)	126.03	(58.49)	26.06	(33.94)

Figure 8 displays the VAT change from Week 12 baseline to Week 36 by week 12 baseline during maintenance phase. The increases were similar for the Serostim 4 mg daily/Serostim 2mg alt days and Serostim 4 mg daily/placebo groups.

Figure 8 VAT change from Week 12 to 36 by Week 12 Baseline



Week 12 to 36 Trunk Fat – Study 24380

Table displays the descriptive statistics in Trunk Fat from week 12 to week 36.

Table 22 Descriptive statistics of maintenance Trunk Fat (week 12-week 36)

	4mg Daily/2mg Alt. Day			4mg Daily/Placebo			Pla/Pla/4mg Daily		
	n	Mean	(SD)	n	Mean	(SD)	n	Mean	(SD)
Trunk Fat at Baseline (Week 0)	75	10.71	(4.19)	79	11.57	(5.21)	62	11.57	(4.30)
Trunk Fat at Week 12 LOCF	75	8.38	(4.10)	79	9.51	(5.18)	62	11.77	(4.59)
Trunk Fat at Week 36 LOCF	75	9.84	(4.27)	79	11.62	(5.52)	62	9.58	(4.75)
Trunk Fat Chg LOCF 12 - LOCF 36	**75**	**1.46**	**(1.46)**	**79**	**2.11**	**(1.76)**	**62**	**-2.19**	**(1.72)**

Week 12 to 24 – Study 22388

At week 12, the high dose (Serostim 4 mg) patients were re-randomized to low dose (Serostim 4 mg alt days) or placebo. The low dose group continued on low dose and the placebo group received Serostim high dose. The mean VAT change (SD) of the 2 re-randomized groups were +3.8 (38.8) and +12.8 (33.6) for the high/low (red) and high/placebo (blue), respectively. The mean VAT changes (SD) were +4.4 (34.5) and -21.4 (34.9) for the low/low (black) and placebo/high (pink) groups, respectively (Figure 9).

Figure 9 Cumulative distribution of VAT change from Week 12 to 24

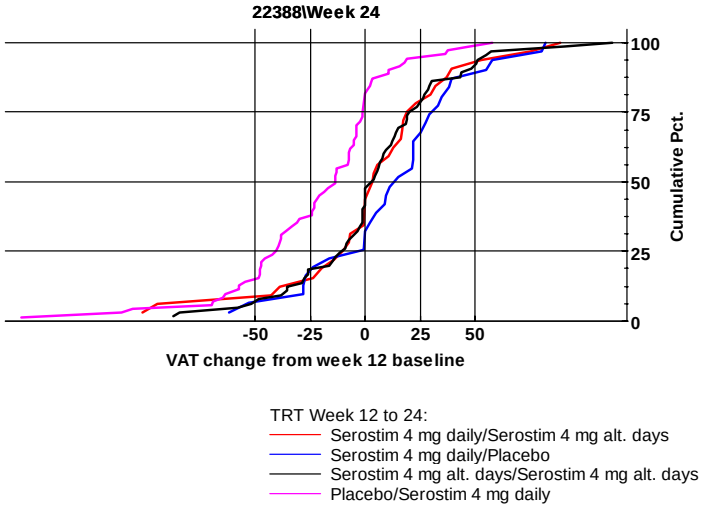
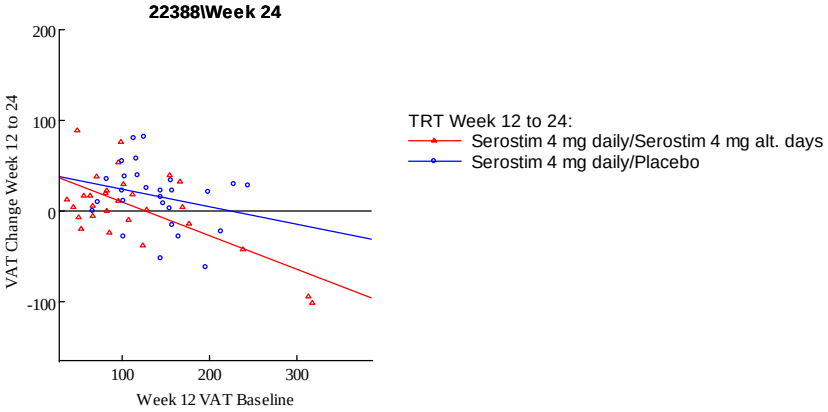


Figure 10 displays VAT change from week 12 to week 24 by baseline.

Figure 10 VAT change from Week 12 to 24 by Week 12 Baseline



Further analysis of Study 22388 maintenance phase was based on data submitted on 4/9/2007. The statistical analysis approach was not hypothesis testing but descriptive only. The comparisons between Serostim and placebo were therefore exploratory in nature.

Treatment with Serostim 4 mg alternate days (QOD) for 12 weeks after a 12-week induction treatment of Serostim 4 mg daily (QD) or Serostim 4 mg alternate days (QOD) afforded better maintenance for HARS than did placebo in male patients. Similar effects in VAT change from week 12 to week 24 were seen between Serostim 4 mg QOD/Serostim 4 mg QOD and Serostim 4 mg QD/Serostim 4 mg QOD (Table 23).

Table 23 displays descriptive statistics for 3 of the 4 treatment sequences (Placebo/Serostim 4 mg QD not shown in Table but shown in Fig. 11).

Figure 11 displays the median VAT at baseline, Week 12 and week 24 by treatment sequence.

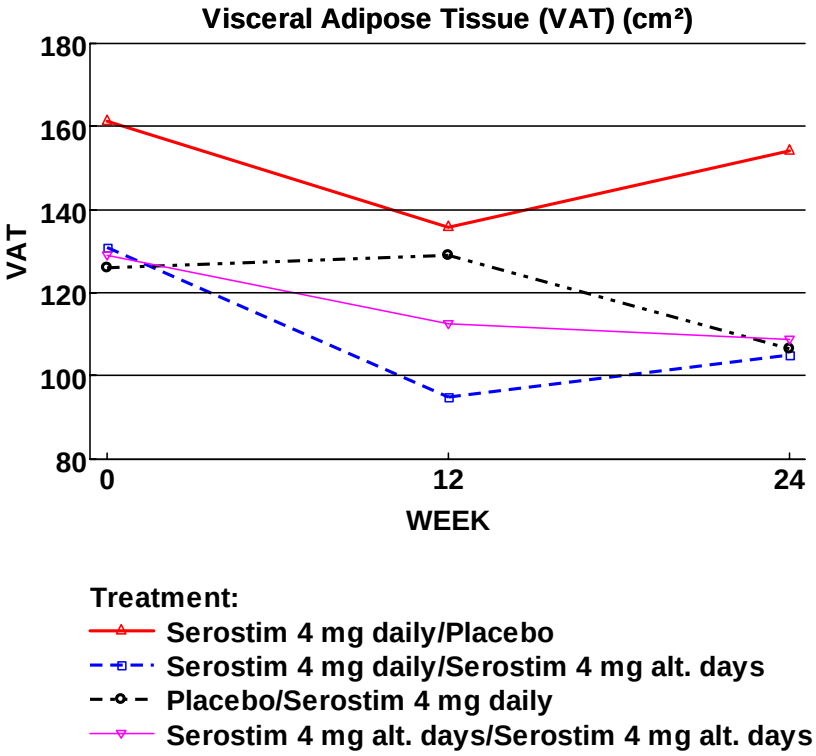
Table 23 Descriptive Statistics, Mean (SD) of Weeks 0 and 12 and change from Week 12 to Week 24

Variable Name	Serostim 4 mg QOD/ Serostim 4 mg QOD				**Serostim 4 mg QD/ Serostim 4 mg QOD***				**Serostim 4 mg QD/ Placebo***			
	n	Wk 0	Wk12	Chg from wk 12	**n**	**Wk 0**	**Wk 12**	**Chg from wk 12**	**n**	**Wk 0**	**Wk 12**	**Chg from wk 12**
Visceral Adipose Tissue(VAT) cm²)	54	143.61 (60.86)	115.72 (50.28)	4.92 (33.42)	**29**	156.94 (76.45)	**112.76 (72.82)**	**4.16 (40.76)**	**27**	164.5 (56.18)	**139.4 (46.28)**	**15.5 (34.92)**
Subcutaneous Adipose Tissue (SAT)(cm²)	54	176.05 (104.88)	171.24 (110.1)	3.3 (25.66)	**29**	151.26 (99.65)	**125.04 (82.32)**	**6.42 (24.24)**	**27**	143.79 (62.11)	**131.72 (50.16)**	**14.46 (29.06)**
Trunk Fat (kg)	51	9.98 (3.70)	8.84 (3.72)	0.04 (1.26)	**26**	9.16 (3.88)	**6.94 (3.68)**	**0.34 (1.2)**	**27**	10.31 (3.87)	**8.28 (3.7)**	**1.16 (1.46)**
Total Body Fat(kg)	51	15.88 (6.21)	14.9 (7.02)	0.02 (2)	**26**	14.04 (6.21)	**11.58 (6.58)**	**0.34 (1.8)**	**27**	16.28 (6.84)	**13.88 (7.06)**	**1.32 (2.18)**
Lean Body Mass (kg)	51	63.4 (7.64)	65.44 (8.18)	-0.12 (1.98)	**26**	60.35 (8.86)	**64.22 (9.66)**	**-1.74 (2.02)**	**27**	63.16 (10.81)	**66.7 (10.48)**	**-2.6 (2.6)**
NonHDL Cholesterol (mg/dL)	61	184.28 (46.73)	169.62 (44.32)	2.5 (32.62)	**33**	167.88 (51.85)	**151.54 (50.62)**	**2.24 (41)**	**30**	184.6 (36.96)	**164.94 (29.04)**	**6.86 (24.4)**
Belly Appearance Distress (BAD)	65	19.23 (15.95)	32.3 (23.26)	9.04 (22.38)	**33**	17.8 (23.60)	**35.22 (23.48)**	**6.82 (25.6)**	**30**	14.58 (15.07)	**45.42 (30.18)**	**-15.84 (27.64)**

* Re-randomized at week 12.

Figure 11 median VAT at baseline, week 12 and week 24

22388



The statistical analysis comparing Serostim 4 mg QD/4 mg QOD and Serostim 4 mg QD/placebo from week 12 to week 24 used treatment as a fixed factor and week 12 baseline as a covariate in the model. The main efficacy variable, VAT change from week 12 to week 24, was significantly different between groups (Table 24) (p=0.03). In addition, the main secondary variables, Trunk fat and BAD changes were also significantly better for the Serostim 4 mg QD/ Serostim 4 mg QOD group than Serostim 4 mg QD/Placebo group.

Table 24 also displays ANCOVA results on VAT change from week 12 to week 24 comparing Serostim 4 mg QOD/Serostim 4 mg QOD and Serostim 4 mg QD/Placebo, a non-randomized comparison. Results were very similar to the comparisons between the 2 re-randomized groups.

The ANCOVA results by gender for VAT (Tables 25 and 26) were similar to the induction phase in that the LSM differences between Serostim and placebo were negative for males but positive for females (-25 vs. +2 and -21 vs. +19). The study the treatment-by-gender interactions were not consistent for the 2 comparisons, being significant (p=0.07) for Serostim 4 mg QOD/Serostim 4 mg QOD but not significant (p=0.24) for Serostim 4 mg QD/Serostim 4 mg QOD.

