Long-term safety and effects of tesamorelin, a growth hormone-releasing factor analogue, in HIV patients with abdominal fat accumulation

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Objective: Treatment of HIV patients with daily tesamorelin, a growth hormone-releasing factor analogue, for 26 weeks resulted in a significant decrease in visceral adipose tissue (VAT) and improvement in lipids. The objective of the 26-week extension phase was to evaluate long-term safety and effects of tesamorelin.

Design: HIV patients with central fat accumulation in the context of antiretroviral therapy were randomized to tesamorelin 2 mg ($n = 273$) or placebo ($n = 137$) s.c. daily for 26 weeks. At week 26, patients originally on tesamorelin were rerandomized to 2 mg tesamorelin (T–T group, $n = 154$) or placebo (T–P group, $n = 50$), whereas patients originally on placebo were switched to tesamorelin (P–T group, $n = 111$).

Methods: Safety included adverse events and glucose parameters.

Results: Tesamorelin was generally well tolerated. The prevalence of adverse events and serious adverse events during the extension phase was comparable with the initial phase. Changes in glucose parameters over 52 weeks were not clinically significant and similar to those after 26 weeks. The change in VAT was sustained at −18% over 52 weeks of treatment ($P < 0.001$ versus baseline) as was the change in triglycerides (−51 mg/dl, $P < 0.001$ versus baseline). Similar sustained beneficial effects were seen for total cholesterol, but high-density lipoprotein decreased minimally over 52 weeks. Upon discontinuation of tesamorelin, VAT reaccumulated.

Conclusion: Treatment with tesamorelin was generally well tolerated and resulted in sustained decreases in VAT and triglycerides over 52 weeks without aggravating glucose. Though effects on VAT are sustained during treatment for 52 weeks, these effects do not last beyond the duration of treatment.

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Introduction

HIV-infected patients receiving antiretroviral therapy (ART) often demonstrate fat accumulation in the abdomen [1,2], as well as dyslipidemia and/or insulin resistance [2,3], which may contribute to increased cardiovascular disease [4,5]. In addition, excess abdominal fat has been shown to have a negative impact on body image and to result in non–adherence to ART [6,7]. No treatment is currently approved to reduce visceral adipose

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tissue (VAT) in this patient population. We recently reported the results from a randomized, placebo-controlled phase 3 study of tesamorelin, a growth hormone-releasing factor (GRF) analogue, which was shown to significantly reduce VAT and improve lipids, without significant effects on glucose over 26 weeks [8]. Data from a 26-week extension phase of that study are now available, which provide further information on the safety of tesamorelin during longer term use over 52 weeks and the sustainability of treatment responses over this time period as well as the durability after treatment discontinuation.

Methods

Patients

Patients with HIV were recruited at 43 sites between June 2005 and April 2006. Eligibility criteria included the receipt of ART for at least 8 weeks and presence of an excessive accumulation of abdominal fat, defined as a waist circumference of at least 95 cm and a waist-to-hip ratio of at least 0.94 for men and a waist circumference of at least 94 cm and a waist-to-hip ratio of at least 0.88 for women (for complete eligibility criteria, see [8]). The study was approved by the Institutional Review Board (IRB) at each site, and all patients provided written informed consent before screening.

Study design and intervention

The study consisted of a 26-week main phase (initial randomized phase) followed by a 26-week rerandomized extension phase. The main phase was designed to assess the primary efficacy endpoint, VAT by computerized tomographic (CT) scan and secondary endpoints, including lipids and safety parameters [8]. In contrast, the extension phase was designed to further evaluate safety of daily 2 mg tesamorelin from weeks 26 to 52 of treatment and to explore duration of effect following the initial 26-week randomized phase. Only patients completing the initial 26-week randomized phase and with fasting blood glucose level less than 150 mg/dl (8.33 mmol/l) were allowed to enter the 26-week extension phase. A data and safety monitoring board met twice to review safety data.

For the extension phase, patients who received tesamorelin in the main phase underwent a second randomization to receive either tesamorelin (T−T group) or matching placebo (T−P group) in a ratio of 3 : 1, whereas patients on placebo were assigned to receive tesamorelin (P−T group) (Fig. 1). Patients and investigators were unaware of assignments to study groups. Assessment of safety was performed at rerandomization (week 26) and at weeks 32, 39 and 52, whereas assessment of body composition was performed at weeks 26, 39 and 52. Tesamorelin and matching placebo were distributed as previously described [8].

