

Effects of Tesamorelin (TH9507), a Growth Hormone-Releasing Factor Analog, in Human Immunodeficiency Virus-Infected Patients with Excess Abdominal Fat: A Pooled Analysis of Two Multicenter, Double-Blind Placebo-Controlled Phase 3 Trials with Safety Extension Data

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Context: HIV patients treated with antiretroviral therapy (ART) often develop increased visceral adipose tissue (VAT).

Objective: Our objective was to perform a pooled analysis of two phase-3 studies of tesamorelin in ART-treated HIV patients with excess abdominal fat.

Design and Setting: Two multicenter, international studies were conducted; a 26-wk randomized, placebo-controlled primary intervention phase was followed by a 26-wk safety extension.

Patients: A total of 806 ART-treated HIV patients with excess abdominal fat were randomized in a 2:1 fashion to receive tesamorelin 2 mg (n = 543) or placebo (n = 263) sc daily. At wk 26, patients initially on tesamorelin were rerandomized to 2 mg tesamorelin (T-T group, n = 246) or placebo (T-P, n = 135) for an additional 26 wk, whereas patients on placebo were switched to tesamorelin (P-T, n = 197).

Interventions: Tesamorelin (GHRH¹⁻⁴⁴) at a dose of 2 mg or identical placebo, sc, was given daily.

Main Outcome Measure: We evaluated percent change in VAT by computed tomography scan at wk 26.

Results: At wk 26, VAT decreased significantly in tesamorelin-treated patients (-24 ± 41 vs. 2 ± 35 cm², tesamorelin vs. placebo, $P < 0.001$; treatment effect, -15.4%). No significant changes were observed in abdominal sc adipose tissue (-2 ± 32 vs. 2 ± 29 cm², $P = 0.08$; treatment effect, -0.6%). Treatment with tesamorelin resulted in significant decreases in triglycerides (-37 ± 139 vs. 6 ± 112 mg/dl, $P < 0.001$; treatment effect, -12.3%) and cholesterol to high-density lipoprotein ratio (-0.18 ± 1.00 vs. 0.18 ± 0.94 , $P < 0.001$; treatment effect, -7.2%) vs. placebo. Tesamorelin improved body image [belly appearance distress ($P = 0.002$)], patient rating of belly profile ($P = 0.003$), and physician rating of belly profile ($P < 0.001$). Mean IGF-I increased 108 ± 112 vs. -7 ± 64 ng/ml ($P < 0.001$ vs. placebo). At wk 52, decreases in VAT [-35 ± 50 cm² ($-17.5 \pm 23.3\%$)], waist circumference (-3.4 ± 6.0 cm), triglycerides (-48 ± 182 mg/dl), cholesterol (-8 ± 38 mg/dl), and non-high-density lipoprotein (-7 ± 38 mg/dl) were maintained (all $P < 0.001$ vs. original baseline) in the T-T group. Treatment with tesamorelin was generally well tolerated. No clinically meaningful differences were observed between groups in glucose parameters at wk 26 and 52.

Conclusions: Treatment with tesamorelin reduces VAT and maintains the reduction for up to 52 wk, preserves abdominal sc adipose tissue, improves body image and lipids, and is overall well tolerated without clinically meaningful changes in glucose parameters. (*J Clin Endocrinol Metab* 95: 4291–4304, 2010)

HIV-infected patients treated with antiretroviral therapy (ART) often develop significant changes in body composition with excess abdominal visceral fat and reduction in abdominal sc fat (1). These changes may contribute to distress over body dysmorphia and reduced quality of life (2). In addition, these changes are associated with metabolic abnormalities including dyslipidemia (3) and may contribute to increased cardiovascular disease in this population (4, 5). HIV-infected patients with increased visceral adiposity demonstrate reductions in GH secretion (6), and we hypothesized that administration of a GHRH (tesamorelin) may induce increased endogenous GH secretion, reduce excess abdominal fat, and improve metabolic and body image abnormalities in this patient population (7). Two similar, but independent phase-3 studies have now been completed with tesamorelin (8–10). The results of these two large studies demonstrated consistent effects to reduce visceral adipose tissue (VAT) and improve body image. Effects on lipids were significant in the first study and trended but did not reach statistical significance in the second study. The primary data from these two studies have now been pooled to further investigate primary and secondary endpoints as well as to determine the effects in specific subgroups, *e.g.* ART class and baseline impaired fasting glucose (IFG), which were not previously performed. Moreover, the pooled analysis investigated the relationship of change in VAT to specific body image and quality of life endpoints and gives more comprehensive data on the effects among women and safety.

Materials and Methods

Design

Two similar randomized placebo-controlled phase-3 trials were performed to assess the efficacy and safety of tesamorelin (8–10). In brief, each study included a randomized placebo-controlled 6-month primary phase followed by a safety extension, whereby patients originally randomized to placebo were switched to tesamorelin and those originally randomized to tesamorelin were randomized to continue on tesamorelin or receive placebo for an additional 26 wk.

Entry criteria for both studies were identical. HIV-infected patients, age 18–65 yr, with CD4 cell counts higher than 100 cells/mm³ and viral load less than 10,000 copies/ml, receiving a stable ART for at least 8 wk and with evidence of abdominal fat accumulation (waist circumference $\geq$ 95 cm and waist to hip ratio $\geq$ 0.94 for males and waist circumference $\geq$ 94 cm and waist to hip ratio $\geq$ 0.88 for females) were recruited (11). Subjects were excluded with 1) fasting glucose of 150 mg/dl or higher

or known history of type I or type II diabetes mellitus requiring medication or 2) history of malignancy or active neoplasm. For a detailed list of exclusion criteria, see Refs. 8–10. Each study was approved by the Institutional Review Board at each site, and participants provided written informed consent.

Study procedures

The primary efficacy phase included assessments at wk 6, 13, 19, and 26 (8–10). Subjects completing the 26-wk efficacy phase were asked to participate in a 26-wk extension phase. Continued eligibility was confirmed based on glucose less than 150 mg/dl. Assessments occurred at wk 32, 39, 45, and 52.

Intervention, randomization, and blinding

Subjects were randomized in a 2:1 fashion (tesamorelin or placebo) to tesamorelin 2 mg sc daily or identical placebo for the primary efficacy phase. Active drug and placebo were provided by Theratechnologies Inc. Randomization was stratified on the basis of the use of testosterone and the presence of IFG (glucose $>$ 110 mg/dl and $<$ 126 mg/dl) or diet-controlled diabetes (glucose $>$ 126 mg/dl but $<$ 150 mg/dl) at screening (first study) or by site and diabetes condition at screening (second study). Investigator, sponsor, and patients were blinded to treatment assignment in all phases of the study. Tesamorelin and placebo were provided as lyophilized powder in two 3.0-ml vials of identical appearance. Subjects were instructed to reconstitute each vial with 1.1 ml sterile water and self-administer by sc injection once a day until the end of the study. Eligible subjects entering the extension phase were rerandomized in a blinded fashion. Subjects initially randomized to tesamorelin were rerandomized in a 1:3 ratio (first study) or 1:1 ratio (second study) to receive tesamorelin (T-T) (2 mg sc daily) or identical placebo (T-P). Subjects receiving placebo were switched to tesamorelin (P-T), using identical doses as in the first phase of the study (see Fig. 1).