Table 24 ANCOVA results of change from Week 12 to Week 24– Exploratory

	Serostim 4 mg QD/Serostim 4 mg QOD vs. Serostim 4 mg QD/Placebo					Serostim 4 mg QOD/Serostim 4 mg QOD vs. Serostim 4 mg QD/Placebo		
	LSM	(SE)	95%	CL	p	LSM (SE)	95% CL	p
Visceral Adipose Tissue(VAT) (cm²)	-19.86	(9.00)	[-37.92	-1.80]	0.0317	-14.62(8)	[-30.54, 1.3]	0.07
Subcutaneous Adipose Tissue (SAT) (cm²)	-8.81	(6.88)	[-22.61	4.99]	0.2060	-8.34(6.28)	[-20.84, 4.16]	0.19
Trunk Fat (kg)	-0.94	(0.36)	[-1.67	-0.20]	0.0134	-1.1(0.32)	[-1.72, -0.46]	<0.01
Total Body Fat (kg)	-1.15	(0.55)	[-2.25	-0.05]	0.0411	-1.28(0.5)	[-2.26, -0.3]	0.01
Lean Body Mass (kg)	0.76	(0.64)	[-0.54	2.05]	0.2453	2.44(0.52)	[1.4, 3.5]	<0.01
Non HDL Cholesterol (mg/dL)	-7.48	(8.49)	[-24.47	9.51]	0.3819	-2.82(6.12)	[-14.98, 9.32]	0.64
Belly Appearance Distress (BAD)	17.06	(5.73)	[5.59	28.53]	0.0042	17.1(4.28)	[8.6, 25.62]	<0.01

ANCOVA model: treatment as fixed effect and week 12 baseline as covariate

Table 25 ANCOVA results of change from Week 12 to Week 24 by gender for Serostim 4 mg QD/Serostim 4 mg QOD vs. Serostim 4 mg QD/Placebo

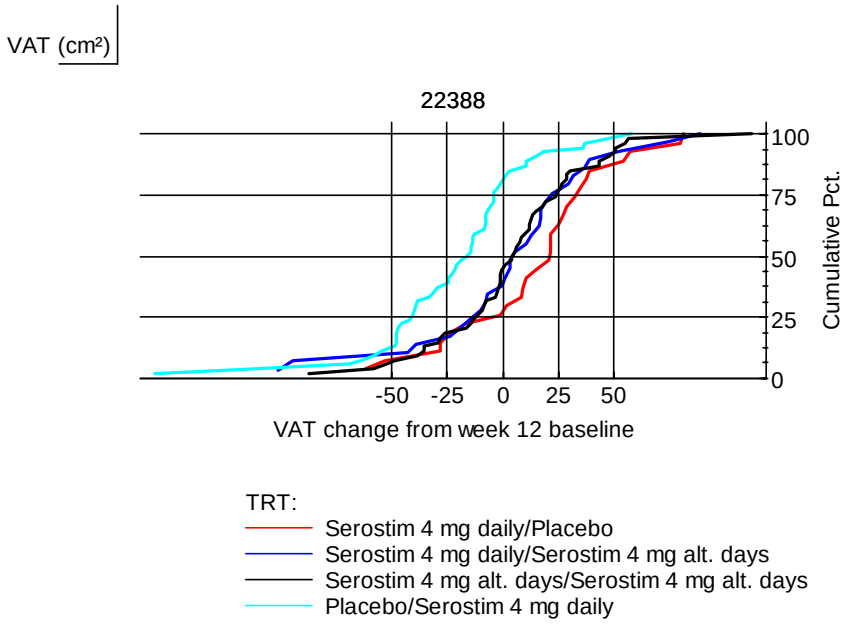
	Male			Female		
Variable	N	LSM (SE)	95% CI	N	LSM (SE)	95% CI
Visceral Adipose Tissue (VAT) (cm²)	25,23	-25.26 (8.9)	[-43.12,-7.38]	4,4	2.34 (21.52)	[-40.86,45.56]
Subcutaneous Adipose Tissue (SAT) (cm²)	25,23	-8 (7.76)	[-23.58,7.56]	4,4	-13.58 (20.12)	[-53.96,26.82]
Trunk Fat (kg)	23,24	-1.1 (0.4)	[-1.9,-0.28]	3,3	0.2 (1.1)	[-2.02,2.44]
Total Body Fat (kg)	23,24	-1.28 (0.6)	[-2.5,-0.06]	3,3	-0.14 (1.7)	[-3.56,3.3]
Lean Body Mass (kg)	23,24	0.82 (0.7)	[-0.6,2.22]	3,3	-0.1 (1.94)	[-3.98,3.8]
Non HDL Cholesterol (mg/dL)	28,26	-10.2 (9.32)	[-28.86,8.48]	5,4	6.44 (22.56)	[-38.72,51.6]
Belly Appearance Distress (BAD)	28,25	19.72 (6.16)	[7.38,32.04]	5,5	7.57 (14.16)	[-20.78,35.9]

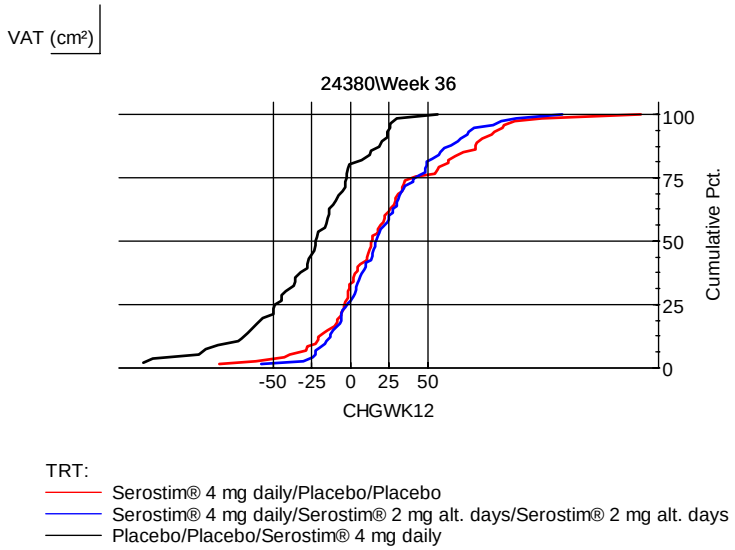
Table 26 ANCOVA results of change from Week 12 to Week 24 by gender for Serostim 4 mg QOD/Serostim 4 mg QOD vs. Serostim 4 mg QD/Placebo

	Male			Female		
	n	LSM (SE)	95% CL	N	LSM (SE)	95% CL
Visceral Adipose Tissue (VAT) (cm²)	48,23	-21.48 (8.32)	[-38.04,-4.9]	6,4	18.54 (20.68)	[-22.66,59.76]
Subcutaneous Adipose Tissue (SAT) (cm²)	48,23	-7.6 (6.76)	[-21.06,5.86]	6,4	-11.08 (18.46)	[-47.82,25.66]
Trunk Fat (kg)	47,24	-1.18 (0.34)	[-1.84,-0.52]	4,3	-0.54 (1.06)	[-2.62,1.56]
Total Body Fat (kg)	47,24	-1.4 (0.52)	[-2.44,-0.36]	4,3	-0.28 (1.66)	[-3.58,3]
Lean Body Mass (kg)	47,24	2.5 (0.56)	[1.36,3.62]	4,3	2.52 (1.7)	[-0.88,5.92]
Non HDL Cholesterol (mg/dL)	53,26	-3.16 (6.62)	[-16.34,10.02]	8,4	-0.62 (17.06)	[-34.54,33.32]
Belly Appearance Distress (BAD)	57,25	21.74 (4.42)	[12.96,30.54]	8,5	-14.26 (10.36)	[-34.84,6.34]

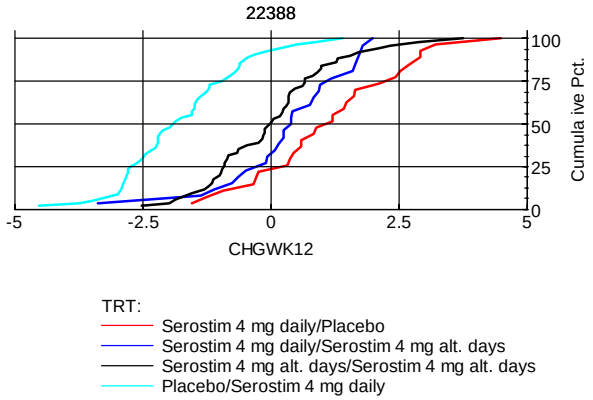
Figure 12 displays the cumulative distribution of change from week 12 to week 24 or 36 VAT , trunk fat and BAD for studies 22388 and 24380. The dataset showed only 2 of the 3 groups for BAD (study 24380).

Figure 12 Cumulative distribution of change from week 12 to week 24 (36) VAT, trunk fat and BAD

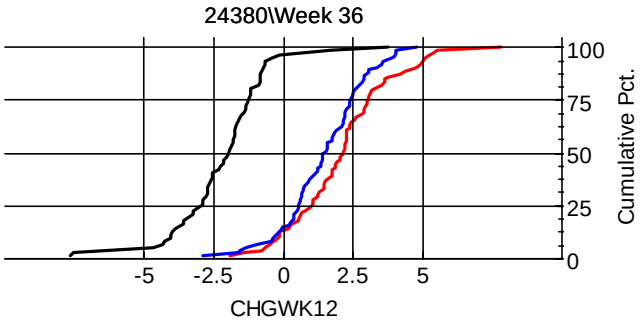




Trunk Fat (kg)

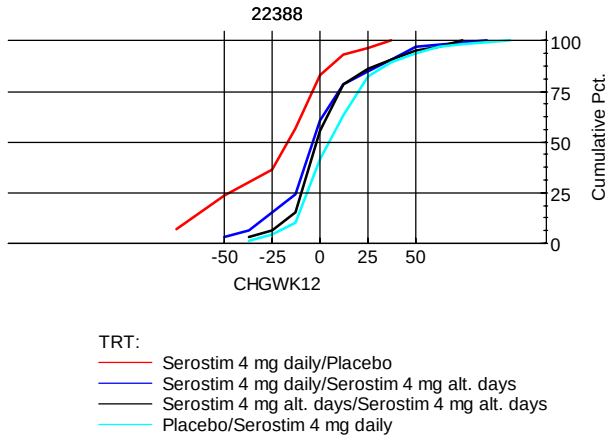


Trunk Fat (kg)

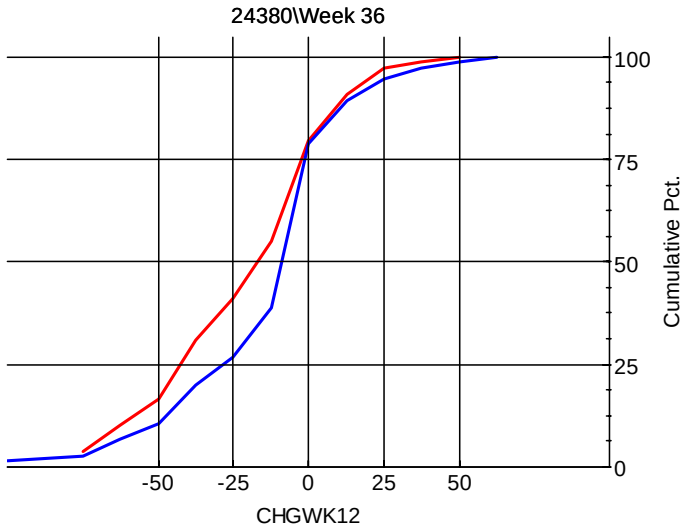


TRT:
Serostim® 4 mg daily/Placebo/Placebo
Serostim® 4 mg daily/Serostim® 2 mg alt. days/Serostim® 2 mg alt. days
Placebo/Placebo/Serostim® 4 mg daily

BAD



BAD



TRT:
Serostim® 4 mg daily/Placebo/Placebo
Serostim® 4 mg daily/Serostim® 2 mg alt. days/Serostim® 2 mg alt. days

3.2 Evaluation of Safety

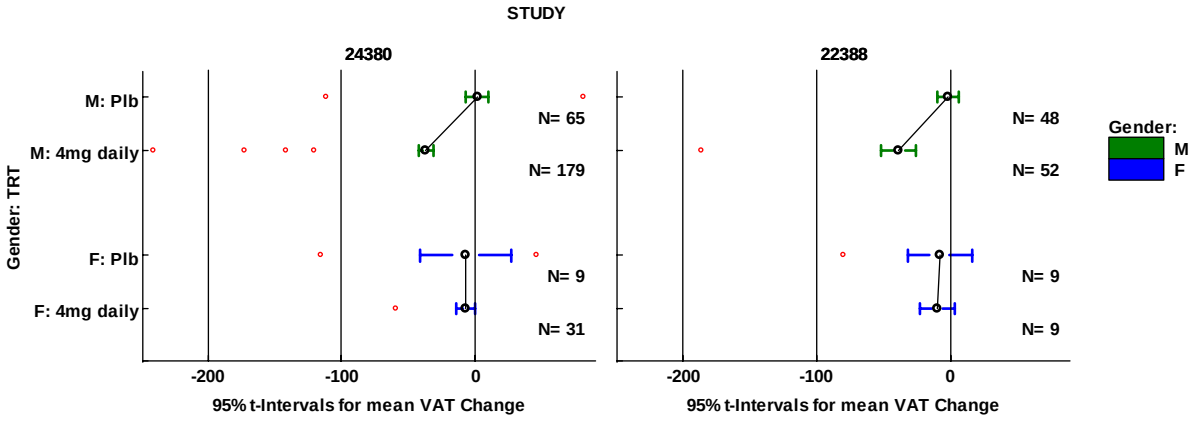
Please refer to the medical officer, Robert Perlstein's review for safety.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Gender:

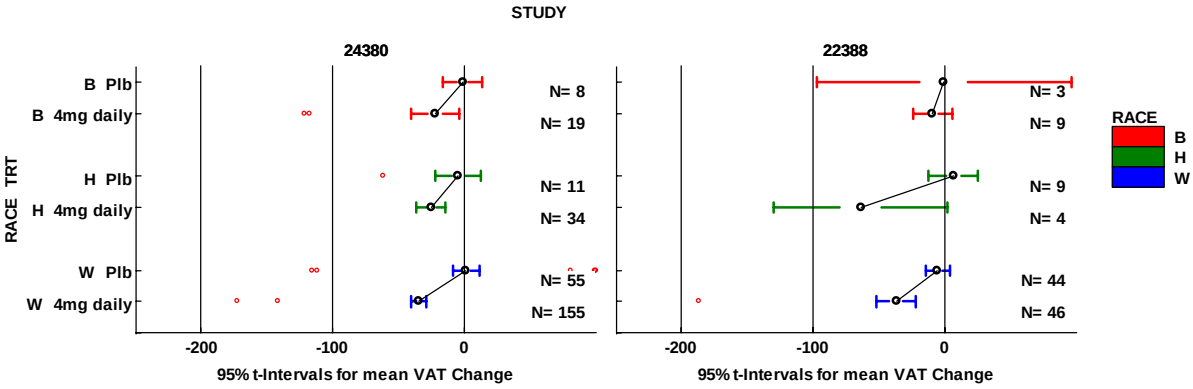
Treatment-by-gender interaction was significant in study 24380 (p<0.01) and study 22388 (p=0.1) (Fig 12).

