

Impact of Tesamorelin (TH9507), a Stabilized Growth Hormone-Releasing Factor (GRF) Analogue, on the Pharmacokinetics of Simvastatin and Ritonavir in Healthy Volunteers

Geneviève Vincent¹, Shirley Teng², Murray P. Ducharme², Josée Morin¹, Saida Hatimi¹, Sophie-Elise Michaud¹, and Kim High¹

¹Theratechnologies Inc., Montreal, Canada; ²Cetero Research, Cary, NC, USA

ABSTRACT

Background: Tesamorelin is under development for the treatment of excess abdominal fat in HIV patients with lipodystrophy. Two independent phase 3 trials showed that daily administration of 2 mg tesamorelin for 26 weeks was well-tolerated and significantly reduced visceral adipose tissue. The literature suggests that human growth hormone (hGH) may modulate cytochrome P450 (CYP) enzyme activity. Therefore, the potential impact of tesamorelin on CYP3A activity was investigated by examining its effect on the pharmacokinetics (PK) of drugs potentially administered concomitantly with tesamorelin: simvastatin (CYP3A-substrate) and ritonavir (CYP3A-inhibitor).

Methods: In two randomized, open-label, two-way crossover studies, subjects were administered 2 mg tesamorelin on Days 1 to 7, with 80 mg simvastatin (N=58) or 100 mg ritonavir (N=32) co-administered on Day 6 (Treatment A), and a single dose of simvastatin or ritonavir alone on Day 6 (Treatment B) in a crossover manner. PK samples collected on Day 6, measured simvastatin, ritonavir and tesamorelin plasma concentrations. The A/B ratios and 90% confidence intervals (CI) within 80-125% would conclude that tesamorelin has no clinically significant impact on simvastatin or ritonavir PKs.

Results: **Simvastatin:** ratios of least squares geometric means (LSM) and corresponding 90% CIs for AUC_{0-4} , AUC_{0-inf} and C_{max} were contained within the acceptance range. For the metabolite simvastatin acid, only the lower CI for AUC_{0-inf} (78.6%) fell slightly outside of the range. **Ritonavir:** ratios and 90% CIs for AUCs were contained within the acceptance range, but for C_{max} the lower CI was 74.8%, suggesting a decrease in the rate (indicated by T_{max}) of exposure. However, since the observed A/B ratios for AUCs and C_{max} parameters were approximately 90%, these are minor decreases and no dose adjustment of ritonavir is required in presence of tesamorelin.

Conclusion: These studies showed that the impact of tesamorelin on CYP3A activity appears to be minimal. Either medication may be co-administered with tesamorelin without changing their dosing regimen.

INTRODUCTION

HIV-lipodystrophy syndrome is a metabolic disorder characterized by fat accumulation and/or loss of peripheral fat affects a large percentage of HIV patients. Tesamorelin, a synthetic human growth hormone releasing factor (hGRF) analogue, has demonstrated efficacy in treating this condition. Results of two independent phase 3 trials showed that daily administration of 2 mg tesamorelin for 26 weeks was well-tolerated without significant clinical effects and significantly reduced visceral adipose tissue (VAT) in HIV-infected patients with excess abdominal fat. VAT loss observed at 26 weeks was sustained in those patients who received tesamorelin over 52 weeks.^{1,2}

Studies in the literature suggest that hGH may alter CYP P450 enzyme expression.^{3,4} Since tesamorelin induces the secretion of GH, it is important to determine whether tesamorelin may interact with other drugs that undergo CYP3A mediated metabolism.

In these randomized, open-label, two-period, two-sequence, two-treatment, crossover studies, we investigated whether there is any clinically significant impact of tesamorelin on the PK profile of simvastatin and ritonavir in healthy volunteers.

SUBJECTS AND DRUG TREATMENTS

Subjects: N=58 (simvastatin study) and N=32 (ritonavir study) healthy adult (male and female) subjects were enrolled. Dosing occurred in two groups for both studies.