Compliance

Treatment compliance was assessed by recording the number of vials (used, unused, or broken) returned at the study visits.

Safety

Subjects were discontinued if asymptomatic with fasting glucose higher than 180 mg/dl or symptomatic with fasting glucose lower than 180 mg/dl or for hypersensitivity reaction beyond the local injection site (8–10). A data safety monitoring board monitored adverse events (AEs) for each study.

Laboratory methods

Body composition, biochemical testing, and body image parameters were determined as previously described (8, 10) (see Supplemental Methods, published on The Endocrine Society's Journals Online web site at <http://jcem.endojournals.org>).

Statistical analysis

Statistical analyses were performed by Octagon Research Solutions (Wayne, PA). The minimum difference needed to detect a clinically relevant difference between tesamorelin and placebo

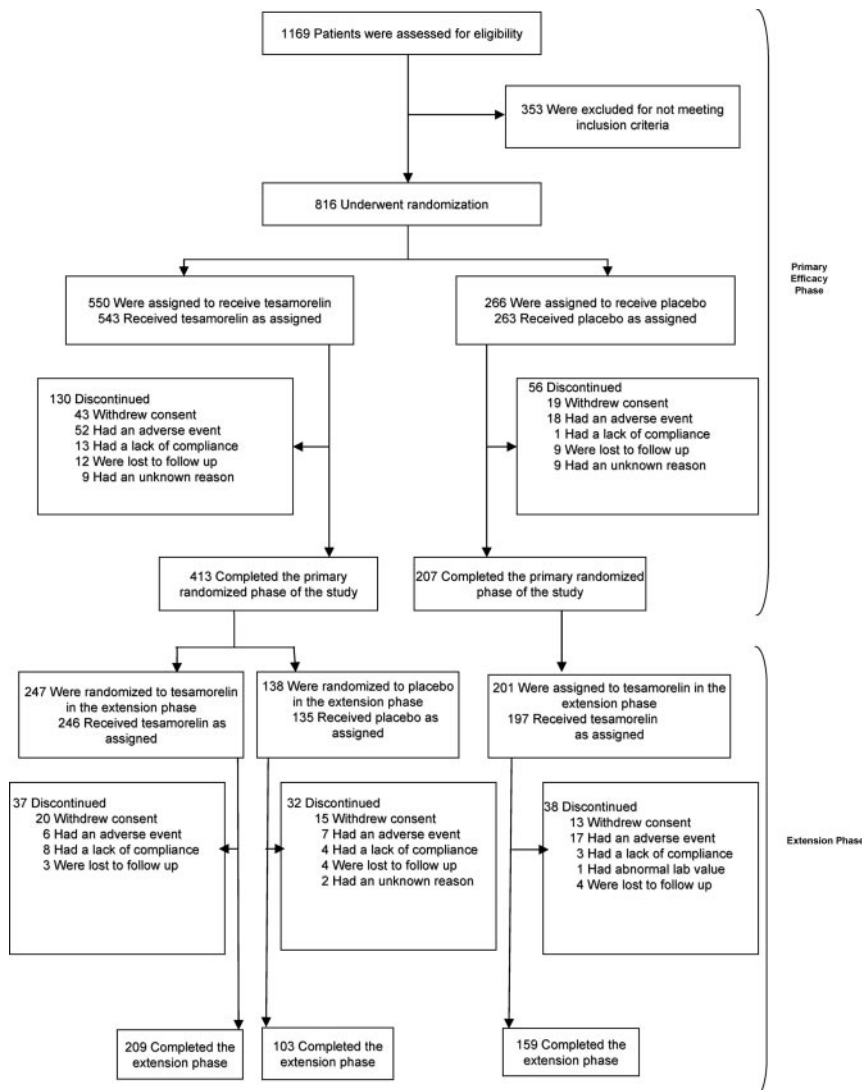


FIG. 1. Enrollment and outcomes.

in VAT, the primary endpoint, was considered to be 8% after consultation with the U.S. Food and Drug Administration (FDA) and based on the recommendation of an expert panel hosted by the Forum for Collaborative Research (12) for each study. Secondary endpoints included IGF-I, triglycerides, total cholesterol to high-density lipoprotein (HDL) cholesterol ratio, and patient-reported outcomes related to body image.

Because each study used similar inclusion and exclusion criteria, endpoint assessments, study design, and statistical analyses, the primary data from each study were pooled for analysis. The pooled statistical analysis was a prespecified analysis, which was part of the Integrated Summary of Efficacy report (requested by the FDA for a New Drug Application Submission) after the individual studies were completed. For each study, there was no effect of enrollment site in the model. Secondary models for VAT and trunk fat were constructed with use of testosterone, IFG/diabetes, age, gender, ART regimen at baseline, and change in ART therapy as covariates. Inclusion of these covariates did not alter the results of the analysis.

The safety and intent-to-treat populations were defined as all randomized subjects who were exposed to study drug. (*i.e.* injection of at least one dose of study drug). These analyses used all

available data on patients including partial data from patients who discontinued. Comparison of variables at baseline was made using an ANOVA model including treatment group and study. The treatment effect in the primary efficacy endpoint was tested using an analysis of covariance (ANCOVA) on the natural log ratio of VAT at wk 26 to baseline VAT. The primary ANCOVA model included treatment, natural log baseline VAT, and study. Using a highly stringent analysis to account for type I error in the pooling of two previously analyzed studies, a *P* value of ≤ 0.001 would be considered statistically significant.

The treatment effect of tesamorelin for primary and secondary variables was estimated by the placebo *vs.* tesamorelin difference in least-squares means from the ANCOVA described above, using the intent-to-treat population and the last-observation-carried-forward method for imputation of missing data as accepted by the FDA in the prespecified statistical analysis plan. Additional sensitivity analyses were performed using the mixed-model repeated-measures method. The change from baseline to wk 26 in lipid levels was analyzed using an ANCOVA model to account for baseline level, the use of lipid-lowering treatments, and study. Ranked ANCOVA models were fitted for belly size evaluation change score, belly appearance distress, and belly profile.

For the safety extension phase, comparisons were made for VAT and secondary variables between those patients originally assigned to tesamorelin and then randomized to stay on tesamorelin (T-T group) or switch to placebo (T-P group) with ANCOVA. Within-group changes from baseline to wk 52 for each treatment group (T-T, T-P, and P-T)

were tested with repeated-measures ANOVA.