Figure 13 Mean VAT change by gender



Treatment-by-race interaction was significant for study 22388 (p=0.095) but not significant for study 24380 (p=0.24) for Serostim 4 mg daily and placebo. The interaction was quantitative in nature. Figure 13 displays mean VAT change from baseline to Week 12 in Blacks (B), Hispanics (H) and Whites (W).

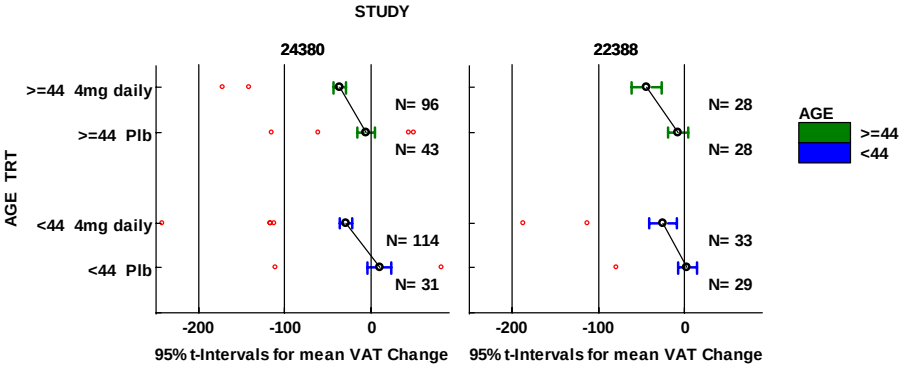
Figure 14 Mean VAT change by race



Age group:

Patients were all less than 65 years of age. Patients were grouped by the median age (44 years). Figure displays VAT change from baseline to Week 12 by age group. No treatment-by-age group interaction was detected.

Figure 15 Mean VAT change by age group



5. SUMMARY AND CONCLUSIONS

5.2 Conclusions and Recommendations

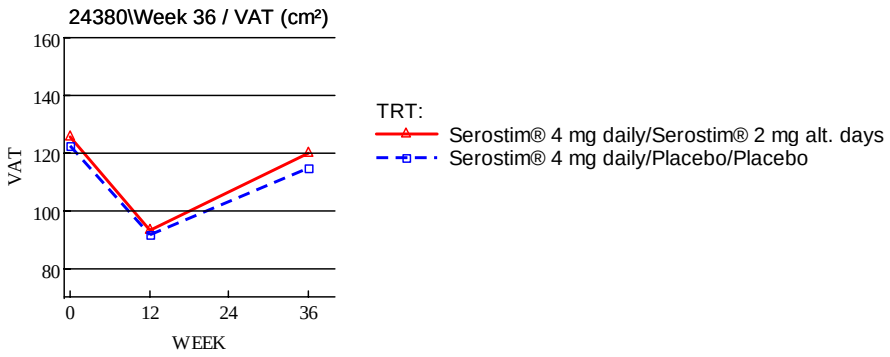
For the 12-week induction phase of both studies, Serostim 4 mg daily (QD) was statistically significantly better than placebo in VAT change from baseline to week 12. The 4 mg alternate day (QOD) dose, which was studied only in the dose finding study, was also significantly better than placebo in VAT change from baseline to week 12. Least-square (LS) mean treatment differences and 2-sided 95% confidence intervals between Serostim 4 mg daily and placebo in mean VAT change from baseline were -17 cm^2 [-29, -5] in Study 24380 and -18 cm^2 [-35, -2] in Study 22388. The -20 cm^2 [-38, -2] LS mean difference between Serostim 4 mg QOD and placebo in Study 22388 was similar to the LS mean treatment difference between Serostim 4 mg QD and placebo in that study.

Randomizations in both studies were stratified by gender. Treatment-by-gender interactions comparing Serostim 4 mg QD and placebo were statistically significant at the 10% level in both studies. VAT LS mean treatment differences were +4 cm^2 in females and -38 cm^2 in males in Study 24380, and -4 cm^2 in females and -32 cm^2 in males in Study 22388.

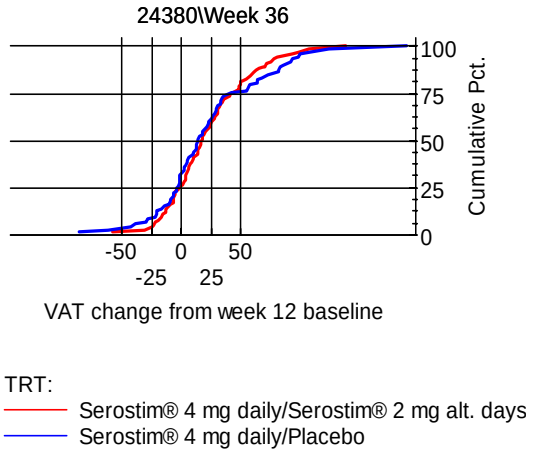
Serostim 4 mg QD and QOD and were significantly different from placebo in truncal fat mean change from baseline to week 12 in both studies. The mean difference between Serostim 4 mg daily and placebo in Study 24380 was -2.4 kg. The treatment-by-gender interactions comparing 4 mg and placebo were not significant in either study.

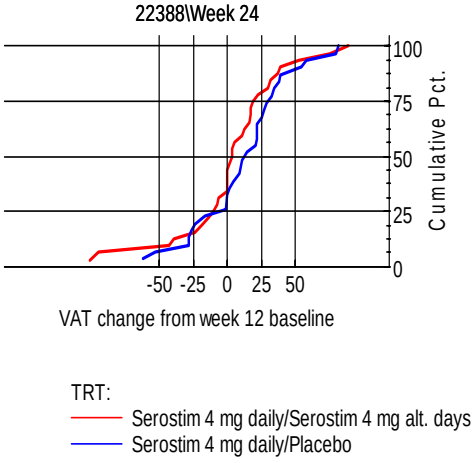
Both studies re-randomized patients at Week 12 to maintenance doses for 24 weeks in Study 24380 and 12 weeks in Study 22388. Patients in Study 24380 initially randomized to Serostim 4 mg QD were re-randomized to maintenance doses of Serostim 2 mg QOD or placebo. Patients in Study 22388 initially randomized to Serostim 4 mg QD were re-randomized to maintenance doses of Serostim 4 mg QOD or placebo.

In Study 24380, the two groups had similar changes in VAT change from Weeks 12 to 36. Mean VAT changes were +23.7 cm^2 for Serostim 2 mg QOD (n=73) and +23.3 cm^2 (n=75) for placebo. In Study 22388, mean VAT changes from Weeks 12 to 24 were +4 cm^2 for 4 mg QOD (n=32) and +13 cm^2 for placebo (n=31). The Figure below depicts median VAT values from week 1 (baseline) to weeks 12 and 36 for the two treatment sequences in Study 24380.



The following Figures depict cumulative distributions for VAT changes from Week 12 to Week 36 in Study 24380 and to From Week 12 to Week 24 in Study 22388.





In conclusion, Serostim 4 mg QD and QOD were statistically significantly superior to placebo and similar to each other in VAT reduction for the 12-week induction periods. Serostim did not reduce VAT in female HARS patients. Serostim 2 mg QOD failed to demonstrate sustained efficacy in the maintenance phase of Study 24380. Results from the dose finding study suggest that a higher dose (Serostim 4 mg QOD) may be required for maintenance of efficacy produced by Serostim 4 mg QD during induction.

APPENDIX: Patient Reported Outcomes (PRO)

Please refer to Dr. Laurie Burke's (OND) review on PRO.

HARS Belly Image

Body Image Scales

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Using “current appearance” as the reference, patients indicated the degree of distress associated with each area of the body evaluated. Only the belly appearance was designated as one of the two PRO variables.

The question was phrased as follows:
Think about your “current appearance”. The following statements are about how you feel about certain aspects of your current appearance.

The structured responses were:

COPYRIGHT MATERIAL

Table 23 displays the ANCOVA results. Serostim 4 mg daily was significant better than placebo in belly size evaluation (BSE) change from baseline to week 12. The treatment-by-gender interaction was not significant.

Table 27 ANCOVA results on Belly Size Evaluation - Study 24380

TRT1C	LSM	StdErr	Lower	Upper
Placebo	-9.02	7.05	-22.91	4.86
Serostim® 4 mg daily	-42.29	5.08	-52.28	-32.29
Difference from placebo	**-33.26**	**7.17**	**-47.38**	**-19.15**

Table 24 and 25 display the descriptive statistics of BSE for all patients and by gender, respectively.

Table 28 Descriptive Statistics of Belly Size Evaluation - Study 24380

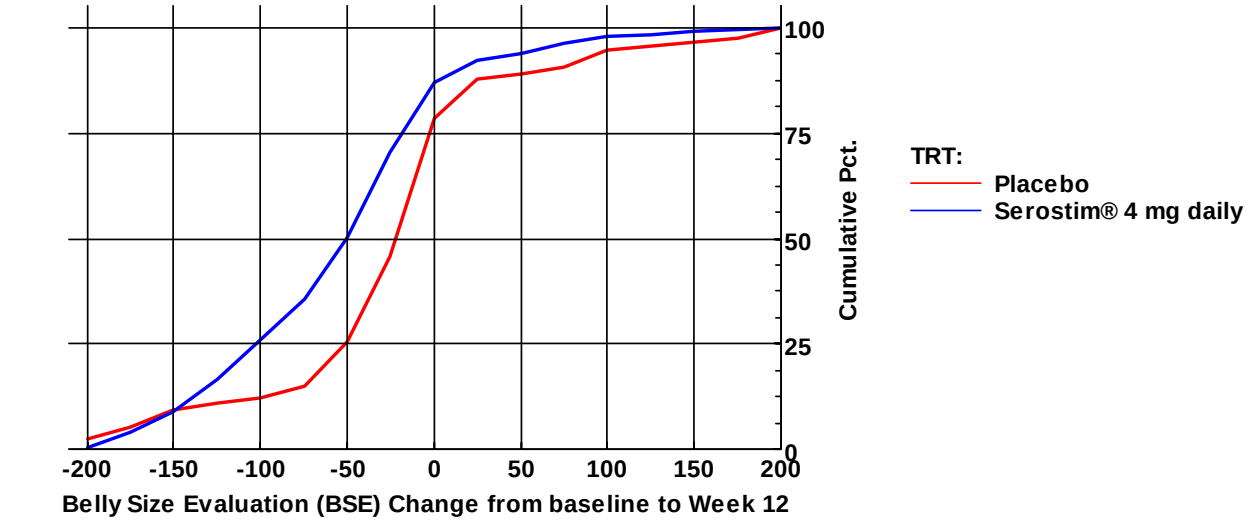
Treatment Weeks 1-12	N	Belly size	Mean	Std Dev	Median
Placebo	74				75.0
		Baseline	53.72	51.96	50.0
		Week 12	40.20	53.77	0.0
		Change	-13.51	78.10	
Serostim® 4 mg daily	190				75.0
		Baseline	52.63	50.19	0.0
		Week 12	7.11	51.65	-50.0
		Change	-45.53	68.62	

Table 29 Descriptive statistics on Belly Size Evaluation by gender - Study 24380

Treatment, Weeks 1-12	Gender	N	Belly Size	Mean	Std Dev	Median
Placebo	Female	9	Baseline	50.00	85.70	100.0
			Week 12	72.22	38.41	75.0
			Change	22.22	101.89	0.0
	Male	65	Baseline	54.23	46.47	75.0
			Week 12	35.77	54.30	50.0
			Change	-18.46	73.86	0.0
Serostim® 4 mg daily	Female	27	Baseline	70.37	42.76	75.0
			Week 12	8.33	57.60	25.0
			Change	-62.04	59.80	-50.0
	Male	163	Baseline	49.69	50.84	75.0
			Week 12	6.90	50.79	0.0
			Change	-42.79	69.76	-50.0

Figure 15 displays the cumulative distribution of BSE change from baseline to week 12.