Study Drugs:

- 2 mL of tesamorelin 1 mg/mL injectable solution administered by subcutaneous injection under fasting conditions once daily for 7 consecutive days (daily dose of 2 mg tesamorelin, manufactured for Theratechnologies Inc., Canada).
- one Zocor® 80 mg tablet (simvastatin) by Merck Frosst Canada Ltd., under fasting conditions.
- one Norvir® SEC 100 mg capsule (ritonavir) by Abbott Laboratories Ltd. Canada, under fed conditions.

Study Events:

	Treatment A	Treatment B
Days 1 to 5	Administer tesamorelin	--
Day 6	Administer tesamorelin; collect samples at 0, 0.1, 0.15, 0.2, 0.25, and 0.5 h	--
	Administer simvastatin; collect samples at 0, 0.5, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 16, 24, 30, 36, and 48 h or Administer ritonavir; collect samples at 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 9, 10, 12, 16, 24 (day 7), 30, 36, and 48 h	--
Day 7	Administer tesamorelin	--

Washout: 14 days between the simvastatin or ritonavir dose administered on Day 6 of Period 1 and the start of Day 1 of Period 2.

ANALYSIS

Bioanalytical: ELISA was used to measure plasma tesamorelin concentrations and LC/MS/MS was used to measure plasma simvastatin, simvastatin acid and ritonavir concentrations.

PK/statistics: PK parameters were calculated using standard noncompartmental approaches.

ANOVAs on ln-transformed AUC_{0-4} , AUC_{0-inf} and C_{max} were conducted for simvastatin, simvastatin acid and ritonavir. Although a significant treatment*group interaction was found for AUC_{0-4} and AUC_{0-inf} for both simvastatin and simvastatin acid, no clinically- or analytically-based reason for the group difference was evident, and data from both groups were pooled together. The final ANOVA models included group, sequence, treatment, and period nested within group as fixed effects and subject nested within group*sequence as a random effect. The treatment*group term was excluded from the models for the groups combined, to be conservative. The 90% CIs for the Treatment A/Treatment B LSM ratios for AUC_{0-4} , AUC_{0-inf} and C_{max} were to be within 80-125% in order to conclude that there is no clinically significant impact of tesamorelin on simvastatin or ritonavir PK.

Blood sampling for tesamorelin was designed to only estimate the PK profile; descriptive statistics were calculated for tesamorelin plasma concentration data to demonstrate that the expected exposure was achieved.

RESULTS

Parameter	Treatment Means		A/B Ratio (%)	90% Confidence Interval (%)
	Treatment A	Treatment B		
Simvastatin				
AUC_{0-4} (pg•h/mL) ^a	94731.59	102715.03	92.2	83.5 - 101.9
AUC_{0-inf} (pg•h/mL) ^a	97748.35	106622.76	91.7	83.0 - 101.3
C_{max} (pg/mL) ^a	16372.51	15552.09	105.3	94.6 - 117.1
T_{max} (h) ^b	1.50 (0.50-5.00)	1.50 (0.50-10.00)	--	--
$T_{1/2}$ (h) ^c	7.62 (53.5)	8.56 (64.3)	--	--
Simvastatin Acid				
AUC_{0-4} (pg•h/mL) ^a	37466.20	43438.29	86.3	80.2 - 92.7
AUC_{0-inf} (pg•h/mL) ^a	39906.42	46833.23	85.2	78.6 - 92.4
C_{max} (pg/mL) ^a	4283.93	4327.58	99.0	91.9 - 106.7
T_{max} (h) ^b	4.50 (4.00-12.00)	4.50 (2.03-12.03)	--	--
$T_{1/2}$ (h) ^c	6.91 (69.5)	8.07 (53.0)	--	--

Table 1. Summary of ANOVA results and PK parameters for simvastatin and simvastatin acid. ^aGeometric mean calculated by exponentiating the LSM from a model using log-transformed response; ^bMedian (range); ^cArithmetic mean (% CV)

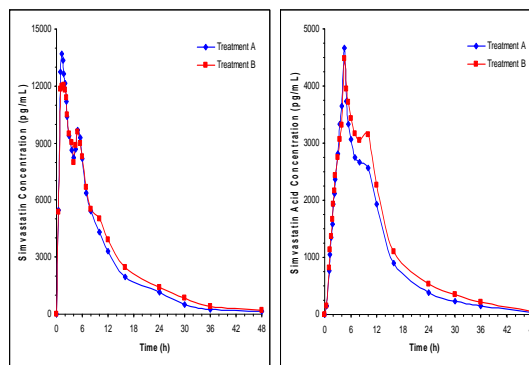


Figure 1. Concentration-time profiles of simvastatin and simvastatin acid with (Treatment A) and without (Treatment B) pre-treatment with tesamorelin.