Theratechnologies funded and designed the study in consultation with Drs Grinspoon and Falutz. The statistical analyses were performed by Quintiles Canada, and body image outcomes were assessed by Phase V Technologies Inc. (Wellesley, Massachusetts, USA).

Assessments

VAT was determined by CT and lean body mass, trunk and extremity fat from dual energy X-ray absorptiometry (DEXA) as previously described [8]. Insulin-like growth factor-1 (IGF-1) was measured at Esoterix (Calabasas Hills, California, USA). Glucose and other safety parameters were assessed at Gamma-Dynacare (Brampton, Ontario, Canada) as previously described [8]. Antitesamorelin IgG antibody titer was defined as the highest dilution factor with an optical density greater than the plate-specific negative cut-off value. Viral load and CD4 cell counts were assessed locally at each site. Body image outcomes, including belly and composite body appearance distress and belly profile silhouette assessments, were measured at baseline, week 26, and week 52 using a validated questionnaire as previously described [8].

Statistical analysis

The objectives of the extension phase of the study were to assess long-term safety of tesamorelin, including adverse events and effects on glucose and insulin, in individuals receiving tesamorelin for 52 weeks and 26-week safety in patients randomized to placebo for 26 weeks in the main phase of the study followed by tesamorelin for 26 weeks in the extension phase, to assess duration of effect on VAT and secondary endpoints among individuals initially randomized to tesamorelin for 26 weeks followed by placebo for 26 weeks in the extension phase, and to collect data on VAT and secondary endpoints in those individuals receiving tesamorelin for 52 weeks. Comparison of long-term efficacy between tesamorelin and placebo over 52 weeks was not an objective and could not be determined based on the design of the extension phase, as there was not a group treated with placebo for 52 weeks.

Baseline characteristics were compared using analysis of variance for quantitative variables and Fisher's Exact test or Pearson χ^2-test, as appropriate, for qualitative variables. Evaluation of safety was based on the safety population, which included all randomized individuals who have received at least one dose of a study drug during the extension phase of the study; patient data were analyzed according to the treatment actually received. The efficacy endpoints were analyzed on the basis of data for patients who had received at least one dose of study drug during the extension phase with the last observation carried forward for those patients not completing the study. Within-treatment comparisons were performed in each treatment group using a repeated-measure analysis of variance. The use of lipid-lowering treatment was added
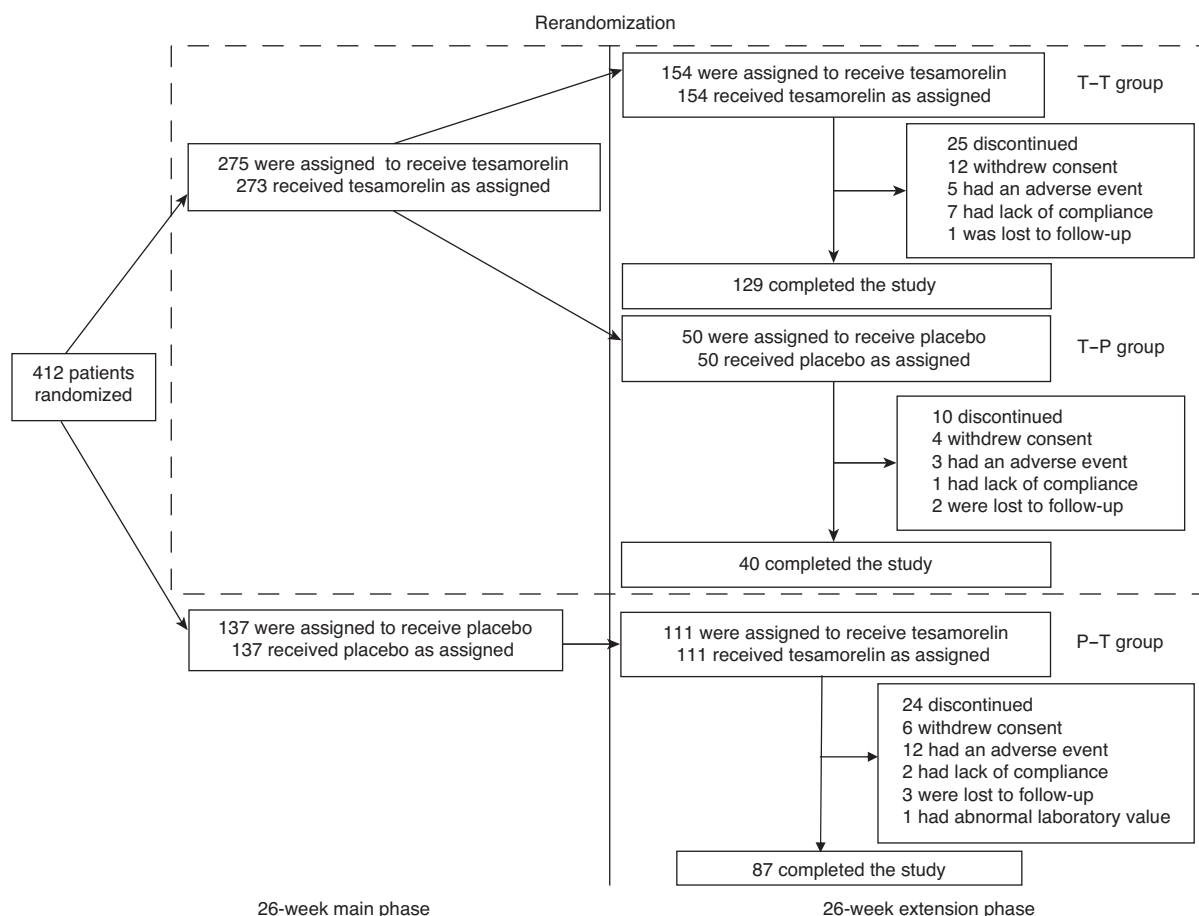
Fig. 1. Flow of patients through the study showing initial 26-week randomized phase (main phase) and then 26-week extension phase. Patient disposition in the main phase has been previously reported [8]. Change from baseline at 52 weeks was determined for T−T and T−P groups (dashed line).

