

Pharmacokinetic/Pharmacodynamic Evaluation of Tesamorelin (TH9507), a Growth Hormone-Releasing Factor (GRF) Analog, Administered Subcutaneously Once Daily for 14 Consecutive Days in Healthy and HIV Positive Populations

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ABSTRACT

Background: Tesamorelin is presently under development for the treatment of abdominal lipohypertrophy associated with HIV-lipodystrophy. Data from two independent Phase 3 studies in HIV-infected patients with excess abdominal fat and on antiretroviral therapy (ART) showed that administration of daily 2 mg tesamorelin for 26 weeks significantly decreased visceral adipose tissue (VAT) and was well tolerated. The objective of this study was to determine the PK/PD profiles of tesamorelin after single and multiple administrations of 2 mg once daily for 14 consecutive days, in healthy volunteers and HIV+ patients receiving stable ART regimen.

Methods: Two phase I, multiple dose studies were conducted in which healthy (N=12, Mean age: 54±5) or HIV+ (N=18, Mean age: 40±9) subjects received a daily s.c. injection of 2 mg tesamorelin during 14 consecutive days. Tesamorelin plasma levels were determined using a validated sandwich ELISA method. The growth hormone (GH, measured in healthy subjects only) and insulin Growth Factor-1 (IGF-I) serum levels were used for PD evaluation.

Results: Tesamorelin PK profiles were comparable between healthy volunteers and HIV+ patients. In both populations, a decrease in AUC (about 10%) and in C_{max} (about 35%) was observed after 14 days. The half-life of tesamorelin from both studies ranged between 13 to 38 minutes. In healthy volunteers, GH release following tesamorelin injection was similar on Day 1 and Day 14 (AUEC Day 1: 23903 (67.3%); Day 14: 29285 (59.8%) pg/h/mL). Baseline IGF-I levels were within normal range and comparable in both populations (healthy: 175 (32.2%), HIV: 164 (37.9%) ng/mL). After 14 Days of daily injection, a similar increase in IGF-I levels was observed in healthy and in HIV+ (115% and 121%, respectively compared to Day 1).

Conclusions: Overall, tesamorelin PK/PD profiles were similar between healthy volunteers and HIV positive patients. Given that the HIV-positive patients in this study were all on stable ART, these results suggest that being HIV positive and on ART therapy have a minimal impact on tesamorelin PK parameters and on tesamorelin-induced IGF-I serum concentration.

INTRODUCTION

HIV+ patients on ART often develop body composition changes and metabolic abnormalities, which may increase cardiovascular risk.^{1,2} GH secretion is reduced in patients with HIV and abdominal fat accumulation.^{1,2,3} Body changes have a negative impact on patient-reported outcomes including body image, and may thereby decrease adherence to ART.⁴ Tesamorelin is a synthetic analog of human Growth Hormone-Releasing Factor (GRF). It is thought to act on the pituitary gland to trigger GH synthesis and secretion. GH exerts diverse metabolic actions including lipid metabolism, mediated directly through the GH receptors and indirectly, via the stimulation of IGF-I production in the liver or locally, in the peripheral target tissues.⁵ The results from phase 1 and 2 studies showed that at daily doses of up to 2 mg, tesamorelin significantly increased mean IGF-I levels within physiological range, decreased fat mass and VAT, increased lean body mass, or improved lipid profile. Treatment with tesamorelin 2 mg was well-tolerated overall in healthy volunteers and HIV+ patients.

SUBJECTS AND METHODS

Two phase I, multiple-dose studies were conducted in which healthy volunteers (N=12, Min-Max age: 45-60 years) or HIV+ patients (N=18, Min-Max age: 26-58 years) received a daily s.c. injection of 2 mg tesamorelin during 14 consecutive days. Tesamorelin plasma levels as well as GH and IGF-I serum levels were determined using a validated analytical method. Patients included in the study were diagnosed HIV positive for an average of 11 years. The main classes of drugs included in the ART regimen of the HIV+ patients are listed in the table below:

Treatment	% of HIV+ patients
Protease inhibitor (PI)	72%
Nucleoside reverse transcriptase inhibitor (NRTI)	100%
Non-nucleoside reverse transcriptase inhibitor (NNRTI)	28%

Statistical Analyses:

PD parameters (GH (in healthy volunteers only) and IGF-I) were compared across days using a repeated-measures analysis on the In-transformed AUEC and E_{max} and the untransformed T_{EMax} (for GH) and on the In-transformed concentrations of Days 1, 7, 13 and 14 (for IGF-I) at the α level of 0.05 with the MIXED procedure in SAS; The corrected Akaike's information criteria (AICc) were used to select the variance-covariance matrix. The ratios of LSM (Day 14 vs Day 1) were determined. PK parameters in healthy volunteers and HIV+ patients were compared across days using a repeated-measures analysis on the In-transformed AUC and C_{max} using the MIXED procedures in SAS at the α level of 0.05. The ratios of LSM (Day 14 vs Day 1), and 90% geometric CIs for the ratios of LSM, based on the least-squares means (LSM) from the analysis of the In-transformed data were also calculated.