RESULTS

Parameter	Treatment Means		A/B Ratio (%)	90% Confidence Interval (%)
	Treatment A	Treatment B		
Ritonavir				
AUC_{0-4} (ng•h/mL) ^a	3378.8	3722.6	90.8	83.8 - 98.3
AUC_{0-inf} (ng•h/mL)	3465.3	3799.9	91.2	84.4 - 98.6
C_{max} (ng/mL) ^a	404.2	452.7	89.3	74.8 - 106.6
T_{max} (h) ^b	4.50 (4.50-16.00)	4.50 (1.50-16.00)	--	--
$T_{1/2}$ (h) ^c	5.72 (23.0)	6.26 (22.0)	--	--

Table 2. Summary of ANOVA results and PK parameters for Ritonavir. ^aGeometric mean calculated by exponentiating the LSM from a model using log-transformed response; ^bMedian (range); ^cArithmetic mean (% CV)

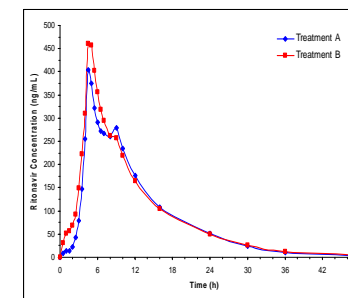


Figure 2. Concentration-time profile of ritonavir with (Treatment A) and without (Treatment B) pre-treatment with tesamorelin.

Parameter	Mean	
	Simvastatin	Ritonavir
AUC_{0-4} (pg•h/mL) ^a	888.4 (37.1)	656.9 (70.0)
AUC_{0-inf} (pg•h/mL) ^a	1052.7 (37.8)	790.4 (47.1)
C_{max} (pg/mL) ^a	3356.3 (33.8)	2699.1 (58.6)
T_{max} (h) ^b	0.15 (0.10 - 0.20)	0.15 (0.10 - 0.20)
$T_{1/2}$ (h) ^c	0.14 (42.0)	0.11 (26.6)

Table 3. Summary of PK parameters for simvastatin in the simvastatin and ritonavir studies. ^aGeometric mean (% CV); ^bMedian (range); ^cArithmetic mean (% CV)

Safety Evaluation

Ritonavir: No severe or significant adverse events (AEs), no serious adverse events (SAEs) were reported during this study; no subject discontinued the study due to an AE

Simvastatin: No SAEs were reported during this study. Three (N=3/58) subjects had significant AEs that resulted in withdrawal from the study as a precautionary measure only: in the simvastatin group one patient had blood creatine phosphokinase (CPK) increased. In the simvastatin + tesamorelin group: one patient had blood CPK increased and one patient had myalgia.

CONCLUSIONS

- The expected exposure to tesamorelin was achieved in these studies.
- For simvastatin, the acceptance limits of 80-125% for the ratio and 90% CI of Treatment A/Treatment B were met for AUC_{0-4} , AUC_{0-inf} and C_{max} . For simvastatin acid, only the lower CI for AUC_{0-inf} (78.6%) fell outside of the acceptance range.
- For ritonavir, the acceptance limits were met for AUC_{0-4} and AUC_{0-inf} . The lower 90% CI for C_{max} was 74.8%. The observed A/B ratios for AUC_{0-4} , AUC_{0-inf} and C_{max} were approximately 90%, thus the prior administration of tesamorelin tended to decrease the exposure to ritonavir; however the effect is not clinically significant.
- The impact of tesamorelin on CYP3A activity appears to be minimal. Both ritonavir and simvastatin may be administered in conjunction with tesamorelin without any change in their dosing regimen.

References

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