Figure 16 Cumulative distribution of Belly Size Evaluation – Study 24380



← **Belly size smaller** **Belly size bigger** →

Table 26 displays the results from ANCOVA on Belly Appearance Distress. The LSM difference between Serostim 4 mg daily and placebo was statistically significant better for Serostim than placebo. Treatment-by-gender interaction was significant (p=0.1). Tables 27 and 28 display descriptive statistics for all patients and by gender, respectively.

Table 30 ANCOVA results on Belly Appearance Distress - Study 24380

TRT	LSM	StdErr	Lower	Upper
Placebo	3.11	3.69	-4.16	10.38
Serostim® 4 mg daily	20.71	2.71	15.38	26.04
Difference from placebo	**17.60**	**3.74**	**10.23**	**24.97**

Table 31 Descriptive statistics on Belly Appearance Distress - Study 24380

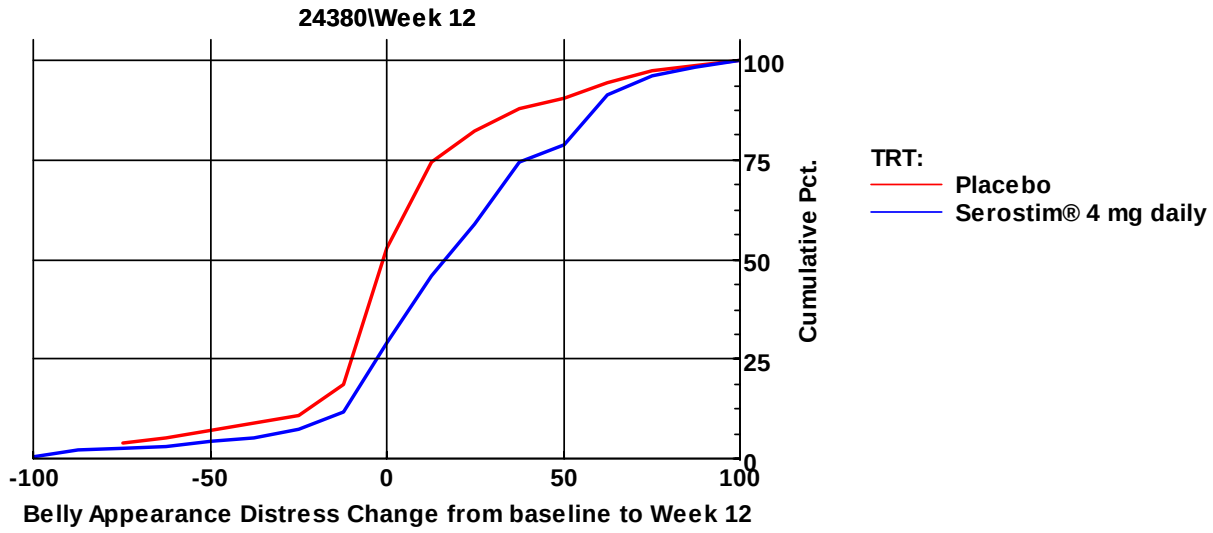
Treatment, Weeks 1-12	N	Belly Appearance Distress	Mean	Std Dev	Median
Placebo	74	Baseline	21.45	22.52	12.5
		Week 12	30.41	27.38	25.0
		Change	8.95	32.22	0.0
Serostim® 4 mg daily	188	Baseline	24.87	24.18	25.0
		Week 12	48.07	27.31	50.0
		Change	23.20	36.55	25.0

Table 32 Descriptive statistics on Belly Appearance Distress by gender - Study 24380

Treatment, Weeks 1-12	Gender	N Obs	Variable	Mean	Std Dev	Median
Placebo	Female	9	Baseline	12.50	33.07	0.0
			Week 12	12.50	16.54	0.0
			Change	0.00	25.77	0.0
	Male	65	Baseline	22.69	20.72	25.0
			Week 12	32.88	27.74	25.0
			Change	10.19	32.99	0.0
Serostim® 4 mg daily	Female	25	Baseline	27.50	28.18	25.0
			Week 12	43.50	26.30	50.0
			Change	16.00	37.93	25.0
	Male	163	Baseline	24.46	23.58	25.0
			Week 12	48.77	27.47	50.0
			Change	24.31	36.33	25.0

Figure 16 displays cumulative distribution for belly appearance distress change from baseline to week 12.

Figure 17 Cumulative distribution of Belly Appearance Distress – Study 24380



More distress **More encouraging**

Figures 17 and 18 display the cumulative distribution of BSE and belly appearance distress for study 22388, respectively.

Figure 18 Cumulative distribution of BSE – Study 22388

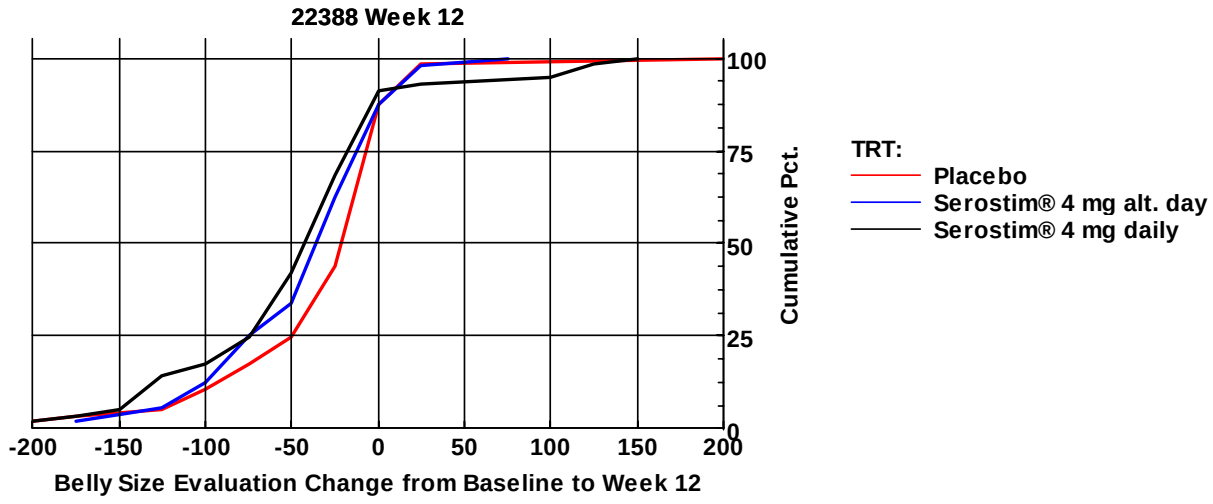


Figure 19 Cumulative distribution of Belly Appearance Distress

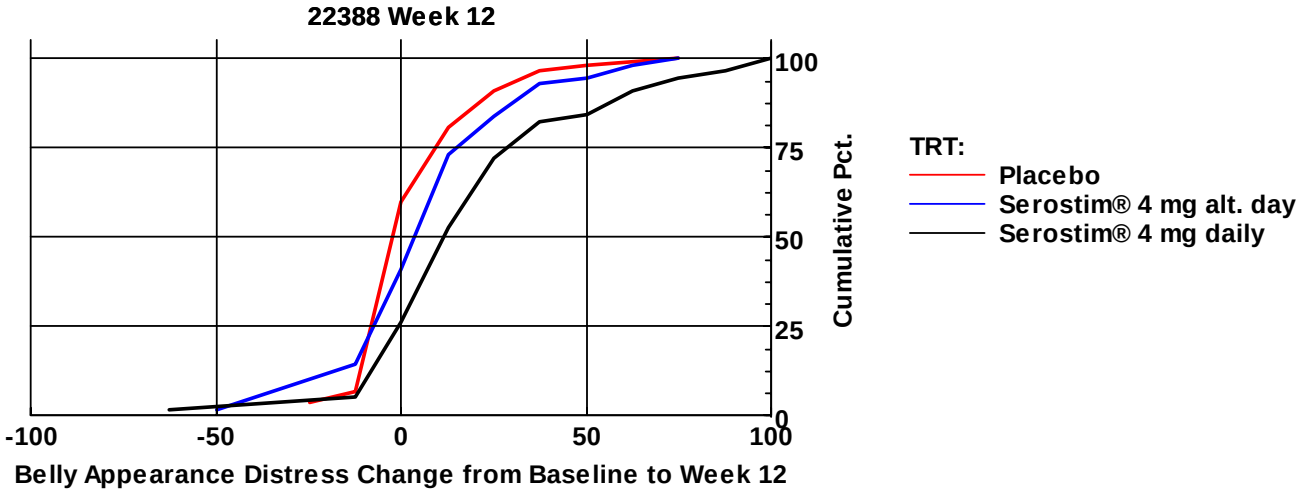
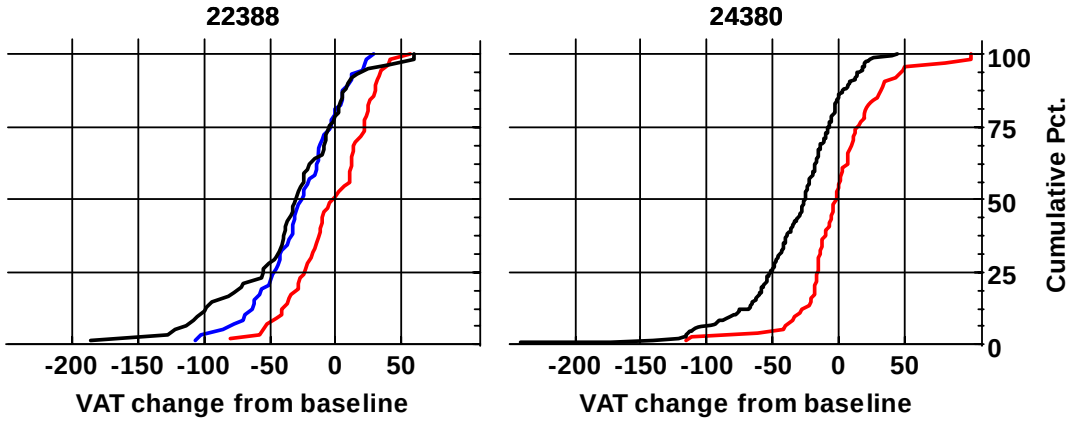
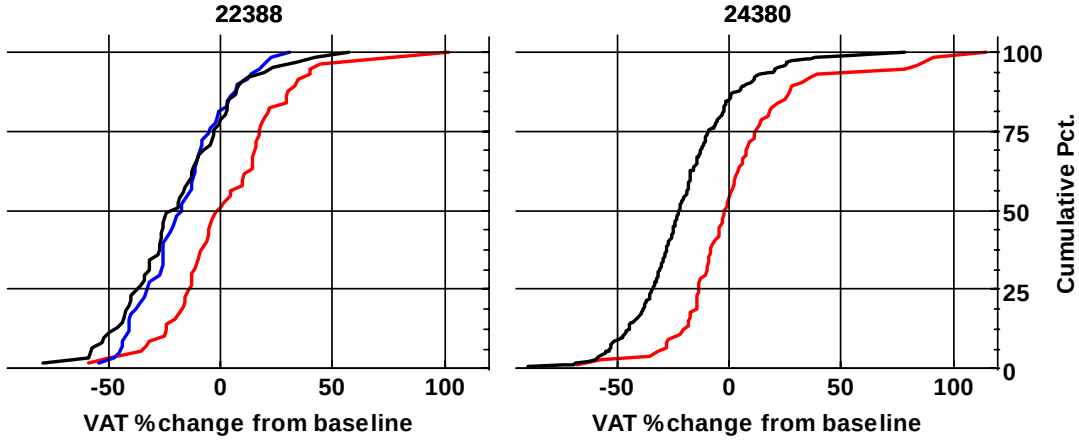