For the safety analyses in both the primary efficacy phase and the safety extension phase, all clinical laboratory values were summarized by treatment group using descriptive statistics. For the primary efficacy phase, the 95% confidence intervals (CIs) are presented for overall AE and serious AE (SAE) rates as well as for AEs seen in more than 10 and 5% of patients, respectively.

Results

For the first study, 570 subjects were screened and 412 were randomized. For the second study, 599 subjects were screened and 404 were randomized. In the primary efficacy phase (0–26 wk), subjects were randomized 2:1 tesamorelin to placebo, resulting in 543 patients receiving tesamorelin and 263 receiving placebo (Fig. 1). Of these subjects, a similar percentage, 207 in the placebo group

TABLE 1. Baseline demographics and clinical characteristics of the patients entering the primary randomized study (n = 806) (0–26 wk)

Variables	Tesamorelin (n = 543)	Placebo (n = 263)
Age (yr)	47.5 ± 7.4	47.9 ± 7.6
Male/female ratio (%)	85.6/14.4	83.7/16.3
Race (%)		
White	77.0	74.1
Black	13.1	12.9
Other	10.0	13.0
Weight (kg)	89.3 ± 13.8	88.6 ± 14.6
BMI (kg/m ²)	29.0 ± 4.2	29.0 ± 4.2
Waist circumference (cm)	105 ± 9	105 ± 9
Waist-to-hip ratio	1.00 ± 0.07	1.00 ± 0.07
Viral Load (%)		
Undetectable	75.0	78.3
50–400 copies/ml	16.9	15.2
>400 copies/ml	8.1	6.5
CD4 cell count (cells/mm ³)	603 ± 295	592 ± 281
CD4 cell classification (%)		
<250 cells/mm ³	8.8	8.7
≥250 cells/mm ³	91.2	91.3
Lipodystrophy rating (%)		
Abdominal lipohypertrophy	100	100
Lipoatrophy of face or limbs	69.8	69.2
Fasting blood glucose (%)		
≤110 mg/dl	70.2	69.2
110–125 mg/dl	22.4	22.7
≥125 mg/dl	7.4	8.1
Use of testosterone (%)	21.4	17.5
Use of lipid-lowering agents (%)	45.7	44.9

(79%) and 413 in the tesamorelin group (76%), completed 26 wk of treatment (Fig. 1).

The baseline characteristics of the study subjects are shown in Table 1. One hundred twenty-one subjects (15%) were female. Twenty-two percent of the subjects had IFG tolerance, and 7.4% had mild diet-controlled diabetes with a fasting glucose higher than 126 and lower than 150 mg/dl at baseline. The proportion of patients receiving specific ART regimens was comparable between groups and was as follows: nucleoside reverse transcriptase inhibitor (NRTI) plus non-NRTI (NNRTI) (33%), NRTI plus protease inhibitor (45%), NRTI plus NNRTI/protease inhibitor (10%), NRTIs alone (5%), and other (7%). Demographic, metabolic, and body composition parameters were not different at baseline between the groups (Tables 1 and 2).

Primary efficacy phase (wk 0–26)

VAT decreased significantly in tesamorelin-treated patients [-24 ± 41 (-13.1%) *vs.* 2 ± 35 ($+2.3\%$) cm², tesamorelin *vs.* placebo, $P < 0.001$, equivalent to a -15.4% treatment effect of tesamorelin relative to placebo], whereas no significant changes were observed in abdominal sc adipose tissue (SAT) [-2 ± 32 ($+0.7\%$) *vs.* 2 ± 29 ($+1.3\%$) cm², $P = 0.08$, -0.6% treatment effect]

(Fig. 2 and Table 2). Similar results were seen using the mixed-model repeated-measures approach. Trunk fat significantly decreased in subjects receiving tesamorelin (Table 2). Limb fat differed between the tesamorelin- and placebo-treated patients at wk 26, but the change in the tesamorelin group was not different from baseline, and the change from baseline was equivalent to 0.2%. Lean body mass increased significantly (Table 2). Waist circumference decreased significantly in the tesamorelin- *vs.* placebo-treated patients (Table 2). No significant differences in body mass index (BMI) were observed between the groups.

The effect of tesamorelin on VAT was similar among subjects stratified by baseline ART regimen (Supplemental Fig. 1), and there was no treatment-by-ART interaction ($P = 0.82$). In addition, the effect of tesamorelin in males was similar to that in females at 26 wk, with no statistically significant treatment-by-gender interaction [percent change in VAT for males was -13.2 *vs.* 2.5% ($P < 0.001$) and for females was -12.5 *vs.* 1.4% ($P = 0.001$) for tesamorelin *vs.* placebo, respectively].

In the pooled analysis, significant effects to reduce triglycerides [treatment effect, -43 mg/dl (95% CI = -54 to -21), -12.3% , $P < 0.001$] and total cholesterol to HDL [treatment effect, -0.36 (95% CI = -0.46 to -0.19), -7.2% , $P < 0.001$] were observed. Less significant but favorable effects of tesamorelin relative to placebo were seen for total cholesterol (-2.3% , $P = 0.01$), HDL ($+3.0\%$, $P = 0.06$), and non-HDL (-3.9% , $P = 0.001$) (Table 2 and Supplemental Fig. 2). No significant effects on fasting glucose, fasting insulin or 2 h glucose on oral glucose tolerance testing were seen in tesamorelin- *vs.* placebo-treated patients (Table 2). Similar results were obtained with an ANCOVA controlling for IFG/diabetes condition at screening. There was no interaction between IFG/diabetes condition and treatment. Mean glycated hemoglobin (HbA_{1c}) increased 0.14% from baseline in the tesamorelin-treated group compared with 0.02% in the placebo group [treatment effect, 0.12% (95% CI = 0.05–0.17), $P < 0.001$]. This change amounted to an increase from 5.26 to 5.39% in the tesamorelin-treated patients. Mean IGF-I levels increased generally within the physiological range of young adults in tesamorelin-treated patients ($84.1 \pm 101.3\%$, $P < 0.001$ *vs.* placebo) (Table 2). Sixty-four percent of patients treated with tesamorelin for 26 wk had an age- and gender-based IGF-I sd score (SDS) of 3 or less.

