Effects of Tesamorelin, a Growth Hormone–Releasing Factor, in HIV-Infected Patients With Abdominal Fat Accumulation: A Randomized Placebo-Controlled Trial With a Safety Extension

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Background: HIV-infected patients receiving antiretroviral therapy often demonstrate excess visceral fat. A growth hormone–releasing factor, tesamorelin, may selectively reduce visceral fat in this population. We investigated the effects of tesamorelin ($GHRH^{1-44}$) in HIV-infected patients with central fat accumulation.

Methods: A 12-month study of 404 HIV-infected patients with excess abdominal fat in the context of antiretroviral therapy was conducted between January 2007 and October 2008. The study consisted of 2 sequential phases. In the primary efficacy phase (months 0–6), patients were randomly assigned to receive tesamorelin [2 mg subcutaneous (SC) every day] or placebo in a 2:1 ratio. In the extension phase (months 6–12), patients receiving tesamorelin were rerandomized to continue on tesamorelin (2 mg SC every day) or switch to placebo. Patients initially randomized to placebo switched to tesamorelin. Patients and investigators were blinded to treatment assignment throughout the study. The primary endpoint was visceral adipose tissue (VAT). Secondary endpoints included body image, IGF-I, safety measures, including glucose, and other body composition measures.

Results: VAT decreased by −10.9% (−21 cm^2) in the tesamorelin group vs. −0.6% (−1 cm^2) in the placebo group in the 6-month efficacy phase, $P < 0.0001$. Trunk fat ($P < 0.001$), waist circumference ($P = 0.02$), and waist-hip-ratio ($P = 0.001$) improved, with no change in limb or abdominal SC fat. Insulin-like growth factor-1 increased ($P < 0.001$), but no change in glucose parameters was observed. Patient rating of belly appearance distress ($P = 0.02$) and physician rating of belly profile ($P = 0.02$) were significantly improved in the tesamorelin vs. placebo-treated groups. The drug was well tolerated. VAT was reduced by approximately 18% ($P < 0.001$) in patients continuing tesamorelin for 12 months. The initial improvements over 6 months in VAT were rapidly lost in those switching from tesamorelin to placebo.

Conclusions: Tesamorelin reduces visceral fat by approximately 18% and improves body image distress in HIV-infected patients with central fat accumulation. These changes are achieved without significant side effects or perturbation of glucose.

Key Words: body image, growth hormone, growth hormone releasing hormone, visceral fat

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INTRODUCTION

HIV-infected patients receiving antiretroviral therapy (ART) often demonstrate changes in fat distribution, which can present as peripheral fat loss and/or central fat accumulation.[1–4] In such patients, excess central fat is usually visceral, with concomitant loss of central subcutaneous (SC) fat.[5] Among HIV-infected patients, increased upper trunk fat and visceral adiposity are strongly associated with dyslipidemia and insulin resistance[6,7] and marked by increased waist circumference (WC).[8] In large studies of non–HIV-infected patients, increased WC is an independent predictor of mortality.[9,10] Although studies linking increased WC to mortality have not yet been performed specifically among HIV-infected patients, there may be a significant metabolic benefit to reduction in central visceral fat, particularly by a strategy that spares SC fat and improves the relative redistribution in the

ratio of central to peripheral fat. Improvement in visceral adiposity may also improve patients' psychological well-being and distress,[11] ultimately contributing to greater compliance with HIV medications and less stigma associated with the use of life-saving antiretroviral medicines.

Growth hormone (GH) secretion is reduced among viscerally obese HIV-infected patients.[12,13] Growth hormone–releasing hormone (GHRH)/growth hormone–releasing factor (GRF) increases endogenous GH pulsatility and feedback inhibition by insulin-like growth factor 1 (IGF-1) remains intact with GHRH, thus physiological dosing is more easily achieved without dose titration. The strategy using tesamorelin, a GRF analogue, has been shown to improve visceral fat, sparing SC fat, and to be well-tolerated in an initial Phase III trial involving mostly patients in North America (United States and Canada).[14,15] In the current study, we report the results of a second large Phase III study, with patients followed in North America and Europe. The design of the current study, including a 6-month randomized, placebo-controlled efficacy phase, and a subsequent 6-month extension phase to assess long-term 12-month effects, including safety, tolerability, and the effects of discontinuation of tesamorelin, was similar to the initial Phase III study.[14,15] This design permitted determination of the long-term effects of tesamorelin and safety in a large number of additional subjects receiving the drug.

METHODS

Participants

HIV-infected patients, aged 18–65 years, with CD4 cell counts >100 cells per cubic millimeter and viral load <10,000 copies per milliliter, receiving a stable ART for at least 8 weeks and with evidence of abdominal fat accumulation (WC ≥95 cm and waist-to-hip ratio ≥0.94 for males and WC ≥94 cm and waist-to-hip ratio ≥0.88 for females) were recruited to the study, which was conducted at 48 sites throughout Europe and North America (Appendix I, list of investigators and sites). Inclusion criteria were similar to entry criteria in prior studies with tesamorelin[14,16] and based on Lemieux et al[17] demonstrating excess visceral adiposity in association with increased waist girth. Women with a normal mammogram within 6 months of study and not pregnant were included. Subjects were excluded with (1) body mass index (BMI) <20 kg/m^2; (2) HIV-related disease/infection within 3 months of study; (3) history of malignancy or active neoplasm; (4) prostate specific antigen (PSA) >5 ng/mL; (5) history of pituitary tumor/-surgery or head irradiation; (6) untreated hypothyroidism; (7) prior use of insulin, oral hypoglycemic, or insulin sensitizing agent within 6 months of study; (8) alanine aminotransferase or aspartate aminotransferase >3 × normal; (9) creatinine >1.5 mg/dL; (10) hemoglobin >20 g/L below normal; (11) fasting blood glucose ≥150 mg/dL, known history of Type I diabetes mellitus or Type II diabetes mellitus requiring medication; (12) fasting triglycerides >0.99 g/dL or change in lipid-lowering regimen within 3 months before study; (13) untreated hypertension; (14) change in testosterone regimen and/or supraphysiological dose of testosterone; (15) estrogen therapy; (16) anoretics/anorexigenics or anti-obesity agents within 3 months of study; (17) GH, GH secretagogues, GRF products, IGF-1, or IGFBP-3 within 6 months of study; (18) drug or alcohol dependence or use of methadone within 6 months of study entry; and (19) participation in a clinical trial with any investigational drug/device within 30 days of screening. The first patient was screened in January 2007 and the last patient finished the study in October 2008. The study was approved by the Institutional Review Board at each site, and participants provided written informed consent. Patients were excluded from the current study if they reported participation in any prior study of tesamorelin.