as a covariate in the model for lipids. A secondary analysis was performed in patients with at least one postdose assessment for the variable VAT and who received a study drug as instructed without a significant protocol violation (per-protocol population).

Results

Patients
Of 315 patients who entered the extension phase of the study, 154 were in the T−T group, 50 in the T−P group, and 111 in the P−T group (Fig. 1). The overall discontinuation rate was 18.7% (16.2% in the T−T group, 20.0% in the T−P group and 21.6% in the P−T group). For patient disposition, see Fig. 1. Baseline characteristics of patients are shown in Table 1.

Safety assessment
Glucose and insulin
As in the first randomized phase, treatment with tesamorelin over 26 weeks in the extension phase (P−T group) did not result in clinically significant changes in glucose parameters (Changes from baseline at

week 52: fasting glucose: 1 ± 14 mg/dl; 2 h glucose: 3 ± 43 mg/dl; fasting insulin: 3 ± 17 µIU/ml). Administration of tesamorelin over 52 weeks did not result in clinically significant changes or worsening in glucose parameters in the T−T group (Table 2).

Immunological parameters
CD4 cell count changes at week 52 were 19 ± 199, -28 ± 174 and 25 ± 167 cells/µl for the T−T, T−P and P−T groups, respectively. In addition, the percentage of patients with undetectable viral load over 52 weeks was comparable with baseline and was as follows: 66.7% (T−T group), 76.9% (T−P group), and 68.7% (P−T group).

Adverse events
During the 26-week extension phase, the percentage of patients with treatment-related adverse events was 14% in the T−T group, and 18% in the T−P group. Nine serious adverse events were reported in the extension phase of the study, including the two previously reported deaths in tesamorelin-treated patients [8], one from coronary artery disease in a patient with a known history of the condition and one from complications of tonsillectomy hemorrhage (Table 3). None of the serious adverse events, including

Table 1. Demographic and baseline characteristics of the patients.