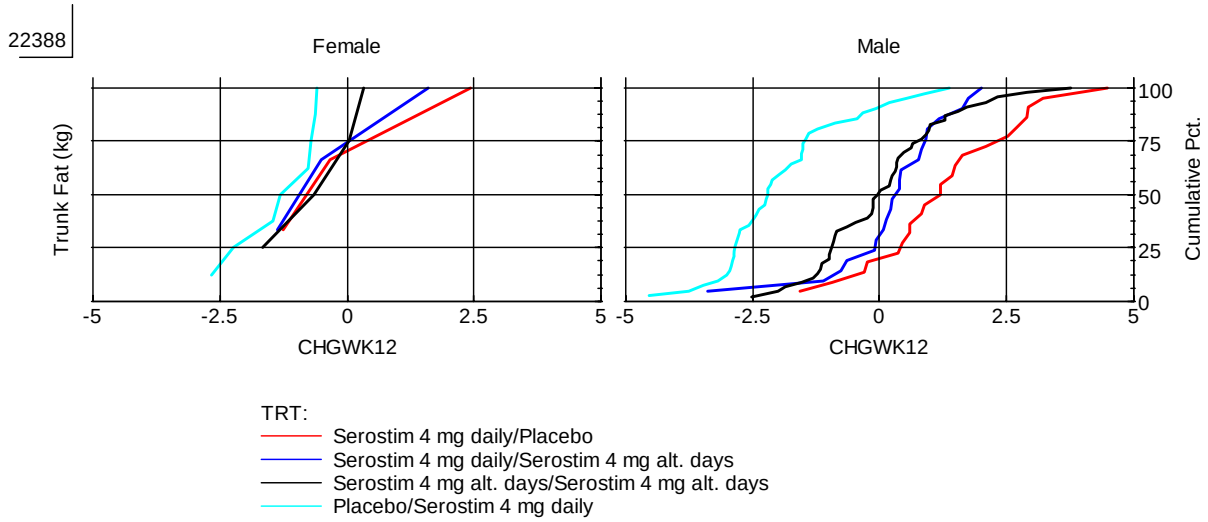
Figure 20 Cumulative distribution function for VAT change and VAT % change from baseline

Change



Percent Change




22388
Female
Male
Trunk Fat (kg)
Cumulative Pct.
-5
-2.5
0
2.5
5
100
75
50
25
0
CHGWK12
TRT:
Serostim 4 mg daily/Placebo
Serostim 4 mg daily/Serostim 4 mg alt. days
Serostim 4 mg alt. days/Serostim 4 mg alt. days
Placebo/Serostim 4 mg daily

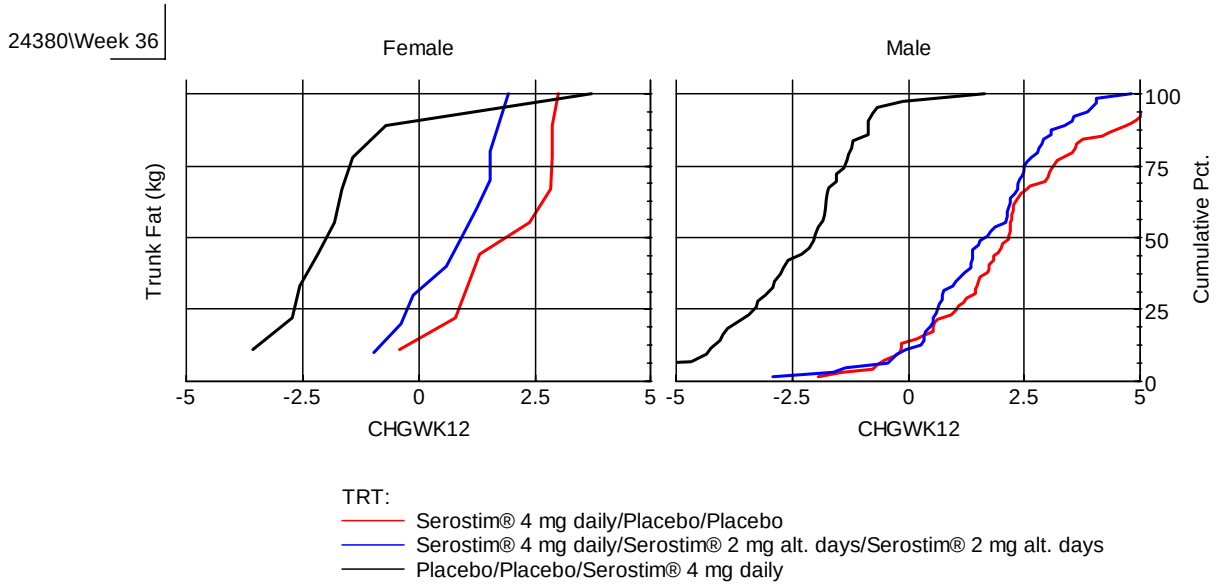
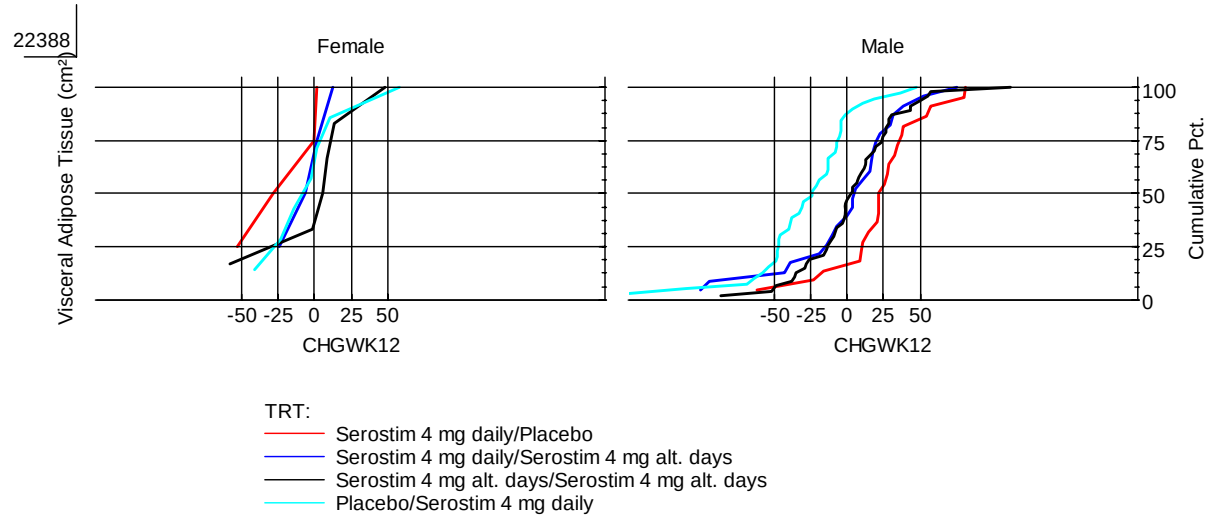
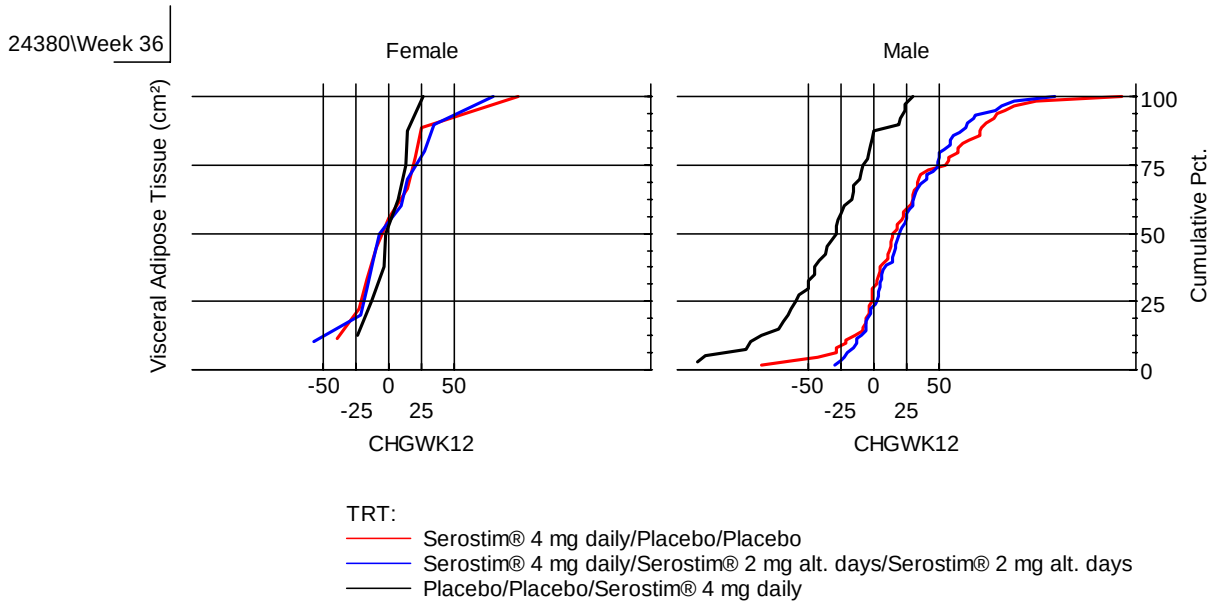

24380\Week 36
Female
Male
Trunk Fat (kg)
Cumulative Pct.
-5
-2.5
0
2.5
5
100
75
50
25
0
CHGWK12
TRT:
Serostim® 4 mg daily/Placebo/Placebo
Serostim® 4 mg daily/Serostim® 2 mg alt. days/Serostim® 2 mg alt. days
Placebo/Placebo/Serostim® 4 mg daily

Figure 21 Cumulative distribution function for VAT change and trunk fat change by gender





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/s/

Todd Sahlroot
7/6/2007 04:28:52 PM
BIOMETRICS
concur with review. Submitted for Dr. Pian.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020604Orig1s040

<u>OTHER REVIEW(S)</u>

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: April 5, 2007

TO: Kati Johnson, Chief, Project Management Staff
Robert Perlstein, M.D., Clinical Reviewer
Division of Metabolism and Endocrinology Products

THROUGH: Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

FROM: Andrea Slavin, RN
Consumer Safety Officer

SUBJECT: Evaluation of Clinical Inspections

NDA: 20-604/S-040

APPLICANT: Serono, Inc.

DRUG: Serostim® [somatropin (rDNA origin) for injection]

THERAPEUTIC CLASSIFICATION: 6, S

INDICATION: HIV-associated adipose redistribution syndrome (HARS)

CONSULTATION REQUEST DATE: October 27, 2006

DIVISION ACTION GOAL DATE: April 14, 2007

PDUFA DATE: April 14, 2007

I. BACKGROUND:

Serostim is human growth hormone produced by recombinant DNA technology. This supplement is for treatment of HIV-associated adipose redistribution syndrome (HARS). The defining characteristic of HARS is abnormal accumulation of truncal, including visceral, adipose tissue (VAT) in the HIV-infected patient.

The goals of the inspections were to assess adherence to FDA regulatory requirements, specifically, investigator oversight, protocol compliance, verification of primary efficacy endpoint data, adequacy of study records and protection of subjects' rights, safety, and welfare. Site selection was based on subject enrollment.

The inspections audited protocol #24380, "A Phase III, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study of the Safety and Efficacy of Serostim® (mammalian cell-derived recombinant human growth hormone, r-hGH) in the Treatment and Maintenance of Human Immunodeficiency Virus-associated Adipose Redistibution Syndrome (HARS)."

II. RESULTS (by protocol/site):

Name of CI and site #, if known	City, State	Protocol	Inspection Date	EIR Received Date	Final Classification
Gary Richmond, MD/527	Ft. Lauderdale, FL	24380	3/12/07-3/16/07	4/3/07	VAI
Stephen Brown, MD/522	W. Hollywood, CA	24380	1/3/07-1/5/07	1/22/07	NAI

Key to Classifications
NAI = No deviation from regulations. Data acceptable.
VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.
VAI-Response Requested = Deviation(s) from regulations. See specific comments below for data acceptability
OAI = Significant deviations from regulations. Data unreliable.

A. Protocol #24380

1. Gary J. Richmond, M.D. (site 527)
315 SE 14th Street
Fort Lauderdale, FL 33316

a. What was inspected: At this site, 44 subjects were screened, 29 subjects were randomized, and 23 subjects completed the study. Eleven subjects' records were audited.

b. Limitations of inspection: None

c. General observations/commentary: Subject #5270044 was taking a prohibited concomitant medication (nandrolone) at screening, yet was enrolled in the study. Subject #5270017 experienced moderate glucose toxicity on Day 1 (2 hr. OGTT glucose value of 208 mg/dL) and the site did not institute a 50% dose reduction.

d. Data from this site appear acceptable.