Study Procedures

Primary Efficacy Phase

Eligibility was determined at a screening visit. Eligible subjects returned for a baseline visit at which weight and anthropometric measurements (waist and hip circumference) were determined. Subjects underwent a single-slice abdominal computerized tomography (CT) scan to determine abdominal visceral and SC fat and a whole-body dual energy x-ray absorptiometry (DEXA) scan to determine lean mass, trunk, and extremity fat. Subjects completed a body image questionnaire. Echocardiography was performed for subjects who presented with ECG signs of ventricular hypertrophy at screening. Fasting blood samples were obtained for glucose, lipids, IGF-I, insulin, IgG anti-tesamorelin antibodies, CD4 cell count, and viral load. A standard 75 g oral glucose tolerance test was performed. Female study subjects had a urine pregnancy test before testing procedures. Interval assessments were performed at weeks 6, 13, 19, and 26. Visits at week 13 and 26 were similar to the baseline visit. Interval assessment at all visits included current medications, adverse events (AEs) and compliance as assessed by vial count. Subjects were asked to return all vials (used and unused) and were provided with new supplies. Antiretroviral treatment was determined and an ECG performed. Fasting blood samples were obtained and female study subjects had a urine pregnancy test before testing procedures.

Extension Phase

At the week 26 visit, subjects were asked to participate in the 26-week extension phase of the protocol. Study investigators confirmed continued eligibility based on completion of the 26-week efficacy phase and fasting blood glucose level <150 mg/dL. Patients returned for visits 6, 13, 19, and 26 weeks after the start of the extension phase, corresponding to weeks 32, 39, 45, and 52 in the study. These visits were identical to those at the corresponding times in the initial efficacy phase of the study except that the body image questionnaire was not administered during the interim visits but was administered at the final visit.

Intervention, Randomization, and Blinding

After screening was completed, subjects were randomized in a 2:1 fashion (tesamorelin:placebo) to tesamorelin 2 mg SC every day or identical placebo for the primary efficacy phase. Active drug and placebo were manufactured by Theratechnologies Inc, Montreal, Canada. Randomization was stratified by site and diabetes condition (fasting blood

glucose value >126 mg/dL at screening). An Interactive Voice Response System (IVRS, Cenduit) was used to assign treatment arm and study treatment kit number according to the randomization schedule using a 3-block algorithm. Investigator, sponsor, and patients were blinded to treatment assignment. Tesamorelin and placebo were provided as lyophilized powder in two 3-mL vials of identical appearance. Each vial of tesamorelin contained 1.1 mg of tesamorelin (peptide content) with 55 mg of mannitol. Each vial of placebo contained 55 mg of mannitol. Subjects were instructed on proper reconstitution and self-administration techniques with instructions to keep refrigerated at 2°C–8°C. Subjects were instructed to reconstitute each vial with 1.1 cc 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 via IVRS as follows. Subjects initially randomized to tesamorelin were rerandomized in a 1:1 ratio to receive tesamorelin (T-T) (2 mg SC every day) 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 (Fig. 1). Using IVRS, subject numbers were provided to the site and randomization was performed. Investigators, sponsor, and patients were blinded to the treatment assignments during the extension phase.

Compliance

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

Safety

Subjects were discontinued from the study for hemoglobin <100 g/L and decreases by at least 20 g/L from screening; aspartate aminotransferase or alanine aminotransferase value >5x upper limit normal; creatinine value >2x upper limit normal; asymptomatic with fasting blood glucose >180 mg/dL or symptomatic with fasting blood glucose <180 mg/dL; or an elevated creatine kinase (CPK) of at least 5 times the normal value; and systemic allergic or hypersensitivity reaction beyond the local injection site. A Data Safety Monitoring Board met twice throughout the course of the study and monitored AEs and safety data.

Outcome Measures

Body Composition Analysis

Visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) (cm^2) were assessed by CT scan from a single 5-mm slice obtained at the level of L4-L5 intervertebral disc. Images were analyzed in a blinded fashion at a Central Imaging Reading Centre (Perceptive Informatics, Waltham, MA). Image acquisition technique was standardized across all enrollment sites. Standardization procedures and central blinded readings were also performed for whole body DEXA imaging (Perceptive Informatics) for total body lean, fat, trunk, and limb fat.

Body Image

Impact on body image was determined by questionnaire as previously described (Phase V Technologies, Inc, Wellesley, MA).[11] Subjects rated their "belly size" by comparing their current appearance to their perceived healthy look [from much thinner (−100) to much bigger (+100)]; and rated their "belly image distress" about belly size [from extremely upsetting and distressing (0) to extremely encouraging (100)]. Furthermore, they rated their "belly profile" by choosing from among 6 silhouettes [scored from "normal" (0) to very dysmorphic]. Physicians also rated belly profile using the same scales.

Biochemical Assays

Lipid levels [triglycerides, total cholesterol (TC), and high-density lipoprotein (HDL) cholesterol] glucose, insulin, and free testosterone were determined by Quintiles Laboratories (Smyrna, GA and W. Lothian, Scotland, United Kingdom) using standardized methodologies. IGF-I level was measured by Esoterix (Calabasas Hills, CA). Antitesamorelin IgG antibodies were measured by Millipore Corporation (St-Charles, MO). Safety laboratories included a standard chemistry panel with liver function tests and complete blood count. Data on inflammatory markers and adiponectin were not collected in the current study.

Statistical Analysis

The primary efficacy endpoint was the percent change in the VAT from baseline to week 26. Secondary endpoints included IGF-I, body image, and biochemical indices. For the extension phase, the primary endpoint was safety, and the efficacy endpoints included 52-week efficacy and duration of effect. Statistical analyses were performed by Quintiles, Canada. The minimum difference needed to detect a clinically relevant difference between active and placebo was considered to be 8% after consultation with the Food and Drug Administration (FDA). Assuming a standard deviation of 18.5%, a power of 90%, a significance level of 5% and a distribution ratio of 2:1 (active:placebo), and a total of n = 255 subjects were required. Assuming a dropout ratio of 25%, then a total sample size of n = 340 subjects was required, but enrollment was increased to 400 to obtain sufficient safety data during the extension phase.

For the analyses, the safety and intent to treat populations were defined as all randomized subjects who were exposed to study drug. (ie, injection of at least 1 dose of study drug). These analyses used all available data on patients including partial data from patients who discontinued. Comparison of variables by treatment group at baseline was made by Analysis of Variance for continuous variables and Fisher exact test for noncontinuous variables. The treatment effect in the primary efficacy endpoint was tested using an ANCOVA on the natural log ratio of VAT at week 26 to baseline VAT. After exponentiation, the dependent variable can be interpreted as the ratio of VAT at week 26 to VAT at baseline, which is similar to the percent change from baseline, except for a difference of 1. The primary analysis of covariance (ANCOVA) model included treatment, natural log baseline VAT, and enrollment site. There was no effect of enrollment site in the model. In secondary models, use of testosterone, impaired glucose tolerance (IGT)/diabetes, gender, prior duration of protease inhibitor (PI) treatment, and change in