Variable	T–T group ($n = 154$)	T–P group ($n = 50$)	P–T group ($n = 111$)
Age (years)	48 ± 7	47 ± 7	48 ± 8
Gender (percentage of men/women)	88/12	86/14	86/14
Race (percentage of C/AA/H)[a]	78/12/8	80/8/8	76/14/8
Weight (kg)	89.1 ± 13.7	92.1 ± 17.3	90.4 ± 13.6
BMI (kg/m^2)	28.9 ± 4.2	30.2 ± 4.7	29.1 ± 4.2
Waist circumference (cm)	104 ± 9	105 ± 12	105 ± 10
Waist-to-hip ratio	1.05 ± 0.06	1.04 ± 0.06	1.05 ± 0.07
Viral load (percentage of patients with)			
Undetectable	71	59	68
50–400 copies/ml	20	31	23
>400 copies/ml	10	10	9
CD4 cell count (cells/µl)	650 ± 311	625 ± 304	572 ± 261
Fasting glucose (percentage of patients with)			
≤ 110 mg/dl	83	80	83
110–125 mg/dl	17	20	15
>125 mg/dl	0	0	3

Data are mean $\pm$ SD, unless otherwise indicated.
[a]AA, African–American; C, Caucasian; H, Hispanic.

the two deaths, was reported by investigators to be related to the study drug.

During the extension phase, two patients in the T–T group and four patients in the P–T group reported urticarial reactions extending beyond the injection site(s) within 4 months after rerandomization into the extension phase of the study; the drug was discontinued in all six patients. The overall rate of urticarial reactions was approximately 2% in patients receiving tesamorelin in the extension phase, similar to that seen in the initial randomized phase. Systemic reactions, including nausea, light-headedness and tachycardia, developed in one of these patients.

Maintenance of tesamorelin effects during the extension phase

Body composition
At week 26, the percentage change from baseline in VAT was −18.4%, and −18.6% for the T–T and T–P groups, respectively. Patients in the T–T group maintained VAT loss over the 52-week treatment period (−18.1%, $P < 0.001$ versus baseline), whereas patients in the T–P group regained VAT lost at week 26 (−1.6%, $P = 0.19$ versus baseline). Patients in the T–P group gained back most of the VAT lost by week 39 of treatment (Fig. 2). Similar changes from baseline in VAT were observed in the per-protocol population, as defined in Methods, at week 52 (−19.8%, $P < 0.001$ versus baseline and 3.0%, $P = 0.72$ versus baseline for the T–T and T–P groups, respectively). The percentage change from baseline to week 52 in VAT was significant in both men and women in the T–T group (−17.4 and −23.4%, respectively). No clinically significant changes from baseline in subcutaneous adipose tissue (SAT) were seen among the patients continuing tesamorelin administration for 52 weeks (Table 2). Changes in trunk fat paralleled those in VAT (Table 2), whereas changes in limb fat were not observed over 52 weeks (Table 2).

Insulin-like growth factor-1
IGF-1 significantly increased from baseline in the T–T group over 52 weeks (+69.0 ng/ml) ($P < 0.001$ versus baseline). In contrast, IGF-1 returned to baseline in the T–P group at 52 weeks (Table 2). When the results were adjusted for age and sex, the mean changes in IGF-1 levels represented a standard deviation score of 1.57 ± 2.24 and -0.33 ± 1.13 for the T–T and T–P groups, respectively, at 52 weeks.

Lipids
The changes in triglycerides (−51 ± 169 mg/dl, $P < 0.001$ versus baseline) and total cholesterol (−7 ± 36 mg/dl, $P = 0.009$ versus baseline) were maintained over 52 weeks in the T–T group. In addition, changes in triglycerides and total cholesterol (−31 ± 98 mg/dl, $P = 0.03$ versus baseline and −11 ± 32 mg/dl, $P = 0.02$ versus baseline for triglycerides and total cholesterol, respectively) were also maintained in the T–P group at week 52, even after discontinuation of tesamorelin (Table 2). No significant changes from baseline to week 52 were observed in the ratio of total cholesterol to high-density lipoprotein (HDL) cholesterol in the T–T group (0.04 ± 1.22, $P = 0.73$ versus baseline at 52 weeks) or the T–P group (0.12 ± 0.7, $P = 0.25$ versus baseline) (Table 2). Mean HDL cholesterol levels decreased minimally, but significantly from baseline in the T–T group ($P < 0.05$ versus baseline) and T–P group ($P < 0.001$ versus baseline) at 52 weeks (Table 2).