Treatment with tesamorelin was associated with improvement in body image, which was at $P < 0.001$ for physician-rated belly profile, $P = 0.002$ for belly appearance distress, and $P = 0.003$ for patient-reported belly profile (Table 2). On the health-related quality of life

TABLE 2. Changes from baseline in body composition, lipid levels, biochemical measures, glycemic measures, belly image, and HRQOL parameters in the primary efficacy phase

Variables	Baseline value		Change from baseline (%) at 26 wk		Absolute difference (95% CI)	Relative difference (%)	P value
	Tesamorelin (n = 543)	Placebo (n = 263)	Tesamorelin (n = 543)	Placebo (n = 263)			
Body composition							
VAT (cm ²)	182 ± 82	182 ± 87	-24 ± 41 (-13.1)	2 ± 35 (2.3)	-26 (-32 to -21)	-15.4	<0.001
SAT (cm ²)	231 ± 124	233 ± 123	-2 ± 32 (0.7)	2 ± 29 (1.3)	-4 (-9 to 0)	-0.6	0.08
Ratio of VAT to SAT	1.27 ± 1.60	1.22 ± 1.41	-0.24 ± 0.86 (-13.1)	0.05 ± 0.59 (2.2)	-0.29 (-0.38 to -0.18)	-15.3	<0.001
Trunk Fat (kg)	15.1 ± 5.5	15.2 ± 5.4	-0.9 ± 2.0 (-6.5)	0.3 ± 1.5 (2.4)	-1.2 (-1.5 to -0.9)	-8.9	<0.001
Waist circumference (cm)	105 ± 9	105 ± 9	-2.4 ± 5.2 (-2.3)	-0.8 ± 4.4 (-0.8)	-1.6 (-2.3 to -0.9)	-1.5	<0.001
Waist-to-hip ratio	1.05 ± 0.07	1.05 ± 0.07	-0.03 ± 0.05 (-2.4)	-0.01 ± 0.05 (-1.3)	-0.02 (-0.02 to -0.01)	-1.1	<0.001
Fat in limbs (kg)	7.3 ± 4.5	7.5 ± 4.4	-0.1 ± 0.9 (0.2)	0.2 ± 0.9 (3.0)	-0.3 (-0.4 to -0.1)	-2.8	0.001
Lean mass (kg)	62.2 ± 10.2	61.0 ± 10.4	1.3 ± 2.4 (2.1)	-0.14 ± 1.9 (-0.1)	1.4 (1.1–1.8)	2.2	<0.001
BMI (kg/m ²)	29.0 ± 4.2	29.0 ± 4.2	0.01 ± 1.31 (0.1)	0.05 ± 1.15 (0.2)	-0.04 (-0.3–0.2)	-0.1	0.68
Lipid levels							
Triglycerides (mg/dl)	245 ± 227	228 ± 144	-37 ± 139 (-2.6)	6 ± 112 (9.7)	-43 (-54 to -21)	-12.3	<0.001
Cholesterol							
Ratio of total cholesterol to HDL	4.62 ± 1.53	4.45 ± 1.44	-0.18 ± 1.00 (-1.6)	0.18 ± 0.94 (5.6)	-0.36 (-0.46 to -0.19)	-7.2	<0.001
Total cholesterol							
HDL (mg/dl)	194 ± 44	192 ± 38	-4 ± 33 (-0.7)	1 ± 27 (1.6)	-5 (-10 to -1)	-2.3	0.01
Non-HDL (mg/dl)	45 ± 14	46 ± 15	1 ± 8 (3.4)	-1 ± 10 (0.4)	2 (-0–2.5)	3.0	0.06
Biochemical measures							
IGF-I (ng/ml)	149 ± 42	146 ± 36	-5 ± 31 (-1.0)	2 ± 26 (2.9)	-7 (-10 to -3)	-3.9	0.001
Glycemic measures							
Glucose (mg/dl)							
Fasting	154 ± 63	159 ± 69	108 ± 112 (84.1)	-7 ± 64 (0.0)	115 (99–128)	84.1	<0.001
At 2 h							
Fasting insulin (μIU/ml)	98 ± 14	98 ± 16	3 ± 16 (3.8)	1 ± 17 (2.0)	2 (-0–4)	1.8	0.10
HbA _{1c} (%)	113 ± 37	114 ± 40	3 ± 38 (7.7)	3 ± 43 (9.1)	0 (-7–6)	-1.4	0.82
Belly image and HRQOL parameters							
(scores)							
Belly appearance distress	22.1 ± 23.0	22.1 ± 24.1	9.8 ± 28.0	5.9 ± 25.8	4 (1.4–6.4)		0.002
Patient-reported belly profile	3.3 ± 1.3	3.3 ± 1.3	-0.6 ± 1.3	-0.3 ± 1.1	-0.3 (0.1–0.5)		0.003
Physician-reported belly profile	3.1 ± 1.2	3.1 ± 1.2	-0.6 ± 1.1	-0.3 ± 1.1	-0.3 (0.1–0.4)		<0.001
HRQOL global analog scale	6.8 ± 1.6	6.7 ± 1.6	0.0 ± 1.5	-0.2 ± 1.5	0.2 (0.1–0.3)		0.029

Data are reported as mean ± SD unless otherwise indicated. To convert the values for triglycerides to millimoles per liter, multiply by 0.0113; to convert the values for total cholesterol and HDL cholesterol to millimoles per liter, multiply by 0.0259; to convert the values of IGF-I to nanomoles per liter, multiply by 0.131; to convert the values for glucose to millimoles per liter, multiply by 0.0555; to convert the values for insulin to picomoles per liter, multiply by 6.945. P values are for the comparison between the changes from baseline in the tesamorelin group and the placebo group.

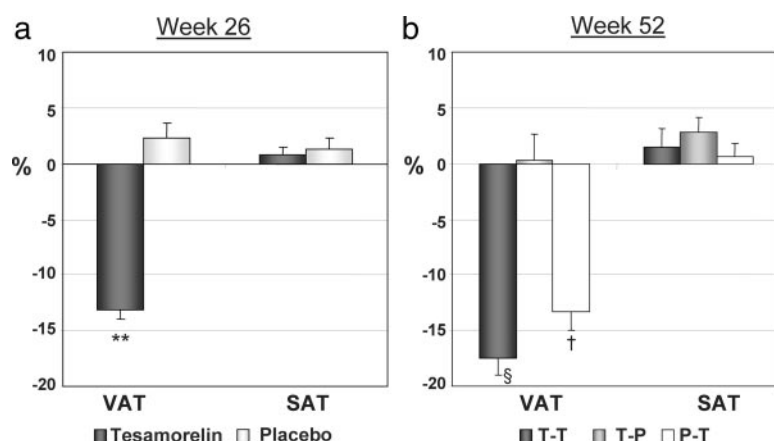


FIG. 2. Percent change from baseline in VAT and SAT at 26 (A) and 52 (B) weeks. Data are mean $\pm$ SEM. **, $P < 0.001$ vs. placebo; §, $P < 0.001$ vs. baseline and vs. T-P; †, $P < 0.001$ vs. baseline.

(HRQOL) global analog scale, subjects assigned to placebo deteriorated, whereas there was no change for subjects assigned to tesamorelin ($P = 0.029$) (Table 2). The changes in body image were significantly associated with the degree in reduction of VAT among the tesamorelin-treated patients (Table 3).

