

Metabolic Effects of Tesamorelin (TH9507), a Growth Hormone-Releasing Factor Analogue, in HIV-infected Patients with Excess Abdominal Fat over a Period of 52 Weeks. A Pooled Analysis of 2 Multicenter, Double-blind, Placebo-controlled Phase 3 Trials with 816 Randomized Patients

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ABSTRACT

Background: HIV patients treated with antiretroviral therapy (ART) often experience increased visceral adipose tissue (VAT). We report pooled analysis from 2 randomized, placebo-controlled Phase 3 studies of tesamorelin in ART-treated HIV patients with excess abdominal fat.

Method: Patients were randomized to receive tesamorelin 2 mg (N=543) or placebo (N=263) subcutaneously daily. At Week 26, patients initially on tesamorelin were re-randomized to 2 mg tesamorelin (T-T group, N=246) or placebo (T-P, n=135) for an additional 26 weeks, whereas patients on placebo were switched to tesamorelin (P-T, N=197). The primary endpoint was the percent change in VAT by CT-scan at Week 26. Secondary endpoints included lipids, IGF-1 and safety. At Week 52, endpoints were safety and duration of effects on VAT.

Results: Baseline age was 48±7 (mean±SD) years and waist circumference 105±9cm. At Week 26, VAT decreased significantly in tesamorelin-treated patients (-13.1±21.1% P<0.001 vs. placebo), while no clinically significant changes were observed in limb fat by DEXA (0.2±13.2%, P=0.001 vs. placebo). No significant changes were observed in abdominal SAT (0.7±15.5%, P=0.08 vs. placebo). Treatment with tesamorelin was associated with a significant decrease in triglycerides (-0.4±1.6 mmol/L, P<0.001 vs. placebo). Mean IGF-1 levels increased within physiological range in tesamorelin-treated patients (84.1±101.3%, P<0.001 vs. placebo). At Week 52, improvements in VAT and triglycerides observed at Week 26 were sustained in the T-T group (-17.5±23.3% and -0.5±2.0 mmol/L, respectively, P<0.001 vs. baseline), while SAT was preserved. Patients in the T-P group regained VAT (0.3±26.3%, P=0.18 vs. baseline). Treatment with tesamorelin was overall well tolerated. No clinically significant differences were observed between groups in glucose parameters at both Weeks 26 and 52.

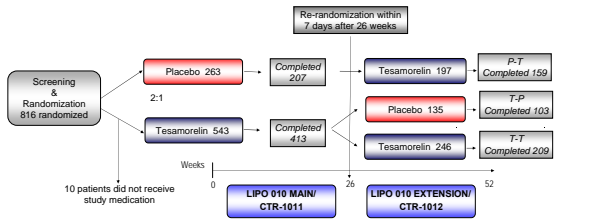
Conclusion: Treatment with 2 mg tesamorelin daily for up to 52 weeks results in sustained VAT reduction, preservation of SAT, improvement in triglycerides and is overall well tolerated without significant changes in glucose parameters.

INTRODUCTION

HIV-infected patients treated with antiretroviral therapy (ART) often demonstrate HIV lipodystrophy, which is characterized by body changes, such as fat accumulation in the abdomen and metabolic abnormalities including dyslipidemia and/or insulin resistance, which may increase cardiovascular risk (1-3). Results from two Phase 3 studies in HIV-infected patients with excess abdominal fat demonstrated that treatment with tesamorelin (TH9507), a stabilized analogue of growth hormone-releasing factor (GRF) or growth hormone-releasing hormone (GHRH), for 52 weeks led to a significant reduction in VAT, improvement in triglycerides as well as patient reported outcome (PRO) related to body image (4,5). Here we report the main efficacy end safety endpoints over a period of 52 weeks for the combined Phase 3 studies.