2. Stephen J. Brown, M.D. (site 522)
AIDS Research Alliance
621-A North San Vicente Boulevard
West Hollywood, CA 90069

a. What was inspected: At this site, 50 subjects were screened and 32 subjects were randomized. Sixteen subjects' records were audited.

b. Limitations of inspection: None

c. General observations/commentary: No significant deviations from FDA regulations were observed.

d. Data from this site appear acceptable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

As discussed above, subject #5270044 at Dr. Richmond's site was taking a prohibited concomitant medication and should not have been enrolled in the study.

Overall, no significant deviations from FDA regulations were observed that would impact on the integrity of the research data or subject safety. Data from these two clinical sites appear acceptable in support of the pending application.

{See appended electronic signature page}

Andrea Slavin, RN
Consumer Safety Officer

CONCURRENCE:

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

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/s/

Andrea Slavin
4/10/2007 09:58:25 AM
CSO

Constance Lewin
4/10/2007 10:25:02 AM
MEDICAL OFFICER

STUDY ENDPOINT REVIEW

SEALD ACTION TRACK NUMBER	2006.002.A.00075
APPLICATION NUMBER	NDA 20-604/S-040
LETTER DATE/SUBMISSION NUMBER	6/8/06
DATE OF CONSULT REQUEST	6/27/06
REVIEW DIVISION	Division of Metabolism & Endocrinology Products
MEDICAL REVIEWER	Robert Perlstein
REVIEW DIVISION PM	Kati Johnson
SEALD REVIEWER(S)	Laurie Burke
REVIEW COMPLETION DATE	3-7-07
ESTABLISHED NAME	somatropin (rDNA origin) (rhGH)
TRADE NAME	Serostim for injection
APPLICANT	Serono, Inc
ENDPOINT(S) CONCEPT(S)	body image in HIV-associated adipose redistribution syndrome (HARS)
INSTRUMENT(S)	Body Image Impact Module (BIIM) from the (b) (4)
INDICATION	Reduction of abnormal truncal, including visceral, adipose tissue (VAT) accumulation in patients infected with HIV

1 EXECUTIVE SUMMARY

This Study Endpoints and Label Development (SEALD) review is provided as a response to a request for consultation by the Division of Metabolism and Endocrinology regarding the adequacy of the Body Image Impact Module (BIM) to support statements in labeling. Prior reviews confirmed the appropriateness of the BIM body size evaluation (BSE) and body appearance distress (BAD) scales as measures for HARS clinical trials. The current consult request was for additional review of the methodology for defining a responder to treatment using these scales. The applicant defines the minimum amount of improvement in scale scores that could be considered evidence of a treatment benefit to patients as a change of 2 units on the BSE or BAD scales. This responder definition is adequate.

In addition to the responder analysis, we recommend an analysis and presentation of data using a cumulative distribution function.

2 ENDPOINT REVIEW NOTES

In a study of HARS patients to determine what would constitute a meaningful change in body size (BSE), 766 HARS patients were asked to review sets of drawings of silhouettes depicting a range of belly and dorsal cervical regions from “excessively abnormal” (scored as 5) to “normal” (scored as 0) profiles and select the figure that represented what they would consider a “smallest acceptable health benefit,” i.e., a meaningful change from their current condition. (All patients’ current profile scored >0.) 90% of patients selected the “normal” profile as the goal. The majority of patients selected a figure at least 2 dysmorphic profiles smaller than their current state as the smallest improvement they would accept as meaningful with treatment.

Clinicians evaluated the same set of silhouettes in conjunction with a specific HARS patient. The clinicians were more likely to accept smaller improvements as meaningful than were patients. Patients with more dysmorphic profile scores of 3, 4 or 5 were considered improved with a change equating to a 2 profile difference. Patients with less dysmorphic profile scores of 1 or 2 were considered improved with a change of 1 profile difference. When this change is averaged at 1.5 and calibrated to the BSE scale (range -100 to +100 with 25 point increments), the BSE score change is 21.6, close enough to 25 to be considered a 1 scale unit change towards “healthy look.” When calibrated to the BAD scale (range 0 to 100 with 12.5 point increments), the corresponding BAD scale change is 11.8, also close enough to 12.5 to be considered a 1 scale unit change to “extremely encouraging.”

Subsequently, a different responder definition was developed and applied to studies 24380 and 22388 data. A BAD responder was defined as a change from baseline to week 12 of more than 20 (moving towards “encouraging”) (i.e., > 1 unit of 12.5) calculated by a regression with patient score change in belly profile ratings multiplied by the patient’s baseline definition of “minimum benefit.” A BSE responder was defined as a change from baseline to week 12 of more than 39 (moving towards “healthy look”) (i.e., > 1 unit of 25) calculated by a regression with patient score change in belly profile ratings multiplied by the patient’s baseline definition of “minimum benefit.” In both definitions, a responder would need to improve by at least 2 scale units to be called a responder.

A cumulative distribution curve provides information on what type of responses contributed to the mean group response and provides more useful data than a simple point estimate of the difference between group mean changes. It also allows a reader/reviewer to determine for themselves the definition of a meaningful response. If the labeling will include information about BSE and BAD, we recommend this tool for presentation of the PRO data, if possible, in order to provide clinicians and patients with full information for their decision-making.

3 BACKGROUND

In March 2004, SEALD gave the following recommendations with respect to the BIIM:

1. The four scales of the Body Image Impact Module (BIIM) from the (b) (4) (b) (4) should be incorporated in the Phase III protocol as secondary endpoints.

- Body Size scale (SN 235 Vol 1, Appendix 1)
- Body Image Distress scale (SN 235 Vol 1, Appendix 2)
- Body Profile scale (patient-reported version, SN 235 Vol 1, Appendix 3)
- Appearance-Specific Symptom Interference scale (SN 235 Vol 1, Appendix 6)

Based on discussion with the Division, we recommend that items referring to the belly and dorso-cervical "hump" in the Body Size and Body Image Distress scales, as well as the self-reported Body Profile scale be the "essential" secondary endpoints for the Phase III clinical protocol. Change from baseline to the end of the 12-week induction phase in the Appearance-Specific Symptom Interference scale could provide additional descriptive information about the impact of reduction in HARS symptoms, but positive outcomes on this scale are not essential efficacy endpoints for Serostim.

2. **BIIM validation substudy.** To aid in the interpretation of changes in each of the concepts measured in the BIIM, Serono is encouraged to identify the magnitude of change in each BIIM scale score that would demonstrate an important treatment benefit. We recommend that the minimum important difference (MID) in each BIIM score be determined using an anchor-based method as the amount of change in each score associated with two or more of the following anchors:

   a. a clinically meaningful decrease in visceral fat (to be determined by Serono from phase II trial data)

   b. an improvement score of +2 or more on a 15 point patient-reported global impression of change

   c. a change prospectively identified using a baseline assessment of the Body Profile Scales (questions 3 and 6)

The patient-reported global impression of change would not be intended for or adequate to support labeling claims; it is included only to aid in the interpretation of

study results. Distribution-based methods for assessing the MID would not be sufficient for clinical trials without first demonstrating validity in relation to clinically relevant anchors. Data collected during the 12-week blinded treatment induction phase of the Phase III protocol may be analyzed to establish the MID for each BIIM scale score prior to unblinding the data. This BIIM validation substudy also should document the adequacy of the measurement properties each BIIM scale in terms of:

(a) how reliable scores for each of the BIIM scales are

(b) how much change in scores for each BIIM scale is associated with a clinically important change in visceral fat, global impression of change, and perceived important change in Body Profile, and

(c) if change in visceral fat is used to establish the MID, whether the amount of change associated with a clinically important change in visceral fat is important to patients.

The ability to interpret observed changes in the Body Image Distress scale may improve if a question is added for the validation substudy to document how distressed the patients feel when they consider all seven areas of the body that are affected by HARS. Like the patient-reported global impression of change, the addition of an overall distress question would not be intended for or adequate for labeling; it is included to aid interpretation of study results by providing an indication of how changes in a patient's perceptions about specific body areas are associated with the patient's overall sense of distress about bodily appearance.

If in the phase 3 studies mean changes in scores for patients receiving Serostim do not exceed the mean changes in scores for the placebo group by the MID established with the blinded data, there will not be convincing evidence of treatment benefit.

Serono also should realize that it will not be possible to interpret trial results if there are marked improvements on some BIIM scale items and marked worsening of other items within the same scale, or if improvements in one "essential" scale are not confirmed by improvements in the other "essential" scales.

3. The protocol should focus patient self-assessments on the most relevant scales and time points for understanding the effects of HARS treatment to reduce the amount of missing questionnaire data. PRO measures used should be limited to the BIIM and those items needed for validation purposes to minimize the burden to patients associated with completing questionnaires and to increase the likelihood of complete patient questionnaire data for all patients in the protocol.

4. The protocol needs to detail the procedures for administration and handling of the patient questionnaires. Serono is encouraged to develop a patient questionnaire administration monitoring tool that captures whether the patient was given the questionnaire to complete as scheduled in the protocol, and if not, provides information on the reason why the assessment was not completed. This tool also can serve as a reminder to the study personnel to review the questionnaire and confirm that all questions were completed.

5. The BIIM scales used in the protocol need to be implemented using exactly the same wording/formatting, and with the same instructions as were used in the validation studies to avoid introducing method artifacts.
6. The term "quality of life" has been used freely in the proposed protocol and discussions with the Sponsor for this IND to refer to all patient-reported endpoints. Such usage should be discouraged to avoid misunderstanding about the likely claims that will be possible from this trial. Comprehensive measurement of all facets of health-related quality of life (HRQL) or HARS-specific HRQL would be required to support broad claims of improvement in HRQL or HARS-specific HRQL (respectively) for labeling or advertising. The measures included in the patient questionnaire (referred to as the "Health-Related Quality of Life Questionnaire" in the protocol and reproduced in Appendix K of the protocol) do not adequately measure all the facets of quality of life in general or of HRQL or HARS-specific HRQL. For example, they do not address the impact of HARS or its treatment on important aspects of HRQL such as sexual functioning, physical functioning, or cognitive functioning. For this reason, success on all scores generated from the PRO questionnaire data would not be adequate to support a broad claim that Serostim improved the HRQL for HARS patients. The patient self-assessment will support only those claims of benefit that it can directly measure

In March 2006, SEALD had the following recommendations concerning a responder definition using the BIIM:

SEALD reviewed proposals for interpretation of endpoint measures for phase III trials derived from the (b) (4) Body Image Impact Module (BIIM) to support statements in labeling regarding changes in perceived body size, distress about body appearance, and evaluation of how well body size conforms to a "healthy look" submitted in IND 61,226 SN 047 [1]. Prior reviews confirmed the appropriateness of the BIIM body size and body size distress scales as measures for HARS clinical trials but noted that it was not clear how much improvement in scale scores would be evidence of a treatment benefit to patients. [2, 3]

Summary of this submission:

- The developer of the BIIM administered the instrument to 766 HARS patients and their clinicians to establish how much improvement in perceived body size would be considered meaningful to patients and to their doctors.
    - HARS patients generally reported that the only acceptable outcome that would be considered a treatment benefit would be to reduce fat to the point that the patient is restored to a "normal" body size.
    - Clinicians considered a reduction in body fat that did not restore a patient to "normal" body size still could represent a clinically meaningful treatment benefit
- The significant discrepancy between patients' and clinicians' evaluation of what would constitute a treatment benefit in change in body size raises questions regarding whose judgment should be used to set endpoint evaluation criteria for clinical trials.
- The sponsor plans to use the clinician's evaluation of what would be an important reduction in body fat.

Recommendations:

- Both patient and clinician interpretations of a meaningful outcome are important considerations for responder definition. A responder definition based on the patient perspective is likely to large and to change over time and one based on the clinician perspective is likely to be too small.

4 APPENDIX

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REFERENCES

[1] IND 61,226, Serial No. 047, Follow-up to March 30, 2005 Type C Meeting Proposal of Evaluation of the cMID (clinical minimal important difference) between treatments in the body self-image instrument used in the TH9507/III/LIPO/010 ongoing clinical trial. Dated January 25, 2006 submitted by Theratechnologies, Inc.