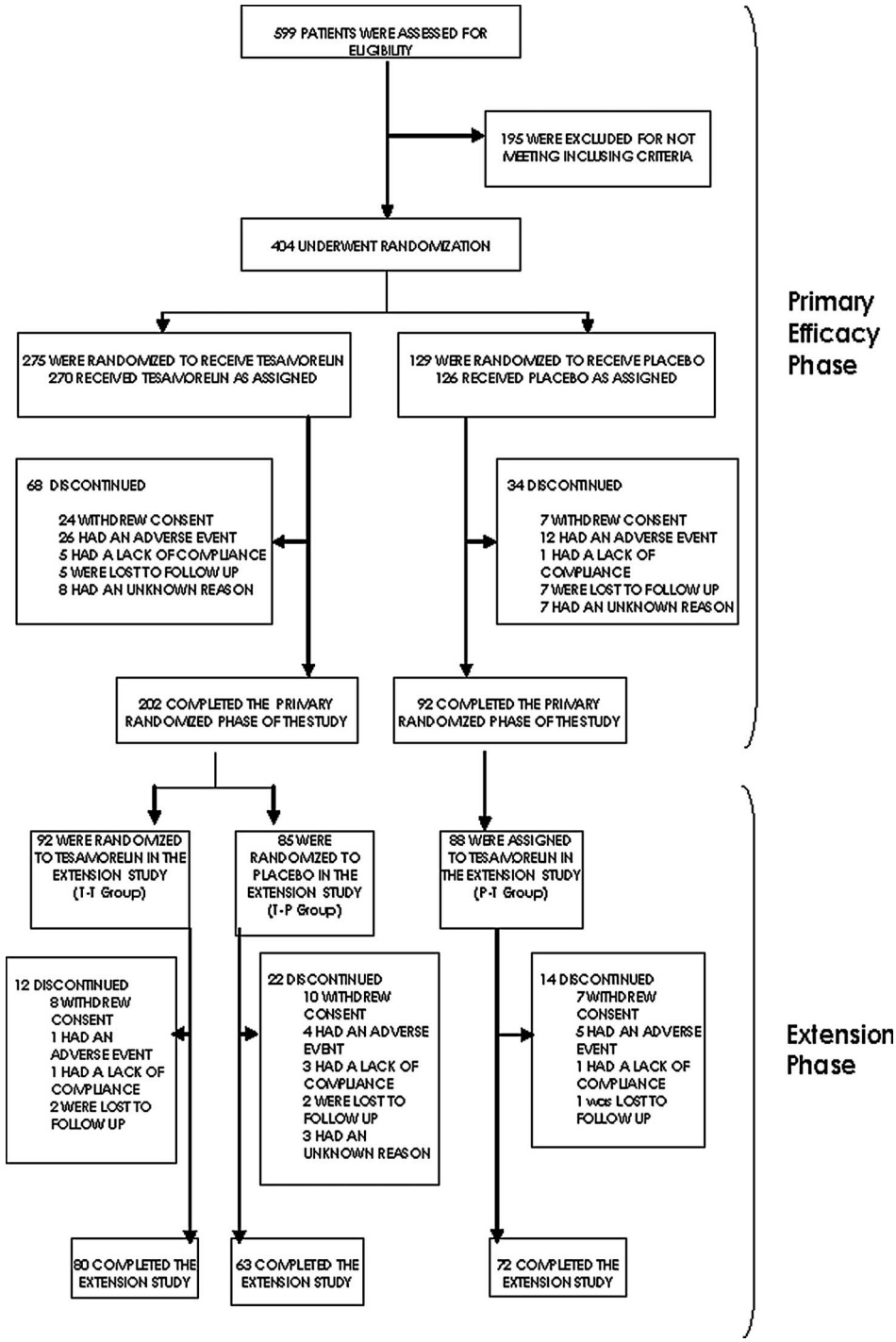

FIGURE 1. Study participant enrollment and discontinuation

ART therapy during the protocol were included as covariates. Inclusion of these covariates did not alter the results of the analysis, and data from the secondary models are not presented. The treatment effect of tesamorelin for primary and secondary variables was estimated by the placebo versus 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. The 95% confidence interval of the treatment effect is given and the relative treatment effect in terms of the difference in the percentage change between treatment groups. The change from baseline to week 26 in lipid levels was analyzed using an ANCOVA model to account for baseline level and for the use of lipid-lowering treatments. Inclusion of duration of prior PI therapy and change in ART as covariates did not affect the results. Ranked ANCOVA models were fitted for Belly Size Evaluation change score and Belly Appearance Distress.

For the safety extension phase, comparisons were made between VAT and secondary variables for 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 week 52 for each treatment group (T-T, T-P, and P-T) were tested with repeated measures analysis of variance.

For the safety analyses in both the primary efficacy phase and the safety extension phase, comparisons were made between treatment groups using ANCOVA for continuous variables and Fisher exact test for noncontinuous variables.

RESULTS

Primary Efficacy Phase

Four hundred four patients underwent randomization; 270 received tesamorelin and 126 received placebo and constituted the intent-to treat population (Fig. 1). Overall, 68 patients (25%) discontinued in the tesamorelin group and 34 patients (27%) discontinued in the placebo group ($P = 0.71$), consistent with the planned dropout rate in a priori projections. At baseline, there were no differences in demographic and clinical characteristics between the groups. Free testosterone levels, drawn in male subjects, were comparable between the groups, 44.6 ± 26.2 and 46.2 ± 22.5 pmol/L, tesamorelin and placebo, respectively. Thyroid function was assessed by thyrotropin-releasing hormone (TSH), with comparable levels in the treatment groups, 1.99 ± 1.02 and 1.83 ± 1.13 μIU/L, tesamorelin and placebo, respectively. By definition, all patients demonstrated abdominal lipohypertophy at baseline, and the majority also demonstrated peripheral lipoatrophy as well (Table 1). Use of PIs, nucleoside reverse transcriptase inhibitors, and nonnucleoside reverse transcriptase inhibitors (NNRTIs) and immune indices were similar between the groups (Table 1). The overall compliance during the efficacy phase was similar and 96.9 ± 18.5 % (mean ± SD) and 97.6 ± 13.0 % for the tesamorelin and placebo groups, respectively.

TABLE 1. Demographics and Clinical Characteristics of the Patients Entering the Primary Randomized Study (n = 396) (0–26 Weeks)

Variables	Tesamorelin (n = 270)	Placebo (n = 126)
Age (yrs)	47.7 ± 7.5	47.7 ± 7.7
Male/female ratio (%)	84.4/15.6	83.3/16.7
Race (%)		
White	77.4	76.2
Black	12.6	9.5
Other	10.0	14.3
Weight (kg)	89.0 ± 13.6	87.1 ± 15.6
Body mass index (kg/m^2)	28.8 ± 4.3	28.7 ± 4.2
WC (cm)	105 ± 9	104 ± 9
Waist-to-hip ratio	1.05 ± 0.07	1.05 ± 0.07
Viral load (%)		
Undetectable	81.9	86.4
50–400 copies/mL	11.1	9.6
>400 copies/mL	7.0	4.0
CD4 count (cells/mm^3)	588 ± 290	600 ± 278
Current drug therapy (%)		
Protease inhibitor	58.9	55.6
Nucleoside reverse transcriptase inhibitor	90.4	88.1
Nonnucleoside reverse transcriptase inhibitor	39.6	35.7
Lipodystrophy rating (%)		
Abdominal lipohypertrophy	100	100
Lipoatrophy of face or limbs	67.0	65.9
Fasting blood glucose (%)		
≤110 mg/dL	77.4	84.9
110–125 mg/dL	14.8	9.5
≥125 mg/dL	7.8	5.6
Use of testosterone (%)	25.2	17.5
Use of lipid-lowering agents (%)	40.4	47.6

No differences were seen for any of the variables between the groups at baseline.