SUBJECTS AND METHODS

STUDY DESIGN AND PATIENT DISPOSITION



ENDPOINTS
Week 26: Primary endpoint: % change in VAT from baseline by computed tomography (CT) scan at L4-L5
Secondary endpoints: Triglycerides, total cholesterol/HDL cholesterol ratio, IGF-1 levels, patient outcomes related to body image, safety (glucose, insulin, adverse events and others)
Week 52: Primary endpoint: Safety (glucose, insulin, adverse events and others)
Other endpoints: Duration of effect on VAT following a 26-week treatment with 2 mg tesamorelin; 52-week efficacy data on VAT

STATISTICAL ANALYSIS

The efficacy endpoints were analyzed on the basis of data for patients who had received at least one dose of study drug with the last observation carried forward for those patients not completing the study, to determine treatment differences between tesamorelin and placebo at Week 26. Within-treatment comparisons were performed in each treatment group using a repeated-measures analysis of variance. Between-treatment comparisons were performed for T-T vs. T-P using an ANCOVA. Evaluation of safety at Week 52 of treatment was based on the safety population, which included all randomized patients who received at least one dose of a study drug during the extension phase of the study.

RESULTS

	T-T (N=246)	T-P (N=135)	P-T (N=197)
Age (years)	48±7	48±7	48±8
Gender (Male/Female %)	89/11	88/12	87/13
Ethnic origin (Race) (W/AA/H %)	79/12/8	84/7/7	78/11/8
BMI (kg/m ²)	28.6±4.1	29.4±4.3	28.8±4.2
VAT (cm ²)	187±83	190±82	186±89
SAT (cm ²)	214±120	231±122	224±121
Waist circumference (cm)	104±9	105±10	104±9
Viral Load % of patients: Undetectable	76	72	77
50-400	15	19	16
>400	9	9	7
CD4 cells count (cells/mm ³)	623±309	596±284	586±270
Triglycerides (mmol/L)	3.0±2.4	2.5±1.8	2.6±1.6
Tot. Chol. (mmol/L)	5.0±1.2	4.9±1.0	5.0±0.9
HDL-C (mmol/L)	1.2±0.4	1.2±0.3	1.2±0.4
Tot. Chol./HDL-C	4.7±1.6	4.5±1.4	4.4±1.3
Glucose (fasting, mmol/L)	5.4±0.7	5.7±0.9	5.5±0.9
IGF-1 (ng/mL)	161±64	150±61	163±73

W, White; AA, African American; B, Black; H, Hispanic

Table 1. Baseline Characteristics. Data are means ± SD.

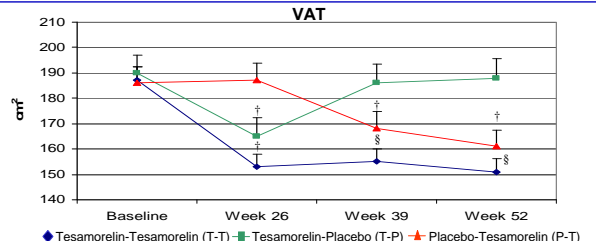


Figure 1. VAT Profile over 52 Weeks. Data are mean ± SEM, *P<0.001 vs. Baseline and vs. T-P †P<0.001 vs. Baseline. Patients randomized in the extension phase were included in the analysis. At week 26, VAT decreased significantly in tesamorelin-treated patients (-24.29±40.52 cm² and -13.1±21.1%, P<0.001 vs. placebo, data not shown).

RESULTS

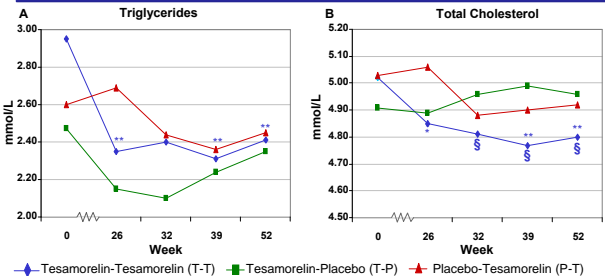


Figure 2. Triglycerides (A) and total cholesterol (B) levels over 52 weeks. Data are mean ± SEM, *P<0.05 vs. T-P; **P<0.001 vs. Baseline. At Week 26, there was a significant decrease from baseline in the tesamorelin group in triglycerides, non-HDL-C, total cholesterol/HDL-C ratio (P<0.001 vs. Placebo) and total cholesterol (P<0.05 vs. Placebo) (data not shown). At Week 52, baseline, total cholesterol/HDL-C ratio did not significantly change in the T-T and T-P groups but increased in the P-T group (P<0.05); non-HDL-C decreased in the T-T group (P<0.01) but no significant changes were observed in the T-P and P-T groups; HDL-C decreased in the T-T (P<0.05) and P-T groups (P<0.001) but no significant changes were observed in the T-P group (data not shown).