[2] SEALD consult 2005.002.A.00019 review of IND 61,226, Serial No. 030 briefing package for March 30, 2005 Type C Meeting to discuss endpoints for phase III clinical trials TH9507 for treatment of HARS dated 16 February 2005 submitted by Theratechnologies, Inc.

[3] SEALD consult 2003.002.A.00309 dated 19 February 2004 reviewing IND 38,087, Serial No. 235 submitted by Serono containing a description of the development and validation of the (b) (4) Respondent and Physician Reported Body Image Impact Module to measure endpoints in phase III clinical trials.

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/s/

Laurie Burke
3/8/2007 06:33:28 PM
INTERDISCIPLINARY

DSI CONSULT: Request for Clinical Inspections

Date: 10/27/06

To: Constance Lewin, M.D., M.P.H., Branch Chief, GCP1, HFD-46
Leslie Ball, M.D., Branch Chief, GCP2, HFD-47

From: Kati Johnson, Chief, Project Management Staff, HFD-510
Division of Metabolism & Endocrinology Products

Subject: **Request for Clinical Site Inspections**
NDA 20-604/S-040
Serono Inc.
Serostim (somatropin (rDHA origin) for injection

Protocol/Site Identification:

As discussed with you, the following protocols/sites essential for approval have been identified for inspection. These sites are listed in order of priority.

This NDA provides data for the following: new indication: Treatment of patients with HIV associated adipose redistribution syndrome (HARS), and indicate if NME. NOT AN NME

Site # (Name and Address)	Protocol #	Number of Subjects	Indication
Stephen Brown, MD AIDS Alliance 621-A North San Vicente Blvd. West Hollywood, CA 90069	24380	32	Treatment of HARS
Gary Richmond, MD 315 SE 14th Street Fort Lauderdale, FL 33316	24380	29	Treatment of HARS

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) March 1, 2007. We intend to issue an action letter on this

application by (division action goal date) April 14, 2007. The PDUFA due date for this application is April 14, 2007.

Should you require any additional information, please contact Kati Johnson, 301-796-1234 or Robert Perlstein, MD (Medical Reviewer) 301-796-1270.

Concurrence: (if necessary)

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/s/

Kati Johnson
10/27/2006 12:33:59 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020604Orig1s040

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 20-604 SUPPL # -040 HFD #

Trade Name Serostim

Generic Name somatropin (rDNA origin) for injection

Applicant Name EMD Serono

Approval Date, If Known 7/13/07****

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

****505(b)(1), the application was submitted as an SE1, but they did not get the indication: they were allowed to include information in the CLINICAL TRIALS section of the package insert.

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 ☒ 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 ☒

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

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

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

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 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 ☒ 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 origin] injection)
NDA#	20-280	Genotropin (somatropin [rDNA origin] for injection)
NDA#	20-522	Nutropin AQ (somatropin [rDNA origin] injection There are multiple other approved NDAs

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. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs 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 ☒ 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 ☒ 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 ☒

(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 ☐

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 ☒

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:

Protocol 22388- Phase 2/3, multicenter, double-blind, randomized, placebo-controlled, parallel-group, dose-finding, safety and efficacy trial of subcutaneously administered Serostim (mammalian cell-derived recombinant human growth hormone, r-hGH) in the treatment of Human Immunodeficiency Virus-associated Adipose Redistribution Syndrome (HARS)

Protocol 24380-A phase III, multi-center, randomized, double-blind, placebo-controlled, parallel groupstudy of the safety and efficacy of Serostim® (mammalian cell-derived recombinant human growth hormone, r-hGH) in the treatment and maintenance of Human Immunodeficiency Virus-associated Adipose Redistribution Syndrome (HARS)

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 ☒
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 upon:

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 ☒

Investigation #2 YES ☐ NO ☒

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"):

Protocol 22388- Phase 2/3, multicenter, double-blind, randomized, placebo-controlled, parallel-group, dose-finding, safety and efficacy trial of subcutaneously administered Serostim (mammalian cell-derived recombinant human growth hormone, r-hGH) in the treatment of Human Immunodeficiency Virus-associated Adipose Redistribution Syndrome (HARS)

Protocol 24380-A phase III, multi-center, randomized, double-blind, placebo-controlled, parallel groupstudy of the safety and efficacy of Serostim® (mammalian cell-derived recombinant human growth hormone, r-hGH) in the treatment and maintenance of Human Immunodeficiency Virus-associated Adipose Redistribution Syndrome (HARS)

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 ☒ ! 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 ☐ ! NO ☐
Explain: ! Explain:

Investigation #2 !
!
YES ☐ ! NO ☐
Explain: ! 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 ☒

If yes, explain:

==========

Name of person completing form: Kati Johnson
Title: Project Manager
Date: 8/16/07

Name of Office/Division Director signing form: Mary Parks, MD
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/s/

Kati Johnson
8/16/2007 10:23:46 AM
signing for Mary Parks, MD

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

PDUFA GOAL DATE EXTENSION

NDA 20-604/S-040

EMD Serono, Inc.
Attention: Paul Lammers, MD
Regulatory Affairs and Quality Assurance
One Technology Place
Rockland, MA 02370

Dear Dr. Lammers:

Please refer to your June 8, 2006 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Serostim (somatropin [rDNA origin] for injection).

On April 10, 2007, we received your April 9, 2007, major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is July 14, 2007.

If you have questions, call me at 301-796-1234.

Sincerely,

{See appended electronic signature page}

Kati Johnson
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Kati Johnson
4/23/2007 06:52:57 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 20-604/S-040

Serono, Inc.
Attention: Pamela Williamson Joyce
VP, Regulatory Affairs and Quality Assurance
One Technology Place
Rockland, MA 02370

Dear Ms. Joyce:

Please refer to your June 12, 2006 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Serostim [somatropin (rDNA origin) for injection].

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on August 13, 2006 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing 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.

If you have any questions, call me at (301) 796-1234.

Sincerely,

{See appended electronic signature page}

Kati Johnson
Chief, Project Management Staff
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Kati Johnson
8/14/2006 08:44:21 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-604/S-040 **PRIOR APPROVAL SUPPLEMENT**

Serono, Inc.
Attention: Lisa Mills
Director, Regulatory Affairs
One Technology Place
Rockland, MA 02370

Dear Ms. Mills:

We have received your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Serostim (somatropin [rDNA origin] for injection)

NDA Number: 20-604

Supplement number: S-040

Review Priority Classification: Standard (S)

Date of supplement: June 8, 2006

Date of receipt: June 14, 2006

This supplemental application proposes the following new indication:

> Serostim is also indicated for the reduction of abnormal trunk fat, including visceral adipose tissue, and associated body image distress in patients infected with the human immunodeficiency virus (HIV) being treated concomitantly with antiretroviral therapy.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 13, 2006 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be April 14 2007.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application. Once the application has been filed we will notify you whether we have waived the pediatric study requirement for this application.

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any question, call me at (301) 796-1234.

Sincerely,

{See appended electronic signature page}

Kati Johnson
Chief, Project Management Staff
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Kati Johnson
7/12/2006 08:07:56 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Beth Duvall-Miller
(cc:d Raquel Peat because I knew you were on leave)

FROM (*Name, Office/Division, and Phone Number of Requestor*): Kati Johnson, CPMS, DMEP

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
6/27/06		20-604/S-040	SE1	6/8/06

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Serostim for injection			2/15/06

NAME OF FIRM: Serono, Inc

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: This supplement provides for a new indication-reduction of abnormal truncal fat and associated body image distress in HIV pts on antiretroviral therapy (HARS). A pre-supplement telecon was held 2/8/06 and a copy of the minutes are attached. The medical officer on this application is Robert Perlstein at 6-1270. The goal date is 4/13/07.
This is an electronic submission (eCTD) in the EDR. Studies 22388 and 24380 both contain PRO that need to be reviewed. The info is in appendix 16 of each study report, according to the firm.
Thanks for your assistance on this. Please call if you need anything.

SIGNATURE OF REQUESTOR
Kati Johnson 6-1234, Room 3366

METHOD OF DELIVERY (Check one)
☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 38,087

Serono Inc.
Attention: Pamela Williamson Joyce
VP, Regulatory Affairs and Quality Assurance, US
One Technology Place
Rockland, MA 02370

Dear Ms. Joyce:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Serostim [somatropin (rDNA origin)] for injection.

We also refer to the teleconference between representatives of your firm and the FDA on February 8, 2006. The purpose of the meeting was to discuss your proposed clinical development plan for the treatment of patients with HIV-associated Adipose Redistribution Syndrome (HARS).

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) 796-1234.

Sincerely,

{See appended electronic signature page}

Kati Johnson
Chief, Project Management Staff
Division of Metabolic & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Attachment-Statistical submission of efficacy datasets

MEMORANDUM OF MEETING MINUTES

TELECON DATE: February 8, 2006
TIME: 11:00 am
APPLICATION: IND 38,087
DRUG NAME: Serostim (somatropin (rDNA origin] injection)
TYPE OF MEETING: pre-sNDA

MEETING CHAIR: Karen M. Mahoney, MD

MEETING RECORDER: Kati Johnson, Project Manager

FDA ATTENDEES: (Title and Office/Division)
Division of Metabolic & Endocrinology Products:
Mary H. Parks, MD-Acting Division Director
Karen M. Mahoney, MD-Acting Team Leader, Diabetes/Growth Hormone
Robert Perlstein, MD-Clinical Reviewer
Kati Johnson-Chief, Project Management Staff
Office of Pharmacoepidemiology and Statistical Science:
Todd Sahlroot, PhD-Team Leader
Lee Ping Pian-Statistical Reviewer
Office of New Drugs/Immediate Office: SEALD Team
Jane Scott, Endpoint Reviewer

EXTERNAL CONSTITUENT ATTENDEES:

Serono, Inc.
Paul Lammers, MD-Chief Medical Officer
Norma Muurahainen, MD, PhD-Senior Medical Director
Susan Kenley, PhD-Worldwide Director, Biostatistics & Statistical Programming
Daena Bock-Biostatistics
Pamela Williamson Joyce-VP, Regulatory Affairs and Quality Assurance
Laurie Ridener-Senior Manager, Regulatory Affairs

BACKGROUND:
Serostim, a recombinant human growth hormone (rhGH) is approved as a liquid and lyophilized powder for the treatment of HIV patients with wasting or cachexia to increase lean body mass and body weight, and improve physical endurance.

The firm requested a meeting on November 22, 2005 to discuss their proposed supplemental submission for HARS (HIV-associated Adipose Redistribution Syndrome). The proposed indication is as follows:

BRAND [somatropin (rDNA) for injection] is indicated for the reduction of abnormal truncal, including visceral, adipose tissue accumulation in patients infected with the human immunodeficiency virus (HIV).

The clinical database to be submitted includes the following:

Study 22388: A 24 week placebo-controlled, double-blind, randomized, parallel-group, dose finding trial in 245 patients with HARS. Patients were randomized to one of the following arms for 12 weeks (induction phase):
-4 mg QD
-4 mg QOD
-placebo
Dosing of rhGH was based on body weight, with a maximum daily dose of 4 mg. At the end of 12 weeks, the following occurred for the respective arms (maintenance phase):
-4mg QD were re-randomized to either placebo or 4 mg QOD
-4mg QOD remained on this regimen
-placebo patients received daily rhGH, up to a maximum dose of 4 mg/day

Study 24380:A 36-week multi-center, randomized, double-blind, placebo-controlled, parallel group study to assess the safety and efficacy of rhGH in reducing VAT in subjects with HARS. For the initial 12 weeks (induction phase), subjects were randomized in a 3:1 ratio to either rhGH 4 mg daily, or placebo. At the end of 12 weeks, the following occurred for the respective arms (maintenance phase):
-4 mg QD-re-randomized to either 2 mg QOD or placebo QOD
-placebo-continued to receive placebo for weeks 12 to 24, then received 4 mg QD for weeks 24 to 36.

Studies 23056 and **25373**, which were extensions of Studies 22388 and 24380, respectively.

MEETING OBJECTIVES:

1. To agree that the results of the HARS clinical development program support the submission of a supplemental NDA for the treatment of patients living with HARS.
2. To agree that the content and format of the proposed electronic Common Technical Document (eCTD) for HARS is acceptable to the FDA.
3. To discuss and agree on any additional requests that the FDA may have regarding the submission.

DISCUSSION POINTS: The firm's questions are followed by our **bolded** responses.

1. Based on the summary integrated safety and efficacy results from the HARS clinical development program presented in the Information Package, does FDA agree that there is sufficient clinical information to support the submission of a HARS eCTD?