Body image
Patients who continued treatment (T–T group) experienced sustained improvements in belly appearance distress (12.2 ± 2.1, $P < 0.001$ for week 52 versus baseline and $P = 0.32$ for week 52 versus week 26), body appearance distress (5.7 ± 1.1, $P < 0.001$ for week 52 versus baseline and $P = 0.45$ for week 52 versus week 26) as well as patient-reported belly profile (−1.0 ± 0.1, $P < 0.001$ for week 52 versus baseline and $P = 0.11$ for week 52 versus week 26) over the 52-week treatment period. On the

Table 2. Changes from baseline in body composition, lipid levels, and biochemical, and glycemic measures.

	Baseline		Week 26		Week 52		Change from Baseline at week 52	
	T–T (n=154)	T–P (n=50)	T–T (n=154)	T–P (n=50)	T–T (n=154)	T–P (n=50)	T–T (n=154)	T–P (n=50)
Body composition								
VAT (cm²)	181±78	174±72	145±72	144±72	148±81	168±71	−32±45 (−18.1%)**	−6±41 (−1.6%)
SAT (cm²)	221±128	239±129	220±127	235±127	214±123	237±124	−7.8±39.0* (−1.6%)	−1.8±30.6 (0.9%)
VAT/SAT	1.43±1.89	1.04±0.99	1.10±1.39	0.79±0.62	1.14±1.44	1.01±0.91	−0.28±0.85**	−0.02±0.54
Trunk fat (kg)	14.7±5.7	15.3.±5.3	13.5±6.0	14.3±5.4	13.6±6.0	15.7±5.4	−1.2±2.2**	0.2±2.0
Waist circumference (cm)	104±9	105±12	101±10	102±12	101±10	104±13	−3.3±5.5**	−0.9±5.4
Waist-to-hip ratio	1.05±0.06	1.04±0.06	1.01±0.07	1.00±0.06	1.02±0.09	1.03±0.06	−0.03±0.07**	−0.01±0.05
Limb fat (kg)	6.9±4.4	7.0±3.7	6.9±4.3	6.9±3.6	6.9±4.4	7.1±3.6	0.0±1.1	0.1±0.9
Lean body mass (kg)	62.1±10.1	62.8±10.5	63.7±10.2	65.2±11.0	63.6±10.4	63.3±11.0	1.4±2.9**	0.1±2.8
Lipid levels								
Triglycerides (mg/dl)	265±207	223±126	208±141	174±103	214±162	192±110	−51±169**	−31±98*
Total chol/HDL chol	4.50±1.46	4.32±1.10	4.15±1.18	4.00±1.17	4.52±1.44	4.44±1.14	0.04±1.22	0.12±0.70
Total chol (mg/dl)	195±46	198±38	185±38	187±32	187±43	187±28	−7±36*	−11±32*
HDL chol (mg/dl)	47±15	48±14	48±15	49±14	44±15	45±12	−2±10*	−4±6**
Biochemical measures								
IGF-1 (ng/ml)	160±57	162±56	291±124	281±105	231±119	148±52	69±107**	−14±50
CRP (mg/l)	3.9±4.6	4.6±11.1	4.0±11.1	3.4±7.2	3.5±6.2	4.4±11.0	−0.3±6.7	−0.2±2.5
Adiponectin (µg/ml)	5.5±4.4	4.9±2.7	6.1±5.4	5.2±3.0	6.8±5.7	5.4±2.7	1.4±2.6**	0.4±1.7
Glycemic measures								
Fasting glucose (mg/dl)	95±13	98±10	98±14	101±19	99±16	94±14	3±14	−3±14
2h glucose (mg/dl)	112±35	111±45	112±42	110±38	112±41	106±38	2±40	0±32
Fasting insulin (µIU/ml)	20±32	17±9	21±17	19±12	20±15	14±7	2±14	−2±9

Data are mean ± SD, unless otherwise indicated. CRP, C-reactive protein; HDL, high-density lipoprotein; IGF-1, insulin-like growth factor-1; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; chol, cholesterol.
*$P<0.05$ for the within-group comparison between baseline and week 52.
**$P<0.001$ for the within-group comparison between baseline and week 52.