RESULTS

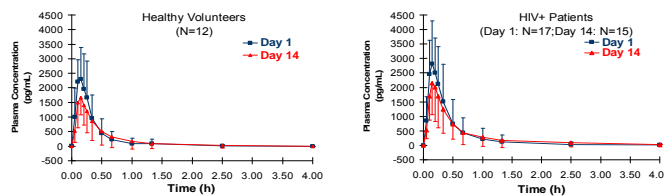


Figure 1. Tesamorelin mean (±SD) plasma concentrations over time profiles following a 2 mg s.c. injection for 14 consecutive days. The tesamorelin PK profiles were comparable between the two populations. The C_{max} was observed within 10 minutes on Day 1 and Day 14 in both healthy volunteers and HIV+ patients. Tesamorelin was rapidly eliminated from the systemic circulation following single and multiple s.c. injections with the mean T_{1/2} of ranging from 13 to 38 minutes in both populations.

PK Parameters	Healthy Volunteers		HIV+ Patients	
	Day 1	Day 14	Day 1	Day 14
AUC ₀₋₄ (pg-h/mL)	634.62 (72.36)	557.80 (78.17)	852.80 (91.87)	794.68 (108.59)
AUC _{0-4h} (pg-h/mL)	710.70 (70.57)	633.78 (75.88)	906.27 (90.58)	850.14 (105.78)
AUC _{0-inf} (pg-h/mL)	706.33 (72.35)	665.71 (78.63)	933.35 (90.94)	940.40 (104.73)
C _{max} (pg/mL)	2874.6 (43.87)	1744.9 (36.54)	2822.3 (48.89)	2013.2 (66.52)
T _{max} ^a (h)	0.150 (0.063)	0.150 (0.013)	0.150 (0.000)	0.150 (0.025)
T _{1/2} ^b (h)	0.21 (108.07)	0.43 (98.93)	0.31 (104.79)	0.63 (96.54)

a = Geometric mean and CV on the geometric mean are presented for the ln-transformed parameters (AUCs and C_{max})
b = Median and interquartile ranges are presented

Table 1. Tesamorelin PK results following a 2 mg s.c. injection. In both populations, a decrease in the AUC (about 10%) and in the C_{max} (about 35%) was observed after 14 days of treatment. However, only the decrease in the C_{max} was statistically significant in both healthy volunteers (p-value=0.0003) and HIV+ patients (p-value=0.0033).

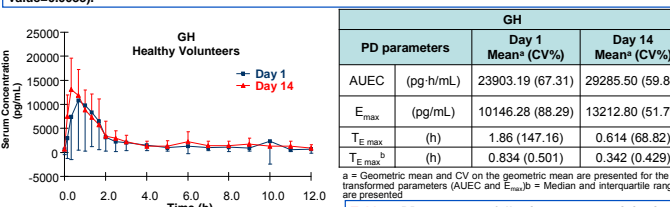


Figure 2. GH mean (±SD) serum concentrations over time profiles in healthy volunteers following a 2 mg s.c. injection.

RESULTS

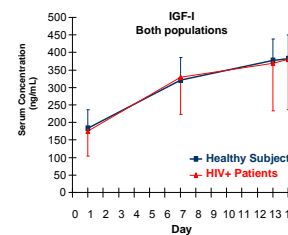


Figure 3. IGF-I mean (±SD) serum concentrations over time profiles following a 2 mg s.c. injection.

Population	IGF-I Concentrations (ng/mL) (Geometric Mean (CV%))	Day			
		1	7	13	14
Healthy Volunteers	ng/mL	175 (32.16)	316 (20.93)	373 (16.52)	377 (18.78)
	N	12	12	12	12
HIV+ Patients	ng/mL	164 (37.94)	313 (33.80)	347 (38.84)	357 (38.21)
	N	18	16	16	16

Table 3. IGF-I levels following a 2 mg s.c. injection. Baseline levels on Day 1 within normal range. IGF-I serum concentrations increased gradually to a maximum of 2-fold in healthy volunteers (ratio of LSM (Day 14/Day 1): 214.84%) and HIV+ patients (ratio of LSM (Day 14/Day 1): 221.37%).

Safety: Overall, few AEs were observed by more than 3 patients: injection site pain (n=6 in HIV+), injection site bruising (n=6 in healthy volunteers) and headache (n=5 in HIV+; n=3 in healthy volunteers). These AEs were generally consistent with those reported in previous studies in healthy volunteers and in HIV-infected patients with excess abdominal fat. Most of the AEs were mild. No severe/significant AEs, or SAEs were reported during these studies.

CONCLUSION

Overall, tesamorelin PK/PD profiles were similar between healthy volunteers and HIV positive patients. Given that the HIV-positive patients in this study were all on stable ART, these results suggest that being HIV positive and on ART therapy have a minimal impact on tesamorelin PK parameters and on tesamorelin-induced IGF-I serum concentration. Moreover, no serious or significant adverse events were noted in both healthy volunteers and HIV+ patients.

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