Body Composition

Visceral fat decreased by −10.9% (−21 cm^2) in the tesamorelin group vs. −0.6% (−1cm^2) in the placebo group, $P < 0.001$, Table 2, Fig. 2). Trunk fat was reduced [mean −1.0 kg (−1.4 to −0.6) of the difference over time between the groups and 95% confidence interval, $P < 0.001$]. WC [−1.3 cm (−2.4 to −0.2), $P = 0.02$] and waist-to-hip ratio [−0.02 (−0.03, −0.01), $P = 0.001$] also improved in patients receiving tesamorelin vs. placebo-treated patients, but no change in limb or abdominal SC fat was observed (Table 2). Lean body mass increased significantly in the tesamorelin vs. placebo-treated patients [1.3 kg (0.8 to 1.7), $P < 0.001$]. No change in BMI was observed between the groups.

Biochemical and Immunological Indices

IGF-I increased significantly [103 ng/mL (83 to 124]), $P < 0.001$ in the tesamorelin vs. placebo treated patients]. Triglyceride levels [−26 mg/dL (−52 to 1), $P = 0.10$] and the ratio of TC to HDL-cholesterol [−0.2 (−0.4 to 0.01), $P = 0.10$] tended to improve in the patients receiving tesamorelin vs. placebo, but no changes were seen in TC or HDL between the groups (Table 3). No changes were seen in glucose parameters (fasting glucose, 2-hour glucose on oral glucose tolerance test (OGTT), and fasting insulin levels) between the groups (Table 2). Neither CD4 count nor viral load changed significantly between the groups (Table 2). Serial changes from baseline in fasting glucose at weeks 6, 13, 19, and 26 were 1 ± 17, 2 ± 19, 3 ± 18, and 2 ± 18 mg/dL for tesamorelin and 1 ± 15, −3 ± 17, 0 ± 19, and 1 ± 19 mg/dL for placebo. At week 13, the changes in insulin were −2 ± 31 vs. −4 ± 15 μIU/mL for the tesamorelin and placebo groups, respectively. Changes in TSH were also minimal and comparable between groups, 0.19 ± 4.19 and 0.26 ± 0.81 μIU/L for the tesamorelin and placebo groups, respectively.

Body Image

Patient rating of belly appearance distress improved (less distress) more in the tesamorelin compared with the placebo-treated patients (8.4 ± 29.0 vs. 5.2 ± 26.6, $P = 0.02$, tesamorelin vs. placebo) and physician rating of belly profile (−0.6 ± 1.2 vs. −0.3 ± 1.1, $P = 0.02$, tesamorelin vs. placebo) was significantly improved in the tesamorelin vs.

TABLE 2. Changes from Baseline in Body Composition, Lipid Levels, Biochemical Measures, Glycemic Measures, and Immune Function in the Primary Efficacy Phase

Variables	Baseline		At 26 Weeks		Absolute Difference (95% CI)*	Relative Difference (%)†	P‡
	Tesamorelin (n = 270)	Placebo (n = 126)	Tesamorelin (n = 270)	Placebo (n = 126)			
			Mean Change From Baseline (Percent)				
Body composition							
Visceral adipose tissue (cm^2)	186 ± 87	195 ± 96	−21 ± 42 (−10.9)	−1 ± 32 (−0.6)	−20 (−28 to −11)	−10.3	<0.001
SC adipose tissue (cm^2)	231 ± 120	226 ± 112	−1 ± 34 (1.1)	1 ± 28 (1.0)	−2 (−9 to 5)	0.2	0.55
Ratio of visceral to SC adipose tissue	1.27 ± 1.60	1.25 ± 1.21	−0.23 ± 1.03 (−10.6)	0.03 ± 0.60 (−0.1)	−0.26 (−0.46 to −0.06)	−10.5	0.001
Trunk fat (kg)	15.3 ± 5.3	15.2 ± 5.1	−0.8 ± 2.1 (−5.5)	0.2 ± 1.5 (1.1)	−1.0 (−1.4 to −0.6)	−6.6	<0.001
WC (cm)	105 ± 9	104 ± 9	−2.2 ± 5.4 (−2.1)	−0.8 ± 4.7 (−0.9)	−1.3 (−2.4 to −0.2)	−1.2	0.02
Waist-to-hip ratio	1.05 ± 0.07	1.05 ± 0.07	−0.02 ± 0.06 (−2.2)	−0.01 ± 0.05 (−0.7)	−0.02 (−0.03 to −0.01)	−1.5	0.001
Fat in limbs (kg)	7.5 ± 4.7	7.3 ± 4.0	−0.1 ± 1.0 (−0.1)	0.1 ± 0.9 (2.2)	−0.2 (−0.4 to 0.0)	−2.4	0.07
Lean mass (kg)	62.4 ± 10.3	60.5 ± 11.2	1.2 ± 2.4 (2.0)	−0.0 ± 1.9 (0.0)	1.3 (0.8 to 1.7)	2.0	<0.001
Body mass index (kg/m^2)	28.8 ± 4.3	28.7 ± 4.2	0.2 ± 1.3 (0.6)	0.1 ± 1.1 (0.4)	0.1 (−0.3 to 0.4)	0.2	0.73
Lipid levels							
Triglycerides (mg/dL)	239 ± 261	223 ± 144	−22 ± 131 (2.8)	3 ± 106 (7.6)	−26 (−52 to 1)	−4.8	0.10
Cholesterol							
Ratio of TC to HDL cholesterol	4.75 ± 1.69	4.61 ± 1.61	−0.05 ± 1.01 (1.5)	0.15 ± 0.92 (5.0)	−0.20 (−0.40 to 0.01)	−3.4	0.10
Total (mg/dL)	191 ± 43	190 ± 37	1 ± 32 (2.1)	5 ± 29 (3.9)	−4 (−11 to 3)	−1.9	0.24
HDL (mg/dL)	44 ± 14	45 ± 15	0 ± 8 (2.8)	−0 ± 10 (1.9)	0 (−2 to 2)	0.8	0.94
Biochemical measures							
Insulin-like growth factor-1 (ng/mL)	146 ± 66	149 ± 59	106 ± 110 (85.8)	3 ± 59 (5.6)	103 (83 to 124)	80.2	<0.001
Glycemic measures							
Glucose (mg/dL)							
Fasting	101 ± 17	99 ± 17	2 ± 18 (3.2)	1 ± 19 (2.7)	1 (−4 to 5)	0.5	0.15
At 2 hrs	117 ± 42	121 ± 41	6 ± 37 (10.5)	−3 ± 41 (1.2)	9 (−1 to 19)	9.3	0.18
Fasting insulin (μIU/mL)	25 ± 30	20 ± 18	−2 ± 30 (44.4)	0 ± 22 (35.7)	−2 (−10 to 5)	8.7	0.46
Immune function							
CD4 count ($cells/mm^3$)	588 ± 290	600 ± 278	−6 ± 152 (2.1)	13 ± 144 (5.5)	−20 (−57 to 17)	−3.4	0.16
Viral load (%)§							
Undetectable	81.9	86.4	84.7	87.1	—	—	0.93‖
50–400 copies/mL	11.1	9.6	9.4	8.6	—	—	—
>400 copies/mL	7.0	4.0	5.9	4.3	—	—	—

Data are reported as mean ± SD, unless otherwise indicated. To convert the values for triglycerides to mmol/L, multiply by 0.0113; to convert the values for TC and HDL cholesterol to mmol/L, multiply by 0.0259; to convert the values of IGF-1 to nmol/L, multiply by 0.131; to convert the values for glucose to mmol/L, multiply by 0.0555; to convert the values for insulin to pmol/L, multiply by 6.945.