Table 3. Adverse events and serious adverse events.

Percentage of patients with	T–T group (n = 154)	T–P group (n = 50)	P–T group (n = 111)
Adverse events			
Any event	57.8	66.0	74.8
Related to treatment	14.3	18.0	36.0
Resulting in study discontinuation	2.6	6.0	11.7
Events reported in >5% of the patients			
Arthralgia	3.9	4.0	14.4
Upper respiratory tract infection	6.5	2.0	4.5
Nasopharyngitis	5.8	2.0	5.4
Pain in extremity	1.9	0.0	5.4
Injection-site erythema	0.6	0.0	7.2
Injection-site pruritus	0.0	0.0	5.4
Sinusitis	5.2	0.0	6.3
Diarrhea	2.6	6.0	2.7
Rash	1.9	10.0	3.6
Back pain	1.3	8.0	2.7
Cough	1.3	6.0	5.4
Serious adverse events			
Any event	2.6	4.0	2.7
Spontaneous abortion	0.6	0.0	0.0
Fatal coronary artery disease[a]	0.6	0.0	0.0
Pneumonia	0.6	0.0	0.0
Cellulitis	0.6	0.0	0.9
Anal cancer[b]	0.0	2.0	0.0
Ludwig's angina	0.0	2.0	0.0
Intestinal perforation	0.0	0.0	0.9
Fatal hemorrhage after tonsillectomy	0.0	0.0	0.9

[a]This patient had a known history of coronary artery disease.
[b]This patient was determined to have a previously undisclosed history of anal cancer.

contrary, patients who discontinued treatment tended to lose improvements seen at week 26 in belly appearance distress (5.0 ± 3.1, $P = 0.12$ for week 52 versus baseline and $P = 0.05$ for week 52 versus week 26), body appearance distress (2.4 ± 1.6, $P = 0.14$ for week 52 versus baseline and $P = 0.09$ for week 52 versus week 26) and patient-reported belly profile (−0.4 ± 0.2, $P = 0.05$ for week 52 versus baseline and $P = 0.04$ for week 52 versus week 26).

Inflammatory and other biochemical markers
The increase in adiponectin level was maintained in the T–T group (1.4 ± 2.6 μg/ml, $P < 0.001$ versus baseline) over 52 weeks. On the contrary, adiponectin level at week 52 was not significantly different from baseline in the
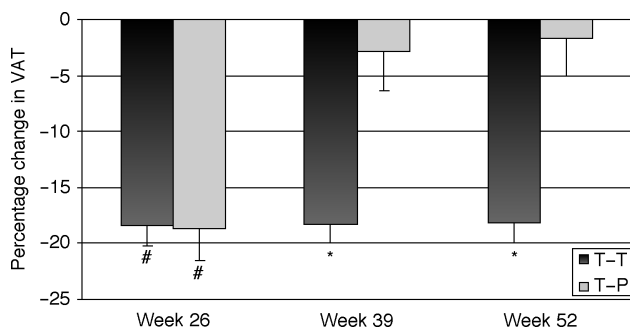

Fig. 2. Percentage changes from baseline in VAT in the T–T and T–P groups from week 26 to 52 in the study. *$P < 0.001$ vs. baseline, #$P < 0.001$ vs. baseline and vs. placebo in main phase. Data are mean ± SEM.

T–P group. Significant changes in C-reactive protein (CRP) levels were not observed in either T–T or T–P group at week 52 (Table 2).

Adherence
During the extension phase, the overall adherence as determined by a count of vials of medication used was 96.6% (97.0 in the T–T group, 98.1% in the T–P group, and 95.4% in the P–T group).