Parameters	T-T (N=246)	T-P (N=135)	P-T (N=197)	
Trunk fat (kg)	Baseline	14.4±5.1	15.7±5.6	15.0±5.4
	Week 26	13.3±5.4*	14.7±6.0*	15.3±5.6
	Week 52	13.3±5.3*	16.0±6.1†	14.2±5.7†
	Change from baseline Week 52	-1.07±2.2	0.30±2.2	-0.80±2.4
P-value T-T vs. T-P		<0.001		
Lean body mass (kg)	Baseline	62.7±9.8	63.0±9.8	61.6±10.1
	Week 26	64.1±10.0*	64.6±9.9*	61.4±9.9
	Week 52	64.0±10.0*	62.9±9.8 †	63.0±10.1†
	Change from baseline Week 52	1.26±2.7	-0.09±2.5	1.44±2.3
P-value T-T vs. T-P		<0.001		
SAT (cm ²)	Baseline	214.0±120.4	231.3±121.7	224.4±121.3
	Week 26	211.1±117.6	229.5±118.6	225.1±121.0
	Week 52	211.3±118.2	231.9±118.8	223.4±119.5
	Change from baseline Week 52	-2.7±42.5	0.6±38.9	-1.0±39.0
P-value T-T vs. T-P		0.582		
Limb fat (kg)	Baseline	6.7±4.2	7.1±4.0	7.1±4.1
	Week 26	6.7±4.2	7.0±3.8	7.2±4.2
	Week 52	6.7±4.1	7.1±3.9	7.1±4.1
	Change from baseline Week 52	-0.06±1.0	0.01±1.3	0.01±1.4
P-value T-T vs. T-P		0.062		

Table 2. Body composition parameters over 52 weeks. Data are mean ± SD. *P<0.001 vs. Baseline. †P<0.001 vs. Week 26.

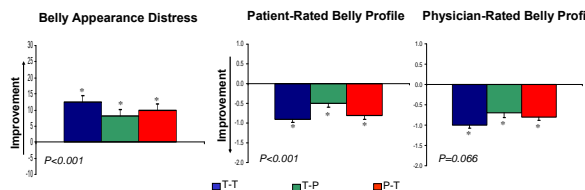


Figure 3. Change from baseline in patient reported outcome parameters at Week 52. Data are mean ± SEM. *P<0.01 vs. Baseline. Displayed P-values are for the between group comparisons (T-T vs. T-P).

	Week 26			Week 52		
	Tesamorelin (N=543)	Placebo (N=263)	P-value	T-T (N=246)	T-P (N=135)	P-value T-T vs. T-P
Δ IGF-1 (ng/mL)	107.9±111.6	-7.4± 63.5	<0.001	126.5±114.5	123.3±102.4	<0.001
Δ Fasting Glucose (mmol/L)	0.15±0.88	0.04±0.92	0.10	0.10±0.80	-0.11±1.57	0.68
Δ 2h Oral Glucose Tolerance (mmol/L)	0.18±2.09	0.19±2.37	0.82	0.06±2.18	0.06±1.87	0.92
Δ Fasting insulin (pmol/L)	0.24±204.8	10.03±153.4	0.50	-2.83±136.5	-48.08±214.0	0.36

Table 3. Changes from baseline in metabolic parameters after 26 and 52 weeks of treatment. Data are mean ± SD.

Safety summary

- No clinically significant safety observations emerged with tesamorelin.
- AEs were mainly injection site related (erythema, pruritus) and those known to be related to GH (peripheral oedema, arthralgia, pain in extremity and myalgia).
- 3% of patients had hypersensitivity reactions. Events were mild or moderate in severity.
- SAEs experienced in tesamorelin group were comparable to those of the placebo group.

CONCLUSIONS

Administration of 2 mg tesamorelin to HIV-infected patients with excess abdominal fat for 52 weeks resulted in improved body composition, including maintenance of VAT loss and preservation of subcutaneous adipose tissue and limb fat. Treatment with tesamorelin was also associated with a clinically significant decrease in triglycerides and improvement in patient reported outcomes. In addition, tesamorelin was well tolerated, without significant clinical effect on glucose parameters. Overall, these results suggest that tesamorelin may be beneficial for the treatment of HIV patients with excess abdominal fat.

References:

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