Response: The statistical review of efficacy will focus on the analysis of <u>each</u> individual study. Pooling is typically reserved for analyses of subgroups where sample sizes for individual studies are inadequate to assess subgroup effects. The Division noted that the

submission showed p-values for study endpoints following the induction phase for integrated data from Studies 22388 and 24380, and not the p-values for each study. In response to a question from the Division about the results from the individual studies, the sponsor indicated that the p-values on the primary endpoint (change in VAT) following the induction phase for both studies were less than 0.001. The validity and utility of your integrated summary of efficacy for the 12 week induction phase (i.e., for labeling purposes) will be determined after review of the data. An integrated summary of safety is acceptable.

2. Does FDA agree that primary endpoint, secondary endpoint and metabolic parameter results from the clinical development program as proposed are appropriate for inclusion in the respective sections of the HARS package insert?

Response: The efficacy language for the Clinical Studies section of the Package Insert will need to be discussed following the Division's review of the your submission.

Safety results for patients with HARS should be presented separately from safety results for patients with HIV-associated wasting in the Adverse Reactions section of the Package Insert.

3. Does FDA agree that the overall content and structure of the eCTD is acceptable to the Agency?

Response: Yes, pending review. The requested format for the statistical presentation is attached at the end of these meeting minutes.

4. Does FDA agree that a new proprietary name can be proposed and will be considered by the Agency for the HARS drug product?

Response: The Division prefers the continued use of the trade name Serostim, since it will be used in the same population as the original NDA application. The sponsor indicated that it was only interested in input from the Division and had not made a final decision in this regard.

5. Does the FDA have any additional requests for information or analyses to be presented in the HARS eCTD?

Response: Yes
Efficacy

- **Please include blinded analyses from Studies 22388 and 24380 to demonstrate how much change in PRO scores for various components of [redacted] (b) (4) PRO instrument (<u>especially</u> the changes in scores for belly- and hump-related body image size/appearance-related distress) is associated with perceived change in body image and with the established minimum clinically meaningful amount of change in VAT. FDA will use these analyses to identify the clinical minimum important difference (MID) for the PRO scores in order to evaluate whether statistically significant mean differences between treatments for changes in PRO scores during the 12 week induction phase of each trial constitute clinically meaningful changes**

- **Please clarify: How does the clinical minimal important benefit (MIB) referred to in your briefing packet differ from the clinical MID? According to the firm, they are the same. They were requested to consistently use MID in the application.**
- **Please provide a detailed analysis of <u>all PRO data</u> collected during the induction phase of both studies, and the maintenance phase of Study 24380, <u>by domain score</u>.**
- **Please provide a detailed analysis of the relationship between change in VAT, truncal fat, and PRO domain scores.**

Safety

- **Please express serum IGF-1 results as standard deviation scores (SDS) and be sure to graphically demonstrate the distribution of response at all time points, including stacked bar graphs. We are especially interested in the percentage of patients at any given time point with IGF-1 SDS >+2.**
- **Please provide a detailed analysis of reasons for dose reductions and study discontinuations, in particular as a consequence of glucose intolerance.**
- **With respect to your analysis of glucose intolerance, please analyze patients with fasting blood glucose (FBG) values ≤100 mg/dL at baseline separately from those with FBG values >100 mg/dL at baseline. In each instance, provide appropriate shift tables, and clinical narratives for patients with sustained or transient FBG values >126 mg/dL or sustained FBG values between 100 and 126 mg/dL.**

DECISIONS (AGREEMENTS) REACHED:

N/A

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

N/A

ACTION ITEMS:

N/A

ATTACHMENTS/HANDOUTS:

Statistical handout-submission of efficacy datasets

PRE-NDA MEETING HANDOUT
SUBMISSION OF EFFICACY DATASETS

Please follow the guidance for the submission of electronic data. This guidance may be found at www.fda.gov/cder/guidance. Choose Electronic Submissions and then choose #3. In the guidance document, go to K. Item 11: Case Report Tabulations (CRT's).

This handout provides further detail regarding the submission of efficacy data.

Submit the following efficacy datasets to the FDA electronic data room (EDR):
1. Primary efficacy dataset
2. Secondary efficacy dataset(s)

These datasets should contain the following variables:
1. unique patient ID
2. center number
3. race
4. age
5. gender
6. treatment group
7. week or month (i.e. visit decoded) where zero denotes the time of randomization
   - this variable is present when the data was collected at several visits; it will be missing when there Is only one record per patient
8. other important demographic/prognostic variables
9. last week completed for the patient
10. completer? (1=yes patient completed whole study, 0=patient discontinued early)
11. LOCF indicator variable (1=record contains the last efficacy value on study; 0=not the last value
12. raw and derived data for the efficacy variables
    - derived data (e.g. change from baseline or percent change from baseline data)
    - baseline should be included with each record as well as for the time 0 record
    - the value at that visit

Provide in hardcopy to the statistical reviewer a printout of the PROC CONTENTS and a printout of about 50 observations for each efficacy dataset.

The following is a general example of how the primary efficacy data may be recorded for two patients; patient 21 completed the study and patient 33 did not complete.

Pt	Ctr	Race	Gender	Trt	Week	Last week	compl	Locf	Base Eff	Eff	CH Eff
21	2	1	1	1	-2	6	1	0	BX	X	x-bx
21	2	1	1	1	0	6	1	0	BX	BX	0
21	2	1	1	1	2	6	1	0	BX	X	x-bx
21	2	1	1	1	4	6	1	0	BX	X	x-bx
21	2	1	1	1	6	6	1	1	BX	X	x-bx
33	3	1	2	0	-2	2	0	0	BX	X	x-bx
33	3	1	2	0	0	2	0	0	BX	BX	0
33	3	1	2	0	2	2	0	1	BX	X	x-bx

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/s/

Kati Johnson
2/22/2006 08:37:19 AM

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/s/

Kati Johnson
6/27/2006 10:26:32 AM

ACTION PACKAGE CHECKLIST

Application Information			
BLA # NDA # 20-604	BLA STN# NDA Supplement # 040	If NDA, Efficacy Supplement Type	
Proprietary Name: Serostim Established Name: somatropin [rDNA origin] for injection Dosage Form:		Applicant: EMD Serono	
RPM: Kati Johnson		Division: DMEP`	Phone # 301-796-1234

NDAs: NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: X 505(b)(1) ☐ 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)	505(b)(2) NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): Provide a brief explanation of how this product is different from the listed drug. ☐ If no listed drug, check here and explain: **Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct.** ☐ Confirmed ☐ Corrected Date:

❖ User Fee Goal Date ❖ Action Goal Date (if different)	7/14/07
❖ Actions	
• Proposed action	X☐ AP ☐ TA ☐AE ☐ NA ☐CR
• Previous actions *(specify type and date for each action taken)*	X☐ None
❖ Advertising *(approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed *(indicate dates of reviews)*	X☐ Requested in AP letter ☐ Received and reviewed

❖ Application Characteristics	
Review priority: X Standard ☐ Priority Chemical classification (new NDAs only): NDAs, BLAs and Supplements: ☐ Fast Track ☐ Rolling Review ☐ CMA Pilot 1 ☐ CMA Pilot 2 X Orphan drug designation NDAs: Subpart H ☐ Accelerated approval (21 CFR 314.510) ☐ Restricted distribution (21 CFR 314.520) Subpart I ☐ Approval based on animal studies BLAs: Subpart E ☐ Accelerated approval (21 CFR 601.41) ☐ Restricted distribution (21 CFR 601.42) Subpart H ☐ Approval based on animal studies NDAs and NDA Supplements: ☐ OTC drug Other: Other comments:	
❖ Application Integrity Policy (AIP)	N/A
• Applicant is on the AIP	☐ Yes ☐ No
• This application is on the AIP	☐ Yes ☐ No
• Exception for review *(file Center Director's memo in* Administrative Documents *section)*	☐ Yes ☐ No
• OC clearance for approval *(file communication in* Administrative Documents *section)*	☐ Yes ☐ Not an AP action
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes X No
• Press Office notified of action	☐ Yes **X** No
• Indicate what types (if any) of information dissemination are anticipated	**X** None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

❖ Exclusivity	
• NDAs: Exclusivity Summary (approvals only) *(file Summary in* Administrative Documents *section)*	X Included
• Is approval of this application blocked by any type of exclusivity?	X No ☐ Yes
• NDAs/BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	XNo ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• NDAS: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	X No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	X No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	X No ☐ Yes If yes, NDA # and date exclusivity expires:
❖ Patent Information (NDAs and NDA supplements only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	**X** Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified
• [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for **each** paragraph IV certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's	☐ Yes ☐ No

notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).	
*If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*	
(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?	☐ Yes ☐ No
*If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**No**," continue with question (3).*	
(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).	☐ Yes ☐ No
*If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*	
(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?	☐ Yes ☐ No
*If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**No**," continue with question (5).*	
(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced	☐ Yes ☐ No

within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	
Summary Reviews	
❖ Summary Reviews (e.g., Office Director, Division Director) *(indicate date for each review)*	X Division Director, 8/14/07
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) *(indicate date)*	N/A
Labeling	
❖ Package Insert	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	X
❖ Patient Package Insert	N/A
• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Medication Guide	N/A
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (**full color** carton and immediate-container labels)	N/A
• Most-recent division-proposed labels (only if generated after latest applicant submission)	
• Most recent applicant-proposed labeling	
❖ Labeling reviews and minutes of any labeling meetings *(indicate dates of reviews and meetings)*	☐ DMETS ☐ DSRCS ☐ DDMAC X SEALD X Other reviews PM labeling ☐ Memos of Mtgs

Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) *(indicate date of each review)*	Not included
❖ NDA and NDA supplement approvals only: Exclusivity Summary *(signed by Division Director)*	X Included
❖ AIP-related documents • Center Director's Exception for Review memo • If AP: OC clearance for approval	N/A
❖ Pediatric Page (all actions)	Not included-no indication granted
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. *(Include certification.)*	X Verified, statement is acceptable
❖ Postmarketing Commitment Studies	X None
• Outgoing Agency request for post-marketing commitments *(if located elsewhere in package, state where located)*	
• Incoming submission documenting commitment	
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	X
❖ Internal memoranda, telecons, email, etc.	N/A
❖ Minutes of Meetings	
• Pre-Approval Safety Conference *(indicate date; approvals only)*	N/A
• Pre-NDA/BLA meeting *(indicate date)*	☐ No mtg 2/8/06
• EOP2 meeting *(indicate date)*	X No mtg
• Other (e.g., EOP2a, CMC pilot programs)	N/A
❖ Advisory Committee Meeting	X No AC meeting
• Date of Meeting	
• 48-hour alert or minutes, if available	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A
CMC/Product Quality Information	
❖ CMC/Product review(s) *(indicate date for each review)*	N/A
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer *(indicate date for each review)*	X None
❖ BLAs: Product subject to lot release (APs only)	☐ Yes ☐ No
❖ Environmental Assessment (check one) (original and supplemental applications)	
• X Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	4/11/07
• ☐ Review & FONSI *(indicate date of review)*	
• ☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) *(indicate date of each review)*	N/A ☐ Not a parenteral product
❖ Facilities Review/Inspection	N/A
❖ NDAs: Facilities inspections (include EER printout)	Date completed: ☐ Acceptable ☐ Withhold recommendation

❖ BLAs: Facility-Related Documents • Facility review *(indicate date(s))* • Compliance Status Check (approvals only, both original and supplemental applications) *(indicate date completed, must be within 60 days prior to AP)*	N/A ☐ Requested ☐ Accepted ☐ Hold
❖ NDAs: Methods Validation	☐ Completed ☐ Requested ☐ Not yet requested X Not needed
Nonclinical Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	N/A
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☐ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No carc
❖ ECAC/CAC report/memo of meeting	
❖ Nonclinical inspection review Summary (DSI)	☐ None requested
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	7/12/07, addendum 7/12/07
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	X
❖ Clinical consult reviews from other review disciplines/divisions/Centers *(indicate date of each review)*	X None
❖ Microbiology (efficacy) reviews(s) *(indicate date of each review)*	X Not needed
❖ Safety Update review(s) *(indicate location/date if incorporated into another review)*	X
❖ Risk Management Plan review(s) (including those by OSE) *(indicate location/date if incorporated into another review)*	N/A
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date of each review)*	X Not needed
❖ DSI Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested
• Clinical Studies	X
• Bioequivalence Studies	
• Clin Pharm Studies	
❖ Statistical Review(s) *(indicate date for each review)*	☐ None 7/6/07
❖ Clinical Pharmacology review(s) *(indicate date for each review)*	X None

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE’s Office of Regulatory Policy representative.

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

/s/

Kati Johnson
8/16/2007 11:14:52 AM