Antibodies
Antitesamorelin IgG antibodies were reported in 50% of patients receiving tesamorelin for 26 weeks in the initial randomized phase. At week 52, antitesamorelin IgG antibodies were detected in 53.7, 21.1, and 67.5% of patients in the T–T, T–P, and P–T groups, respectively. All the individuals affected with urticarial reactions during the extension phase, with the exception of one, tested positive for IgG antibodies against tesamorelin. No significant differences in IGF-1 and VAT levels were observed between patients with and without antibodies in the T–T group (changes from baseline at week 52: VAT: −20.5 versus −18.1% for patients with versus without antibodies, $P = 0.44$; IGF-1: 78 ± 92 versus 64 ± 108 ng/ml for patients with versus without antibodies, $P = 0.41$). Moreover, there were no significant differences in the changes from baseline in IGF-1 and VAT levels by antitesamorelin IgG antibody titers among tesamorelin-treated patients at week 26 [IGF-1: 125 ± 104, 120 ± 111, 137 ± 145, and 106 ± 80 ng/ml for antitesamorelin IgG antibody titer categories 0,

25–50, 100–200, ≥400, respectively, $P = 0.79$; VAT: -16.4 ± 22.3, -18.4 ± 21.8, -21.8 ± 23.0, and $-18.2 \pm 20.3\%$ for the same titer categories, $P = 0.55$ (data not previously reported for the main phase of the study)], nor among patients receiving tesamorelin over 52 weeks (T–T group) [IGF-1: 64 ± 108, 71 ± 94, 86 ± 79, and 102 ± 116 ng/ml for antitesamorelin IgG antibody titer categories 0, 25–50, 100–200, ≥400, respectively, $P = 0.72$; VAT: -18.1 ± 24.7, -21.6 ± 25.7, -20.7 ± 26.1, $-13.7 \pm 16.8\%$ for the same titer categories, $P = 0.74$].

Discussion

The primary purpose of this extension study was to determine the safety of 52 weeks dosing of tesamorelin. Secondary objectives were to determine the durability of effect after treatment discontinuation in a small subset of individuals who were initially treated with tesamorelin for 26 weeks and then with placebo for 26 weeks and the sustainability of response in those patients treated for 52 weeks. The primary results indicate that tesamorelin dosing over 52 weeks was well tolerated, including with regard to critical safety parameters such as glucose. Reduction in VAT seen over 26 weeks was sustained with 52 weeks of dosing, but VAT reaccumulated to baseline levels after treatment was discontinued.

Assessment of safety was the primary goal of this extension study. In terms of adverse events and serious adverse events, the percentages were similar during the 26-week extension phase as during the primary randomized phase among patients treated with tesamorelin. Discontinuation rates were better with tesamorelin, but that was likely related to the fact that patients who were not tolerant had already dropped out by week 26. Two deaths occurred in the patients treated with tesamorelin, as previously reported [8]. During the extension phase, randomization between tesamorelin and placebo was not equal, as the primary goal was to collect safety data on patients maximally exposed to tesamorelin. Initial randomization and rerandomization were weighted toward treatment, and 84% of individuals were receiving tesamorelin versus 16% of individuals receiving placebo during the 26-week extension phase. A true comparison of event rates between tesamorelin and placebo-treated patients during the extension phase was not possible due to the much greater preponderance of tesamorelin-treated patients, but the death rate in terms of overall person-year exposure to tesamorelin (2/270 patient years, 7.4/1000 person-year), is well below expected mortality rate of patients treated in the modern era of ART (25.4/1000 person-year, 95% confidence interval 23–28) [9]. Furthermore, the deaths were not reported as likely due to the study drug by the study investigators.

Urticarial rash was seen in six tesamorelin-treated patients in the extension phase, a similar number to that reported in the first randomized phase. All but one was self-limiting, and all patients were discontinued from the study and did well without known sequelae. Five out of six patients with an urticarial rash tested positive for IgG antibodies against tesamorelin in the extension phase. In contrast, antibodies were seen in approximately half of all tesamorelin treated patients. Of note, antitesamorelin IgG antibody titers decreased once tesamorelin dosing was discontinued in those patients with urticarial rash who had follow-up visits. Our results suggest that a small percentage of patients exposed to tesamorelin may experience a generally localized urticarial skin reaction, which may become systemic. For those experiencing such reactions, continued treatment is not recommended. Further research on the antigenicity of tesamorelin and the significance of antibodies is needed.