Data from the safety extension phase (wk 26–52)

Baseline characteristics of subjects entering the extension phase are shown in Table 4. At wk 52, improvements in VAT ($-35 \pm 50 \text{ cm}^2$), trunk fat ($-1.1 \pm 2.2 \text{ kg}$), waist circumference ($-3.4 \pm 6.0 \text{ cm}$), triglycerides ($-48 \pm 182 \text{ mg/dl}$), total cholesterol ($-8 \pm 38 \text{ mg/dl}$), and IGF-I ($78 \pm 110 \text{ ng/ml}$) were sustained in the T-T group (all $P < 0.001$ vs. baseline) whereas SAT and limb fat were preserved (Table 5). Seventy-seven percent of patients treated with tesamorelin for 52 wk had an age- and gender-based IGF-I SDS of 3 or less. No changes in glucose or insulin were seen after 52 wk of tesamorelin in the T-T group (Table 5).

Patients in the T-P group regained VAT after switching to placebo. The VAT level in this group was not significantly different from baseline at wk 52 ($-2 \pm 48 \text{ cm}^2$, $P = 0.18$ vs. baseline) (Fig. 2). A similar pattern was observed for trunk fat, although waist circumference remained re-

duced from baseline by 2 cm at 52 wk in those switching to placebo (Table 5). Improvements in belly appearance distress as well as in physician- and patient-rated belly profile persisted among patients in the T-T group. Patients in the T-P group (vs. T-T group) tended to lose improvements in belly appearance and patient-rated belly profile seen at wk 26, although the changes in these parameters at wk 52 were still significantly different from baseline (Table 5).

Safety

Overall AEs and treatment-related AEs were higher in the tesamorelin group, whereas AE's resulting in study discontinuation and SAEs were not different between the two groups based on 95% CIs in the primary efficacy phase (Table 6). One patient died in the tesamorelin group (lung adenocarcinoma metastatic), and one patient died in the placebo-treated group (arrhythmia). Events occurring in more than 10% of patients, arthralgias, headaches, and injection site bruising, were not different between the tesamorelin and placebo groups. For AEs occurring at more than 5% frequency, injection site erythema, pruritis, peripheral edema, and myalgias occurred more frequently in the tesamorelin group, with 95% CIs that did not overlap 0. No differences were seen in other AEs. The majority of patients in each of the treatment groups had undetectable viral load, and most had CD4 cell counts at least 250 cells/mm³ at baseline (Table 1). At wk 26, the percentages of patients shifting to higher viral load category were comparable between the groups and were 11.8% in the tesamorelin and 12.1% in the placebo group. Furthermore, the proportion of patients shifting from CD4 cell counts of at least 250 cells/mm³ to a lower CD4 cell count category was 2% in the two groups.

In the extension phase, overall AEs and SAEs were also similar between the tesamorelin and placebo groups (Table 7). Two deaths occurred, one in the T-T group (cor-

TABLE 3. Correlation between percent change in VAT and changes in belly image parameters at wk 26 in the primary efficacy phase

Belly image parameters	Tesamorelin (n = 542)		Placebo (n = 263)	
	Correlation coefficient ^a	P value	Correlation coefficient ^a	P value
Belly size	-0.179	<0.001	-0.059	0.344
Belly appearance distress	-0.229	<0.001	0.047	0.445
Patient-reported belly profile	0.341	<0.001	0.016	0.796
Physician-reported belly profile	0.219	<0.001	0.096	0.123

^a Spearman's rank correlation (ρ).

TABLE 4. Baseline demographics and clinical characteristics of the patients entering the extension phase (n = 578)

Variables	T-T (n = 246)	T-P (n = 135)	P-T (n = 197)
Age (yr)	47.7 ± 7.2	48.1 ± 7.1	48.3 ± 7.7
Male/female ratio (%)	89.0/11.0	88.1/11.9	86.8/13.2
Race (%)			
White	79.3	83.7	78.2
Black	11.8	7.4	10.7
Other	8.9	8.9	11.1
Weight (kg)	88.7 ± 13.3	90.7 ± 15.1	88.7 ± 14.5
BMI (kg/m ²)	28.6 ± 4.1	29.4 ± 4.3	28.8 ± 4.2
Waist circumference (cm)	104 ± 9	105 ± 10	104 ± 9
Waist-to-hip ratio	1.05 ± 0.07	1.05 ± 0.06	1.05 ± 0.06
Viral load (%)			
Undetectable	75.6	71.9	76.6
50–400 copies/ml	15.4	18.5	16.2
>400 copies/ml	8.9	8.9	7.1
CD4 cell count (cells/mm ³)	623 ± 309	596 ± 284	586 ± 270
CD4 cell classification (%)			
<250 cells/mm ³	6.5	9.6	8.6
≥250 cells/mm ³	93.5	90.4	91.4
Lipodystrophy rating (%)			
Abdominal lipohypertrophy	100	100	100
Lipoatrophy of face or limbs	70.7	70.4	71.6
Fasting glucose (%)			
≤110 mg/dl	71.8	67.4	71.3
110–125 mg/dl	25.3	22.2	21.5
≥125 mg/dl	2.9	10.4	7.2
Use of testosterone (%)	23.6	20.0	17.3
Use of lipid-lowering agents (%)	49.6	48.9	44.7

onary artery arteriosclerosis) and one in the P-T group (postprocedure hemorrhage) (Table 7). At wk 52, the percentages of patients shifting to higher viral load category were comparable between the groups and were 10.5% in the T-T, 11.5% in the T-P, and 8.0% in the P-T group. The percentages of patients shifting from CD4 cell counts of at least 250 cells/mm³ to the lower CD4 cell count category were 2.1% in the T-T, 0% in the T-P, and 2.1% in the P-T group.

During the primary efficacy phase, hypersensitivity reactions were seen in 2.9% of tesamorelin and 0.4% of placebo patients. Only one event, which occurred in a placebo-treated patient, was reported as an SAE. During the extension phase, hypersensitivity reactions were observed in 1.2, 0, and 4.1% of patients in the T-T, T-P, and P-T groups, respectively.

Antibodies

See Supplemental Results and Methods.

Compliance

Compliance from the first dose to wk 26 was 98.1 and 97.8% in the tesamorelin and placebo groups, respectively. In the extension phase, mean compliance was 95.2, 94.2, and 96.1% in the T-T, T-P, and P-T groups, respectively.