*The values are for the difference between the changes from baseline in the tesamorelin group and the placebo group.

†The values are for the difference between the percent change from baseline in the tesamorelin group and the placebo group.

‡The *P* values are for the comparison between the changes from baseline in the tesamorelin group and the placebo group.

§For viral load, the values are the percentages of patients at baseline and at week 26, plus the *P* value at week 26.

‖The *P* value from Fisher exact test comparing the tesamorelin group to the placebo group at week 26.

CI, confidence interval.

placebo-treated groups over 26 weeks. Patient rating of belly size (14.8 ± 27.8 vs. 11.7 ± 25.2, $P = 0.21$) did not change significantly between the groups, whereas patient rating of belly profile tended to improve in the tesamorelin-treated patients (−0.5 ± 1.3 vs. −0.3 ± 1.0, $P = 0.08$), tesamorelin vs. placebo, respectively.

Safety

The drug was well tolerated with similar rates of subject discontinuations, overall AEs and serious adverse events (Table 3), though more AEs were judged as related to treatment in the tesamorelin-treated patients. For events seen in more than 10% of patients, injection site erythema and pruritis were seen more often in tesamorelin-treated patients (Table 3). A hypersensitivity skin reaction was seen in 3.3% of tesamorelin and 0.8% of placebo patients. Five tesamorelin and 1 placebo-treated patient were discontinued for hypersensitivity reactions. Two deaths occurred in the study, 1 patient in the tesamorelin group died of lung cancer, which was diagnosed 5 months after discontinuation of treatment, and 1 patient in the placebo group died of an arrhythmia. The patient with lung cancer received tesamorelin for only 3 months and was

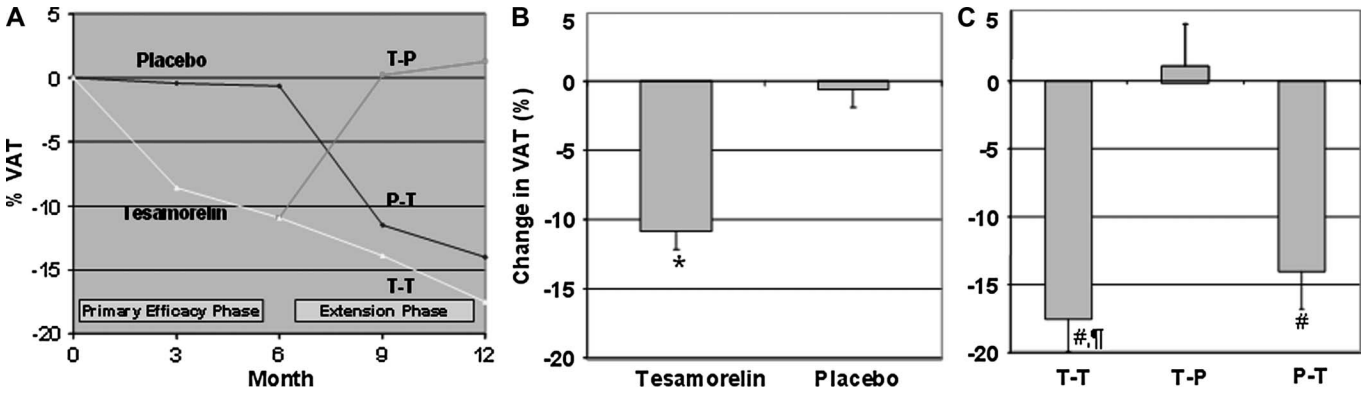

FIGURE 2. Change in VAT over time by treatment group. A, Descriptive graph for the entire study by initial randomization groups in the primary efficacy phase and then re-randomized groups in the extension phase. Percent change during extension phase refers to change from baseline. For patients re-randomized into the T-T (n = 92) and T-P (n = 85) groups, 6 month changes from baseline in VAT were −17% and −11%, respectively. B, Percent change over 6 months in VAT for patients in the tesamorelin and placebo-treated groups in the primary efficacy phase. C, Percent change over 12 months in VAT for patients in the T-T, T-P, and P-T groups in the safety, extension phase. *$P < 0.001$ tesamorelin compared with placebo in efficacy phase, #$P < 0.001$ for each group vs. baseline (baseline refers to Week 0, initial start of study), ¶$P < 0.001$ T-T vs. T-P during the safety extension phase.

discontinued due to injection site reactions and itchiness. Investigation of his IGF-I level after the completion of the study demonstrated that it remained in the normal range throughout his time on the study medication. At week 26, IgG antibodies to tesamorelin were seen in 49% of tesamorelin-treated patients and 3% of placebo, but neither VAT nor IGF-I change differed significantly in those with and without antibodies. Similarly, there was no effect of antibody titer on clinical responses.

Extension Phase

Body Composition and Biochemical Indices

Demographic and clinical characteristics of the patients entering the extension phase are shown in Table 4. VAT improved by 17.5 % over 52 weeks among patients in the T-T group ($P < 0.001$) but was not different from baseline after 52 weeks among those in the T-P group (1.3%, $P = 0.432$), indicating that the improvement in VAT in this group was not sustained after treatment discontinuation (Table 5, Fig. 2). Similar patterns were seen in other body composition variables, except WC, in which patients in the T-T group showed a loss of −3.8 cm over 52 weeks of treatment ($P < 0.001$). Those in the T-P group demonstrated a sustained loss of −2.4 cm at 52 weeks, 26 weeks after treatment was discontinued, which was statistically significant compared with baseline ($P < 0.001$), and marginally different as compared with the T-T group ($P = 0.049$) (Table 5). No significant changes in glucose parameters or immunological function were observed. TC decreased over 12 months by 10 mg/dL in the T-T group ($P < 0.05$), and this change was different from that in the T-P group, amounting to a net difference of −19 mg/dL ($P < 0.05$). IGF-I level remained significantly increased in the T-T group and reverted to baseline in the T-P group.

Body Image

Patient rating of belly appearance distress (13.2 ± 33.8, $P < 0.01$ vs. baseline for less distress), physician rating of belly profile (−1.0 ± 1.3, $P < 0.01$), patient rating of belly profile (−0.9 ± 1.3, $P < 0.01$), and belly size (20.9 ± 29.7, $P < 0.01$) all remained significantly improved after 52 weeks in the T-T group. Changes in each parameter also remained significantly improved in the T-P group (9.9 ± 24.3, $P < 0.01$; −0.7 ± 1.3, $P < 0.01$; −0.5 ± 1.2, $P < 0.01$; 13.5 ± 24.3, $P < 0.01$, respectively). For belly distress ($P = 0.005$), physician ($P = 0.04$) and patient rating of belly profile ($P = 0.02$), the change over 52 weeks was significantly greater in the T-T than the T-P groups. For patient rating of belly size, the changes over 52 weeks in the T-T and T-P groups were not significantly different ($P = 0.10$) (Table 5).