IgG antibody levels decreased in the group of patients who switched from tesamorelin to placebo, but the study was not extended long enough to determine if and when these antibodies would completely disappear. The data do not suggest that these antibodies are neutralizing, as similar changes in IGF-1 and VAT were seen in those with and without antibodies. Moreover, this was confirmed by investigating differences by antitesamorelin IgG antibody titers, and no differences in changes in VAT or IGF-1 were seen by antibody titer either in the main phase or in the extension phase of the study. Prior data with other GRF analogues also suggest a high degree of antibody formation [10–13], and this may relate to the antigenicity of the underlying chemical structure or to an adaptation made in the manufacturing process. Further investigation on the nature of the antitesamorelin antibodies and their clinical significance is necessary, but data over 1 year do not suggest they are neutralizing over this period.

An important aim of the current protocol was to determine the effects of long-term tesamorelin on glucose levels. Consistent with the 26-week data, long-term treatment with tesamorelin did not result in clinically significant changes in glucose parameters. Approximately 16% of the individuals included had either impaired glucose tolerance or diet-controlled type 2 diabetes mellitus with fasting blood glucose less than 150 mg/dl. Overall, long-term treatment with tesamorelin over 52 weeks appears not to aggravate glucose homeostasis in HIV-infected patients with central fat accumulation and insulin resistance.

Reduction in VAT was maintained in patients receiving long-term tesamorelin over 52 weeks. The average decrease of 18% in this group of patients is large and clinically significant. These data suggest there is no tachyphylaxis to the effects of ongoing tesamorelin therapy and results can be sustained with up to 1 year of treatment. Conversely, the data demonstrate that discontinuation of

tesamorelin is associated with regain of visceral and truncal fat to baseline, as seen with growth hormone (GH) [14,15]. There is little precedent in terms of duration of effects on VAT outlasting treatment with strategies using GH. Among non-HIV-infected patients receiving GH for GH deficiency, changes in body composition and particularly body fat quickly revert after treatment is discontinued [16]. One theoretical advantage of GRF is that it might induce a long-term increase in pituitary GH secretion beyond the duration of therapy, but this was not shown to be the case by our study, and treatment effect is clearly limited to treatment duration, as is the case with GH.

It is interesting to compare the results of long-term GRF with that of long-term low dose GH [17]. With each strategy, IGF-1 increased by approximately the same amount, but the effect on VAT with tesamorelin was almost twice that seen with GH, and side effects, especially with respect to effects on glucose, were not seen with tesamorelin as they were with even physiological GH dosing. This may relate to the more physiological effects of GRF on GH pulsatility compared with exogenous GH.

The improvement in triglycerides and total cholesterol seen with tesamorelin were maintained over 52 weeks of treatment, and this was also the case for patients who received tesamorelin for 26 weeks followed by placebo. In patients receiving tesamorelin over 52 weeks, HDL cholesterol decreased minimally, but statistically significantly from baseline. However, the study did not include a 52-week placebo arm, and thus comparisons for efficacy over 52 weeks versus placebo are not possible. Overall, 52-week data suggest improvements that are at least sustained for triglycerides and total cholesterol, but not for HDL cholesterol. Further investigation will help to determine the long-term effects of tesamorelin on lipid components other than triglycerides.

Improvements in belly image distress and belly profile were sustained with long-term 52-week treatment with tesamorelin, but were lost after treatment discontinuation. These results mirror those seen for VAT and provide further evidence that the improvements in VAT with tesamorelin were clinically significant and resulted in improved body image.

This study has a number of clinical implications. A significant number of HIV-infected patients in the current era of highly active antiretroviral therapy (HAART) exhibit absolute or relative central fat accumulation in the context of peripheral fat loss. Our data suggest that tesamorelin may be useful for this population. Tesamorelin resulted in physiological increases in IGF-1 and dose titration is not necessary. Tesamorelin is not yet approved for use but if approved, patients who use this drug could expect, on average, a significant 18% decrease in VAT over 52 weeks of treatment, with simultaneous moderate improvements in triglyceride levels and body image, without aggravation of glucose. Thus, tesamorelin would be among the most potent therapeutic options available for HIV-infected patients with fat accumulation, with good long-term tolerability over 1 year. Importantly, tesamorelin has selective effects on visceral fat, and does not result in clinically significant changes in subcutaneous and extremity fat. However, dosing studies might be useful, as benefits do not last beyond the duration of therapy, and thus long-term therapy might be needed. Additional studies will be useful to determine whether prolonged and/or cyclical treatment could be beneficial over the long-term.

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