Discussion

Increased abdominal fat accumulation has been described in approximately 30% of HIV patients in the current era of highly active ART (HAART) (1, 13). The excess abdominal fat is uniquely composed primarily of excess VAT, because SAT is reduced (14). The excess in VAT may contribute to reduced QOL and patient distress (2). Moreover, excess VAT is associated with dyslipidemia (3) and increased coronary artery calcification in HIV patients (4). In a recent longitudinal study involving HIV patients on ART, increased VAT was one of three factors, along with age and low-density lipoprotein to contribute to coronary artery calcium progression (4). It is also known that GH secretion is inversely correlated with excess VAT in HIV patients and that reduced GH secretion may itself contribute independently to metabolic abnormalities in this population (6, 15). We hypothesized that increasing endogenous GH secretion via the use of a GH-releasing factor, tesamorelin, would improve body composition and metabolic endpoints in HIV patients receiving ART with excess abdominal fat. We have previously shown in two large, multicenter randomized phase-3 studies that use of tesamorelin reduces VAT in association with mean IGF-I levels comparable to what is observed in young adults (8–10). New data from the pooled analysis demonstrate that the great majority of patients treated for 1 yr with

TABLE 5. Changes from baseline in body composition, lipid levels, biochemical measures, glycemic measures, belly image, and HRQOL parameters in the extension phase

Variables	Baseline, mean ± sd			Change from baseline (%) at 52 wk, mean ± sd		
	T-T (n = 246)	T-P (n = 135)	P-T (n = 197)	T-T (n = 246)	T-P (n = 135)	P-T (n = 197)
Body composition						
VAT (cm ²)	187 ± 83	190 ± 82	186 ± 89	−35 ± 50 (−17.5) ^{c,e}	−2 ± 48 (0.3)	−25 ± 44 (−13.3) ^c
SAT (cm ²)	214 ± 120	231 ± 122	224 ± 121	−3 ± 42 (1.4)	1 ± 39 (2.8)	−1 ± 39 (0.6)
Ratio of VAT to SAT	1.43 ± 1.68	1.28 ± 1.92	1.30 ± 1.53	−0.31 ± 0.78 (−17.3) ^{c,e}	−0.01 ± 0.60 (−1.8)	−0.14 ± 0.56 (−13.3) ^c
Trunk fat (kg)	14.4 ± 5.1	15.7 ± 5.6	15.0 ± 5.4	−1.1 ± 2.2 (−7.7) ^{c,e}	0.3 ± 2.2 (2.6)	−0.8 ± 2.4 (−5.7) ^c
Waist circumference (cm)	104 ± 9	105 ± 10	104 ± 9	−3.4 ± 6.0 (−3.3) ^{c,e}	−2.0 ± 6.0 (−1.7) ^c	−3.0 ± 6.0 ^a (−2.8) ^a
Waist-to-hip ratio	1.05 ± 0.07	1.05 ± 0.06	1.05 ± 0.06	−0.03 ± 0.07 (−3.1) ^{c,d}	−0.02 ± 0.05 (−1.6) ^c	−0.03 ± 0.05 (−3.1) ^c
Fat in limbs (kg)	6.7 ± 4.2	7.1 ± 4.0	7.1 ± 4.1	−0.1 ± 1.0 (0.8)	0.0 ± 1.3 (2.6)	0.0 ± 1.4 (1.5)
Lean mass (kg)	62.7 ± 9.8	63.0 ± 9.8	61.6 ± 10.1	1.3 ± 2.7 (2.1) ^{c,e}	−0.1 ± 2.5 (−0.1)	1.4 ± 2.3 (2.5) ^c
BMI (kg/m ²)	28.6 ± 4.1	29.4 ± 4.3	28.8 ± 4.2	−0.11 ± 1.55 (−0.3)	0.05 ± 1.80 (0.3)	0.15 ± 1.57 (0.6)
Lipid levels						
Triglycerides (mg/dl)	261 ± 209	219 ± 155	230 ± 141	−48 ± 182 (−4.2) ^c	−11 ± 154 (0.6)	−14 ± 138 (3.6)
Cholesterol						
Ratio of Total Cholesterol to HDL	4.69 ± 1.56	4.53 ± 1.40	4.42 ± 1.32	−0.07 ± 1.44 (2.0)	0.11 ± 1.04 (4.3)	0.19 ± 1.06 (6.4)
Cholesterol						
Total (mg/dl)	194 ± 46	190 ± 40	194 ± 35	−8 ± 38 (−2.1) ^{c,d}	2 ± 36 (3.2)	−4 ± 33 (−1.5)
HDL (mg/dl)	45 ± 15	44 ± 13	47 ± 15	−1 ± 10 (−0.2) ^a	−1 ± 8 (1.0)	−3 ± 9 (−3.2) ^c
Non-HDL (mg/dl)	149 ± 44	145 ± 37	147 ± 35	−7 ± 38 (−1.1) ^{a,d}	3 ± 34 (4.5)	−1 ± 32 (0.4)
Biochemical measures						
IGF-I (ng/ml)	161 ± 64	150 ± 61	163 ± 73	78 ± 110 (63.1) ^{c,e}	−9 ± 52 (−0.7) ^a	73 ± 113 (56.0) ^c
Glycemic measures						
Glucose (mg/dl)						
Fasting	97 ± 13	102 ± 17	99 ± 17	2 ± 14 (2.9)	−2 ± 28 (−1.2)	1 ± 17 (2.2)
At 2 h	112 ± 34	112 ± 40	116 ± 40	1 ± 39 (6.4)	1 ± 34 (6.8)	5 ± 41 (8.1)
Insulin (μIU/ml)	19 ± 20	26 ± 31	21 ± 24	−0 ± 20 (28.8)	−7 ± 31 (8.3)	1 ± 28 (39.4)
HbA _{1c} (%)	5.23 ± 0.50	5.27 ± 0.47	5.32 ± 0.51	0.07 ± 0.37 (1.7)	0.08 ± 0.54 (1.8)	0.09 ± 0.36 (1.8)
Belly image and HRQOL parameters						
(scores)						
Belly appearance distress	22.5 ± 23.1	19.3 ± 19.1	20.6 ± 23.3	12.6 ± 29.4 ^{b,e}	8.1 ± 24.0 ^b	9.8 ± 27.4 ^c
Patient-reported belly profile	3.3 ± 1.3	3.3 ± 1.3	3.3 ± 1.3	−0.9 ± 1.4 ^{b,e}	−0.5 ± 1.2 ^b	−0.8 ± 1.4 ^b
Physician-reported belly profile	3.1 ± 1.2	3.2 ± 1.2	3.1 ± 1.3	−1.0 ± 1.3 ^b	−0.7 ± 1.3 ^b	−0.8 ± 1.2 ^b
HRQOL global analog scale	6.7 ± 1.6	6.9 ± 1.6	6.7 ± 1.5	0.2 ± 1.5	0.1 ± 1.5 ^a	0.2 ± 1.4 ^a

Data are reported as mean ± sd unless otherwise indicated. To convert the values for triglycerides to millimoles per liter, multiply by 0.0113; to convert the values for total cholesterol and HDL cholesterol to millimoles per liter, multiply by 0.0259; to convert the values of IGF-I to nanomoles per liter, multiply by 0.131; to convert the values for glucose to millimoles per liter, multiply by 0.0555; to convert the values for insulin to picomoles per liter, multiply by 6.945.

^a *P* < 0.05 for the within-group comparison between baseline and wk 52.

^b *P* < 0.01 for the within-group comparison between baseline and wk 52.

^c *P* < 0.001 for the within-group comparison between baseline and wk 52.

^d *P* < 0.05 for the comparison between the changes from baseline in the T-T group and the T-P group.