Safety

AEs and discontinuation rates in the 3 groups are shown in Figure 1 and Tables 3 and 6. Tesamorelin was well-tolerated over 12 months of treatment and AE rates in patients continuing with tesamorelin during the 6-month extension phase were similar to those observed during the primary efficacy phase. Hypersensitivity reactions were seen in 1.1%, 0%, and 3.5% patients in the T-T, T-P, and P-T groups, respectively. One patient in the T-T and 1 in the P-T group were discontinued for hypersensitivity reactions. There was no effect of presence of antitesamorelin IgG antibodies or titers on VAT or IGF-I responses at week 52. Six months after tesamorelin discontinuation, 16.1% of the T-P patients had persistent antibodies and 98.2% of these patients had low titers (<1:400 dilution category). IGF-I levels were similar in T-P patients with and without antibodies at 52 weeks.

COMMENT

In this study, we demonstrate that tesamorelin significantly improves body composition, with a highly significant, but selective reduction in VAT and body image among HIV-infected patients with abdominal fat accumulation. These benefits occurred without any significant increases in glucose or insulin levels, a major concern for any strategy to augment GH secretion in the HIV population. Moreover, from the

TABLE 3. AEs and Serious Adverse Events in the Primary Efficacy Phase (0–26 Weeks)

Events	Tesamorelin (n = 270) % Patients	Placebo (n = 126) % Patients	*P*
AEs*			
Any event	74.1	69.8	0.398
Related to treatment	53.0	37.3	0.005
Resulting in study discontinuation	10.0	8.7	0.855
Events reported in >10% of the patients			
Injection site erythema	14.1	4.8	0.006
Arthralgia	12.2	11.1	0.868
Injection site pruritus	10.4	1.6	0.002
Injection site bruising	5.6	10.3	0.095
Events reported in >5% of the patients			
Diarrhoea	7.4	7.1	—
Pain in extremity	7.0	2.4	—
Pyrexia	2.6	5.6	—
Nasopharyngitis	3.3	6.3	—
Upper respiratory tract infection	3.0	6.3	—
Headache	5.6	3.2	—
Cough	4.1	5.6	—
Serious AEs*			
Any events	3.3	6.3	0.187
All events reported			
Anemia	0.4	0.0	—
Arrhythmia	0.0	0.8	—
Cardiac arrest	0.0	0.8	—
Abdominal hernia obstructive	0.0	0.8	—
Small intestinal obstruction	0.4	0.0	—
Lung cancer	0.4	0.0	—
Hypersensitivity	0.0	0.8	—
Appendicitis	0.0	0.8	—
Infection	0.4	0.0	—
Benign prostatic hyperplasia	0.4	0.0	—
Perianal abscess	0.4	0.0	—
Humerus fracture	0.4	0.0	—
Procedural pain	0.0	0.8	—
Rib fracture	0.4	0.0	—
Electrocardiogram abnormal	0.4	0.8	—
Breast cancer in situ	0.0	0.8	—
Hodgkin disease	0.0	0.8	—
Cerebellar syndrome	0.4	0.0	—
Trigeminal neuralgia	0.4	0.0	—

*Treatment emergent.

TABLE 4. Demographics and Clinical Characteristics of the Patients Entering the Extension Phase (n = 263)

Variables	T-T (n = 92)	T-P (n = 85)	P-T (n = 86)
Age (yrs)	47.7 ± 6.9	48.9 ± 7.2	48.4 ± 7.9
Male/female ratio (%)	90.2 ± 9.8	89.4 ± 10.6	87.2 ± 12.8
Race (%)			
White	81.5	85.9	81.4
Black	10.9	7.1	5.8
Other	7.6	7.1	12.8
Weight (kg)	88.0 ± 12.6	89.9 ± 13.6	86.6 ± 15.4
Body mass index (kg/m^2)	28.3 ± 3.9	29.0 ± 3.9	28.5 ± 4.3
Waist circumference (cm)	104 ± 8	106 ± 9	104 ± 9
Waist-to-hip ratio	1.05 ± 0.09	1.05 ± 0.06	1.05 ± 0.06
Viral load (%)			
Undetectable	83.7	80.0	88.2
50–400 copies/mL	8.7	11.8	7.1
>400 copies/mL	7.6	8.2	4.7
CD4 count (cells/mm^3)	579 ± 300	580 ± 272	604 ± 283
Current drug therapy (%)			
Protease inhibitor	52.2	61.2	53.5
Nucleoside reverse transcriptase inhibitor	92.4	87.1	90.7
Nonnucleoside reverse transcriptase inhibitor	41.3	42.4	34.9
Lipoatrophy rating (%)			
Abdominal lipohypertrophy	100	100	100
Lipoatrophy of face or limbs	62.0	69.4	70.9
Fasting glucose (%)			
≤ 110 mg/dL	79.7	74.1	84.9
110-125 mg/dL	16.3	15.3	9.3
≥125 mg/dL	4.3	10.6	5.8
Use of testosterone (%)	34.8	22.4	17.4
Use of lipid-lowering agents (%)	45.7	47.1	41.9

Clinical and demographic characteristics were not different between the groups entering the extension phase.

design of the current study, with a 6-month extension phase beyond the 6-month primary efficacy phase, we were able to show that the decrease in VAT persists in those patients treated continuously for 12 months, with a total reduction of 17.5% in VAT in this group amounting to a 3.8-cm loss in WC, that was comprised entirely of loss of VAT. Although this effect is largely lost in patients switching off therapy for 6 months, residual benefits in body image persisted which may be important to patients.

Increased abdominal fat accumulation, particularly visceral fat, is increasingly recognized as contributing to increased coronary heart disease.[18] Selective surgical removal of a small amount of visceral fat improves metabolic risk factors, whereas liposuction to remove considerable SC fat has little effect.[19,20] Moreover, in the general population, WC has been shown to be independently associated with myocardial infarction risk in the Interheart Study,[9] controlling for traditional risk factors and more recently, to independently contribute to increased mortality above and beyond BMI.[10] HIV-infected patients beginning ART demonstrate a loss of peripheral fat and a relative sparing or increase in central fat.[2,3] Moreover, recent studies demonstrate a significant increase in VAT among ART-naive patients beginning a PI, NNRTI, or combined PI/NNRTI strategy.[21] Increased upper trunk and visceral fat have been shown to correlate most strongly with insulin resistance and dyslipidemia in HIV-infected patients.[6–8] Moreover, recent data in HIV-infected patients receiving ART suggest increased VAT is significantly related to coronary calcium progression.[22] The adverse effects of increased WC shown in non–HIV-infected patients may be even larger among HIV patients, in whom WC is made up of increased VAT with loss of SAT, as opposed to non–HIV-infected patients, with obesity and excess VAT and

TABLE 5. Changes from Baseline in Body Composition, Lipid Levels, Biochemical Measures, Glycemic Measures, and Immune Function in the Extension Phase