^e *P* < 0.001 for the comparison between the changes from baseline in the T-T group and the T-P group.

TABLE 6. AEs and SAEs in the primary efficacy phase (0–26 wk)

Events	% Patients		95% CI difference
	Tesamorelin (n = 543)	Placebo (n = 263)	
AE ^a			
% Patients with any event	78.3	71.1	0.0068–0.1365
Related to treatment	53.2	36.5	0.0955–0.2390
Resulting in study discontinuation	9.6	6.1	–0.0031–0.0730
Events reported in >10% of patients			
Arthralgia	13.3	11.0	–0.0251–0.0697
Headache	10.9	11.0	–0.0476–0.0444
Injection site bruising	7.4	10.3	–0.0718–0.0138
Events reported in >5% of patients			
Diarrhea	7.6	8.4	–0.0483–0.0320
Injection site erythema	8.5	2.7	0.0277–0.0885
Injection site pruritus	7.6	0.8	0.0433–0.0925
Edema peripheral	6.1	2.3	0.0110–0.0650
Fatigue	3.7	5.7	–0.0524–0.0120
Upper respiratory tract infection	4.2	6.5	–0.0565–0.0119
Nasopharyngitis	4.2	5.3	–0.0429–0.0211
Pain in extremity	6.1	4.6	–0.0171–0.0474
Myalgia	5.5	1.9	0.0109–0.0616
Back pain	3.1	5.3	–0.0528–0.0089
SAE ^a			
% Patients with any event	3.7	4.2	–0.0339–0.0239
All events reported			
Anemia	0.2	0.0	
Arrhythmia	0.0	0.4	
Cardiac arrest	0.0	0.4	
Cardiac failure congestive	0.2	0.0	
Abdominal hernia obstructive	0.0	0.4	
Diarrhea	0.2	0.0	
Small intestinal obstruction	0.2	0.0	
Chest pain	0.0	0.4	
Cholecystitis acute	0.0	0.4	
Hypersensitivity	0.0	0.4	
Sepsis	0.4	0.0	
Abdominal abscess	0.2	0.0	
Appendiceal abscess	0.2	0.0	
Appendicitis	0.0	0.4	
Bronchitis viral	0.2	0.0	
Perianal abscess	0.2	0.0	
Upper respiratory tract infection	0.2	0.0	
Humerus fracture	0.2	0.0	
Procedural pain	0.0	0.4	
Rib fracture	0.2	0.0	
Electrocardiogram abnormal	0.2	0.4	
Dehydration	0.2	0.0	
Arthralgia	0.2	0.0	
Mobility decreased	0.2	0.0	
Basal cell carcinoma ^b	0.2	0.0	
Breast cancer <i>in situ</i>	0.0	0.4	
Hodgkin's disease	0.0	0.4	
Rectal cancer ^b	0.2	0.0	
Cerebellar syndrome	0.2	0.0	
Neuropathy peripheral	0.2	0.0	
Trigeminal neuralgia	0.2	0.0	
Bipolar II disorder	0.2	0.0	
Dependence	0.2	0.0	
Major depression	0.0	0.4	
Benign prostatic hyperplasia	0.2	0.0	

^a Treatment emergent.^b This patient was determined to have a previously undisclosed history of cancer before randomization.

TABLE 7. AEs and SAEs in the extension phase (26–52 wk)

Events	% Patients		
	T-T (n = 246)	T-P (n = 135)	P-T (n = 197)
AE ^a			
% Patients with any event	62.6	60.0	74.1
Related to treatment	21.5	20.7	42.1
Resulting in study discontinuation	2.0	4.4	8.1
Events reported in >10% of patients			
Arthralgia	5.7	5.9	14.7
Events reported in >5% of patients			
Diarrhea	2.8	5.2	4.1
Injection site pruritus	2.0	0.0	8.1
Injection site erythema	1.2	0.0	6.6
Injection site pain	0.0	0.0	5.1
Upper respiratory tract infection	7.3	3.7	4.1
Sinusitis	4.9	0.0	5.1
Pain in Extremity	3.3	0.7	7.6
SAE ^a			
% Patients with any event	2.8	2.2	3.0
All events reported			
Arteriosclerosis coronary artery ^b	0.4	0.0	0.0
Chorioretinopathy	0.4	0.0	0.0
Abdominal pain	0.0	0.7	0.0
Intestinal perforation	0.0	0.0	0.5
Chest pain	0.4	0.0	0.0
Cellulitis	0.4	0.0	0.5
Ludwig's angina	0.0	0.7	0.0
Pneumonia	0.4	0.0	0.0
Postprocedural hemorrhage	0.0	0.0	0.5
Anal cancer ^c	0.0	0.7	0.0
Hodgkin's disease	0.0	0.0	0.5
Spontaneous abortion	0.4	0.0	0.0
Mental status changes	0.4	0.0	0.0
Nephrolithiasis	0.0	0.0	0.5
Asphyxia	0.0	0.0	0.5
Dyspnea	0.0	0.0	0.5

^a Treatment emergent.^b This patient had a known history of coronary artery disease.^c This patient was determined to have a previously undisclosed history of anal cancer.

tesamorelin will have an age- and gender-adjusted SDS within an acceptable range. The pooled analysis, constituting over 800 patients, is the largest intervention for abdominal fat changes in the HIV population.

The pooled analysis demonstrates a net reduction of VAT of 15.4% over 26 wk relative to placebo. For subjects rerandomized to placebo after 26 wk of treatment with tesamorelin, VAT was regained, but among those continuing with tesamorelin, the net reduction in VAT after 52 wk is approximately 18%, translating into a 3.4-cm reduction in waist circumference. This reduction in waist circumference is almost exclusively a result of a reduction in VAT, because tesamorelin did not have a significant effect on abdominal SAT. This is important because SAT is increasingly shown to be a beneficial fat depot contributing to improved cardiometabolic risk (16). In the general population, increased waist circumference and VAT have been shown to contribute independently to mortality above and beyond BMI (17) (18, 19), and thus, reduction

in waist circumference via a reduction in excess VAT may also reduce cardiovascular risk. The effects of tesamorelin were consistent among patients on different ART regimens and among women.

Treatment with tesamorelin resulted in significant reductions in triglycerides (−12.3%) and total cholesterol to HDL cholesterol ratio (−7.2%) relative to placebo in the pooled analysis. A somewhat stronger effect of tesamorelin was observed in the first phase-3 study compared with the second phase-3 for lipids, but the trends toward improvement in the tesamorelin group and deterioration in the placebo group were consistent in the two studies. In the combined analysis with additional power, we are able to show favorable effects of tesamorelin across multiple lipid parameters using a highly stringent *P* value. Nonetheless, the differences between the two studies demonstrate that heterogeneity may be seen in lipid responses to tesamorelin, and for some parameters, including total cholesterol (−2.3%) and HDL (+3.0%), the treatment effect *vs.* pla-

cebo, represented as percent change, was small and of unclear clinical significance. Increasing endogenous GH may reduce triglycerides and overall cholesterol levels through inhibition of *de novo* lipogenesis and increase in fat oxidation. Recent data suggest that, in the general population, increased waist circumference and triglyceride level together predict CVD mortality, independent of other cardiovascular risk markers (20), and thus, the improvement in these two parameters in HIV patients may be useful.

Tesamorelin improved body image distress and reduced patient and physician rating of belly image. These data suggest an important psychological benefit from tesamorelin. The improvement in distress related to body composition changes may allow patients to be more compliant with ART use, knowing that excess fat can be reduced even while therapy with ART is ongoing. In addition, there was a relative improvement in overall QOL between tesamorelin- and placebo-treated patients. The changes in body image distress and QOL were correlated with the reduction in VAT.

Glucose parameters, including fasting glucose, 2-h glucose on oral glucose tolerance testing, and fasting insulin were not significantly increased with tesamorelin relative to placebo. There was a slight but statistically significant increase in HbA_{1c} in tesamorelin- *vs.* placebo-treated patients, but the mean HbA_{1c} remained well within the normal range in the tesamorelin-treated group. With over 800 patients included in the pooled analysis, there was adequate statistical power to detect a safety signal for glucose, but a clinically meaningful signal was not observed for the overall group. Nonetheless, for a small number of individual patients, glucose levels may rise, and these should be monitored on therapy. In contrast to tesamorelin, a GH-releasing factor, even physiological dosing of GH, resulting in the same increase in IGF-I, resulted in a significant 20-point deterioration in 2-h glucose on oral glucose tolerance testing (21). The differences between the adverse effects of GH and minimal adverse effects of tesamorelin on glucose may relate to the more physiological effects of a GH-releasing factor to induce endogenous GH pulsatility. Our data suggest that at least for patients with mild elevations of fasting glucose (>110 and <150 mg/dl), tesamorelin is unlikely to further perturb glucose homeostasis in a clinically relevant way.

Overall dropout rates were similar in tesamorelin and placebo groups and had no impact on the results as confirmed in sensitivity analyses accounting for missing data. In terms of AEs, tesamorelin was associated with more AEs than placebo, but these were generally mild and most often related to injection site reactions, such as pruritis or erythema. SAEs and deaths were not different between

tesamorelin and placebo groups. One case of lung cancer was diagnosed in a tesamorelin-treated patient who had received tesamorelin for only 3 months in the study and whose diagnosis was made 5 months after the last dose of tesamorelin. In this patient, IGF-I levels remained within the normal range during treatment. From the pooled analysis, hypersensitivity reactions, defined as an itching erythematous reaction extending beyond the injection site, were observed in 2.9%. This percentage was consistent between the trials. These AEs were largely mild and treated by discontinuation from the study without known sequelae. Therefore, a small percentage, approximately 3%, of subjects receiving tesamorelin would be expected to have this side effect, necessitating discontinuation of treatment. Arthralgias were not different between the groups. In contrast, myalgias (5.5 *vs.* 1.9%) and edema (6.1 *vs.* 2.3%), although seen in relatively a small percentage of patients, were more common in patients receiving tesamorelin. A small percentage of patients receiving tesamorelin can therefore be expected to develop signs consistent with relative GH excess. AEs and SAEs during the extension phase were similar in frequency and scope to those in the primary efficacy phase and suggest that long-term dosing for up to 1 yr is generally well tolerated and associated with relatively few AEs, most of only mild to moderate intensity.

IgG antibodies to tesamorelin were seen in approximately 50% of subjects after 26 wk of treatment but diminished with time once therapy was discontinued, persisting in 18% of patient 26 wk off therapy. We did not observe any differences in the change in IGF-I or magnitude of decrease in VAT in those patients treated with tesamorelin with and without antibodies. Low-titer neutralizing antibodies were seen in small percentage and did not affect IGF-I or VAT.

No treatment strategies are now approved specifically for improvement in body composition among HIV patients. Although lifestyle modification may be useful to decrease abdominal fat accumulation in this population (22) and should be considered as an initial intervention in appropriate patients, this strategy has not been as consistent or robust in terms of VAT reduction as tesamorelin. Treatment with metformin has been shown to result in modest reductions in VAT but may result in loss of sc fat, whereas treatment with tesamorelin appears to be highly specific to reduce VAT and neutral to SAT (23). Neither rosiglitazone nor pioglitazone has been shown to reduce VAT in HIV-infected patients (24, 25).

The primary results of this pooled analysis demonstrate the degree to which one can expect critical variables to change with tesamorelin therapy among HIV-infected patients with abdominal fat accumulation in the context of

ART. These changes amount to a -26 cm^2 , -15.4% treatment effect for VAT and a -43 mg/dl , -12.3% treatment effect for triglycerides, with improvement in body image parameters. These effects have to be balanced against the safety profile of the drug. A small percentage of patients will experience local hypersensitivity reactions, and individual patients may experience glucose increases and signs of GH excess. Nonetheless, the overall safety profile in over 800 patients was good. Data from this pooled analysis suggest that tesamorelin may be a useful strategy with an acceptable risk-benefit profile to significantly reduce VAT and improve body image, while improving lipids in those HIV-infected patients with excess abdominal fat accumulation in the context of ART.

Acknowledgments

We thank the patients for their participation in the research studies. We also thank Drs. Sophie-Elise Michaud and Monika Zoltowska for their contribution to the study and its analysis and Dr. Gary Koch for his advice on the statistical analyses.

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The studies were funded by Theratechnologies and designed in consultation with S.G. and J.F.. The sponsor collected the data, and analyses were performed by Octagon Research Solutions. S.G. drafted the current manuscript and had access to the data and all analyses.

Clin Trials Registration Numbers: NCT 00123253, NCT00435136, and NCT00608023.

Disclosure Summary: J.M., D.P., G.S., H.L., and C.M. are employees of Theratechnologies. J.F. has received consultant fees from Tibotec, Theratechnologies, Abbott, and Boehringer Ingelheim; lecture fees from Gilead, Bristol-Myers Squibb, Abbott, and Roche; and grant support from Theratechnologies. G.M. has received grant support from Theratechnologies, Bristol-Myers Squibb Co., Inc., GlaxoSmithKline, Gilead Sciences, Merck Inc., Ardea Biosciences, Abbott, and Pfizer and served as a consultant to Theratechnologies, Bristol-Myers Squibb, GlaxoSmithKline, Gilead Sciences, Merck, Ardea Biosciences, Pfizer, Tobira Pharmaceuticals, Tibotec, and Johnson and Johnson. R.T. has received grant support from Theratechnologies and is employed by Phase V Technologies. S.G. has received grant support from Theratechnologies, Bristol-Myers Squibb, GlaxoSmithKline, and Amgen and served as a consultant to Theratechnologies, EMD Serono, and Elixir Pharmaceuticals.

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