Variables	Baseline, Mean ± SD			At 52 Weeks, Mean ± SD			Absolute Difference (95% CI)*	Relative Difference (%)†
	T-T (n = 92)	T-P (n = 85)	P-T (n = 86)	T-T (n = 92)	T-P (n = 85)	P-T (n = 86)		
				Mean change from Baseline (Percent)				
Body composition								
Visceral adipose tissues (cm^2)	197 ± 91.2	200 ± 86.3	199 ± 100	−41 ± 57 (−17.5)‡	0 ± 53 (1.3)	−26 ± 47 (−14.0)‡	−41 (−57 to −25)§	−18.8
SC adipose tissues (cm^2)	202 ± 107	227 ± 118	208 ± 102	5 ± 47 (6.1)	1 ± 44 (2.9)	1 ± 37 (1.9)	4 (−10 to 17)	3.2
Ratio of visceral to SC adipose tissue	1.45 ± 1.28	1.42 ± 2.29	1.36 ± 1.28	−0.34 ± 0.62 (−18.9)‖	0.19 ± 2.27 (−0.6)	−0.19 ± 0.47 (−15.8)‡	−0.5 (−1.0 to −0.0)¶	−18.3
Trunk fat (kg)	13.8 ± 4.0	15.9 ± 5.7	14.6 ± 4.8	−0.8 ± 2.1 (−5.1)‡	0.4 ± 2.3 (2.6)	−0.7 ± 2.3 (−5.1)‖	−1.2 (−1.9 to −0.5)§	−7.7
WC (cm)	104 ± 8	106 ± 9	104 ± 9	−3.8 ± 6.0 (−3.5)‡	−2.4 ± 6.0 (−2.3)‡	−3.0 ± 6.8 (−3.0)‡	−1.4 (−3.1 to 0.4)¶	−1.2
Waist-to-hip ratio	1.05 ± 0.09	1.05 ± 0.06	1.05 ± 0.06	−0.04 ± 0.06 (−3.6)‖	−0.02 ± 0.05 (−1.8)‖	−0.03 ± 0.06 (−3.0)‖	−0.02 (−0.04 to −0.00)¶	−1.8
Fat in limbs (kg)	6.5 ± 3.9	7.2 ± 4.2	6.7 ± 4.0	−0.2 ± 0.9 (−0.8)	−0.1 ± 1.5 (1.2)	−0.0 ± 1.4 (0.6)	−0.1 (−0.5 to 0.2)	−2.0
Lean mass (kg)	63.8 ± 9.2	63.0 ± 9.5	61.2 ± 11.0	1.0 ± 2.5 (1.7)‡	−0.3 ± 2.4 (−0.3)	1.3 ± 2.3 (2.3)‡	1.3 (0.6 to 2.0)§	2.0
Body mass index (kg/m^2)	28.1 ± 3.8	28.9 ± 4.0	28.4 ± 4.3	−0.1 ± 1.6	0.0 ± 2.1	0.1 ± 1.5	−0.1 (−0.7 to 0.5)	
Lipids levels								
Triglycerides (mg/dL)	256 ± 214	217 ± 170	215 ± 123	−37 ± 196 (1.4)	4 ± 177 (7.0)	1 ± 120 (4.0)	−41 (−96 to 15)	−5.7
Cholesterol								
Ratio of total SC cholesterol to HDL cholesterol	5.01± 1.69	4.66 ± 1.54	4.57 ± 1.42	−0.23 ± 1.75 (−0.9)	0.13 ± 1.19 (4.9)	0.06 ± 1.01 (2.9)	−0.36 (−0.81 to 0.10)	−5.9
Total (mg/dL)	193 ± 45	185 ± 41	190 ± 34	−10 ± 42 (−2.7)‖	9 ± 36 (6.9)‖	−1 ± 32 (−0.1)	−19 (−31 to −7)¶	−9.6
HDL (mg/dL)	42 ± 14	42 ± 12	45 ± 15	0 ± 9 (2.5)	1 ± 8 (4.4)	−1 ± 8 (−0.8)	−1 (−3 to 2)	−1.9
Biochemical measures								
Insulin-like growth factor-1 (ng/mL)	162 ± 73	143 ± 64	153 ± 65	92 ± 113 (68.9)‡	−6 ± 52 (1.5)	90 ± 125 (71.2)‡	98 (72 to 125)§	67.4
Glycemic measures								
Glucose (mg/dL)								
Fasting	99 ± 15	104 ± 18	98 ± 19	0 ± 16	−2 ± 34	1 ± 21	2 (−6 to 11)	—
At 2 hrs	114 ± 32	116 ± 38	118 ± 39	−2 ± 38	2 ± 35	7 ± 37	−4 (−18 to 10)	—
Insulin (μIU/mL)	22 ± 28	30 ± 34	19 ± 16	−5 ± 26	−10 ± 40	4 ± 30	5 (−7 to 17)	—
Immune function								
CD4 Count ($cells/mm^3$)	579 ± 300	580 ± 272	604 ± 283	6 ± 158	0 ± 191	52 ± 222	5 (−56 to 67)	—
Viral load (%)#								
Undetectable	83.7	80.0	88.2	84.0	78.2	95.4	—	—
50–400 copies/mL	8.7	11.8	7.1	13.3	14.5	1.5	—	—
>400 copies/mL	7.6	8.2	4.7	2.7	7.3	3.1	—	—

Data are reported as mean ± SD, unless otherwise indicated. To convert the values for triglycerides to mmol/L, multiply by 0.0113; to convert the values for TC and HDL cholesterol to mmol/L, multiply by 0.0259; to convert the values of IGF-1 to nmol/L, multiply by 0.131; to convert the values for glucose to mmol/L, multiply by 0.0555; to convert the values for insulin to pmol/L, multiply by 6.945.

*The values are for the difference between the changes from baseline in the T-T group and the T-P group.

†The values are for the difference between the percent change from baseline in the T-T group and the T-P group.

‡$P < 0.001$ for the within-group comparison between baseline and week 52.

§$P < 0.001$ for the comparison between the changes from baseline in the T-T group and the T-P group.

‖$P < 0.05$ for the within-group comparison between baseline and week 52.

¶$P < 0.05$ for the comparison between the changes from baseline in the T-T group and the T-P group.

#For viral load, the values are the percentages of patients at baseline and at week 52.

CI, confidence interval.

SAT. Therefore, there may be a particularly strong logic to selectively reducing VAT in the HIV population. The data from the current randomized placebo-controlled study add to the growing body of literature on the effects of tesamorelin on VAT. In randomized placebo-controlled studies enrolling almost 900 patients, there has been a very consistent reduction in VAT in response to tesamorelin.

In contrast to prior studies with GH, treatment with tesamorelin was again shown in this study not to reduce SC fat. The selective effect to reduce visceral fat is important among HIV-infected patients, the majority of whom also demonstrate SC fat loss with long-term ART, as seen in the current study in which two-thirds of the subjects noted lipoatrophy and baseline extremity fat by DEXA was low. Indeed, recent studies suggest that the SC depot may be protective in terms of metabolic abnormalities[23] and a strategy which does not contribute to a further loss in SC fat is ideal for the HIV population.

A number of studies have now shown GH secretion to be relatively reduced among HIV-infected patients with increased abdominal fat accumulation.[12,13] These studies show normal

TABLE 6. AEs and Serious Adverse Events in the Extension Phase (26–52 Weeks)

Events	T-T (n = 92)	T-P (n = 85)	P-T (n = 86)
	% Patients		
AEs*			
Any event	73.9	57.6	76.7
Related to treatment	37.0	23.5	53.5
Resulting in study discontinuation	2.2	4.7	4.7
Events reported in >10% of the patients			
Injection site pruritus	4.3	0.0	10.5
Arthralgia	8.7	7.1	16.3
Pain in extremity	6.5	1.2	12.8
Events reported in >5% of the patients			
Diarrhoea	3.3	4.7	5.8
Injection site erythema	3.3	0.0	5.8
Injection site pain	0.0	0.0	5.8
Upper respiratory tract infection	8.7	4.7	3.5
Musculoskeletal stiffness	1.1	0.0	5.8
Paraesthesia	2.2	3.5	5.8
Insomnia	0.0	0.0	5.8
Serious adverse events*			
Any events	3.3	1.2	3.5
All events reported			
Retinopathy	1.1	0.0	0.0
Abdominal pain	0.0	1.2	0.0
Chest pain	1.1	0.0	0.0
Hodgkin disease	0.0	0.0	1.2
Mental status changes	1.1	0.0	0.0
Nephrolithiasis	0.0	0.0	1.2
Dyspnoea	0.0	0.0	1.2

*Treatment emergent.

GH pulsatility, but reduced pulse height and width, suggesting a reduction in GHRH-stimulated GH pulsatility.[13] Prior studies have begun to investigate the effects of a novel strategy, using a GRF analogue, to augment endogenous GH pulsatility and thus address a fundamental metabolic abnormality in HIV-infected patients with excessive central fat accumulation.[24]

In contrast to GHRH, which results in more physiological increases in GH and IGF-I, dosing with exogenous GH requires careful titration to avoid significant GH excess. Large Phase III studies using GH at high doses resulted in pharmacological increases in GH, with concomitant increases in glucose,[25,26] not seen with tesamorelin. Importantly, in the current and prior studies with tesamorelin, glucose was not disturbed even among patients with IGT diet-controlled diabetes, who were permitted to enroll and constituted 15%–20% of the study population. Indeed, even low dose GH, carefully titrated to maintain physiological levels of IGF-I, significantly increased 2-hour glucose, achieving a comparable, but smaller 9% reduction in VAT over a longer period of 18 months compared with a 17.5% reduction over 12 months in response to tesamorelin in the current study.[27]

Although it is reassuring that tesamorelin does not significantly adversely affect glucose homeostasis, it is important to consider why glucose was not improved given the significant reduction in VAT in this study. The mechanism of action of tesamorelin is a highly specific effect on the pituitary to increase endogenous GH release. GH is known to be directly antagonistic to insulin and low dose GH itself, as opposed to tesamorelin, worsens glucose in the setting of improved visceral fat among HIV-infected patients.[27] In contrast, tesamorelin improves VAT but is neutral to glucose. One potential hypothesis is that there is some mild aggravation of insulin action, as a result of increased pituitary GH secretion, but of a degree that is counterbalanced by the improvement in VAT, so that the net effect is neutral. It is also possible that concomitant use of insulin antagonistic antiretroviral drugs counters the improvements in glucose that would ordinarily be expected with reductions in VAT among HIV-infected patients.

In contrast to a prior study of tesamorelin, the current study did not show a significant decrease in triglycerides, but rather a trend, amounting to a net reduction in triglycerides of 26 mg/dL compared with placebo over 6 months. The treatment effect was larger in the prior study, 59 mg/dL, but entry triglyceride levels were higher in that study.[14] One explanation may be that the current study included European sites, where dietary and lifestyle patterns may differ. Importantly, a similar proportion of patients were receiving PIs in both studies. TC was reduced significantly for subjects receiving tesamorelin for 12 months in the current study suggesting at least 1 additional cardiovascular benefit beyond that of a reduction in VAT.

The effects of tesamorelin on body image are important and consistent between the 2 Phase III studies. Patients receiving tesamorelin in this double-blinded placebo-controlled study reported less distress regarding abdominal hypertrophy, and physician rating of the abdominal profile also improved. This reduction in stress related to body image may contribute to increased compliance with ART. At a minimum, the significant reduction in belly distress suggests that the benefit in VAT reduction and WC were clinically significant to patients. We also assessed the important question as to whether effects on body image persist over 12 months. In the current study, we demonstrate data that the improvement in body image indeed persisted in those receiving 12 months of treatment in the T-T group, but also persisted, in those in the T-P group who switched off tesamorelin. The persistence of these effects after discontinuation of tesamorelin was stronger in the current study than in the prior study.[15]

Overall, AE rates and SAEs did not differ between tesamorelin and placebo in the primary efficacy phase and did not increase further with continuing treatment over 12 months in the safety extension phase. The development of lung cancer in one of the tesamorelin-treated patients was most likely unrelated to study medication, given the short exposure period of 3 months and physiological IGF-I during treatment. A small percentage of patients experienced a hive-like rash that did extend beyond the injection site in some patients. These patients were discontinued and improved, without further consequence. A small percentage of patients treated with tesamorelin can be expected to have such a reaction, and for such patients, treatment discontinuation is prudent.

How does tesamorelin compare with other strategies to reduce visceral fat in HIV-infected patients? Neither metformin nor lifestyle modification including, thrice weekly exercise, significantly reduce visceral fat to the degree of tesamorelin,[28–30] but these strategies improved markers of glucose homeostasis, whereas tesamorelin was neutral to glucose. Effects of tesamorelin on lipids are stronger than that seen with metformin and lifestyle modification. Body image was not assessed in response to metformin and or lifestyle modification and was significantly improved in response to tesamorelin.

Tesamorelin is not yet approved for use in North America or Europe. However, we now report completion of a second Phase III study, again demonstrating significant efficacy of tesamorelin (18% reduction in VAT) and good safety with ongoing treatment to 12 months in a randomized placebo-controlled study of over 400 patients. With these new data, there are now consistent results from 2 large Phase III, randomized placebo-controlled studies to suggest that this is a potentially useful clinical strategy to selectively reduce VAT and improve body image among HIV-infected patients with abdominal fat accumulation in the context of ART treatment.

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APPENDIX I: STUDY INVESTIGATORS

The following investigators participated in the study: Ottawa Hospital, Ottawa, Ontario, Canada—J. Angel; Hospital CU de Santiago, Unidad de Enfermedades Infecciosas, Santiago de Compostela, Spain—A. Antela López; Hendry Glades Department of Health, Labelle, FL—J. Beal; Northstar Medical Center, Chicago, IL—D. Berger; Central Texas Clinical Research, Austin, TX—C. Brinson; AIDS Research Alliance, West Hollywood, CA—S. Brown; Hôpital de l'Hôtel Dieu Lyon, Lyon Cedex 02, FRANCE—L. Cotte; CHU St-Pierre, Clinique des Maladies Infectieuses, Brussels, BELGIUM—N. Clumeck; UCLA School of Medicine, Los Angeles, CA—J. Currier; ACRIA, New York, NY—J. Ernst; Clínico San Carlos, Enfermedades Infecciosas, Hospital de Dia, Madrid, SPAIN—V. Estrada; Montreal General Hospital,

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