CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-505

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

NDA: 22-505	Submission Date(s): 05/29/2009
Brand Name	EGRIFTA
Generic Name	Tesamorelin Acetate
Reviewer	Ritesh Jain, Ph.D.
Team Leader	Sally Choe, Ph.D.
OCP Division	Clinical Pharmacology –II
OND division	Metabolism and Endocrinology Products
Sponsor	Theratechnologies Inc.
Submission Type; Code	Original NDA 505(b)(1); Standard
Formulation; Strength(s)	Lyophilized powder containing 1.1 mg of tesamorelin acetate and 55 mg of mannitol.
Proposed Indication	To induce and maintain a reduction of excess abdominal fat in HIV-infected patients with lipodystrophy

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1 Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology / Division of Clinical Pharmacology II (OCP/DCP-II) has reviewed the clinical pharmacology data submitted under NDA 22-505, dated 05/29/2009, and finds it acceptable provided that a mutual agreement regarding the label language can be reached between the sponsor and the Agency.

1.2 Phase IV Commitments

None

1.3 Summary of Important Clinical Pharmacology Findings

The sponsor has submitted NDA 22-505 for EGRIFTA (Tesamorelin Acetate or Tesamorelin), which is proposed to be indicated to induce and maintain a reduction of excess abdominal fat in human immunodeficiency virus (HIV)-infected patients with lipodystrophy. The proposed daily dose for tesamorelin is 2 mg administered by subcutaneous (s.c.) injection to HIV patients with lipodystrophy. Lipodystrophy affects a significant proportion of HIV infected patients treated with combination antiretroviral therapy (ART) and is characterized by excess visceral adipose tissue (VAT) accumulation, loss of extremity and subcutaneous fat in association with dyslipidemia and insulin resistance. Increased VAT in these patients is associated with elevated cardiovascular risk. HIV lipodystrophy is also associated with lowered growth hormone (GH) levels (basal and pulse amplitude).

Mechanism of Action

Tesamorelin is a synthetic analogue of human hypothalamic Growth Hormone-Releasing Factor (hGRF), also known as Growth Hormone-Releasing Hormone (GHRH). Tesamorelin has 44- amino acid sequence of hGRF on which a hexenoyl moiety, a C6 chain with a double bond on position 3, has been anchored on Tyr at the N-terminal part of the molecule. With the addition of this hydrophobic side chain, binding affinity to hGRF receptors has been shown to be comparable to that of hGRF, while resistance to enzymatic degradation in human serum is increased. Tesamorelin, like hGRF, acts on the pituitary somatotroph cells to stimulate the synthesis and release of endogenous growth hormone (GH). Growth hormone is known to play an important physiological role in the formation and the function of fat cells, as well as in the overall regulation of fat metabolism. GH has been shown to reduce total fat mass through a combination of several actions, including inhibition of adipocyte differentiation, and stimulation of fat mobilization and oxidation.

Sponsor's Phase 3 Program

The Phase 3 program for this NDA consisted of two multicentre, randomized, double-blind, placebo-controlled pivotal Phase 3 studies to assess the efficacy and safety of Egrifta in HIV infected patients with lipodystrophy. The primary endpoint for the Phase 3 studies was to demonstrate a reduction in visceral adipose tissue (VAT), as assessed by computed tomography (CT), after 26 weeks of treatment with tesamorelin 2 mg per day

as compared to placebo. The secondary efficacy endpoints, in the Phase 3 trials, included improvement in blood lipids (triglycerides, total cholesterol: high density lipoprotein-cholesterol [HDL-C] ratio), improvement in patient related outcome (PRO) related to body image, and increase in insulin-like growth factor-1 (IGF-1) levels. Sponsor's analysis of the Phase 3 data suggests that 2 mg daily s.c. dose of tesamorelin for 26 weeks, in the pooled studies, resulted in a significant decrease from baseline in VAT (13.1% in tesamorelin -treated patients versus an increase of 2.3% in placebo-treated patients) and this effect was sustained during the second 26 weeks of the trials (studies TH9507III/LIPO/010 (extension phase) and TH9507-CTR-1012).

Sponsor's Clinical Pharmacology Programs

Clinical pharmacology of tesamorelin, under this submission is supported with 10 clinical pharmacology studies. Amongst these 10 studies, six studies are single or multiple doses pharmacokinetics (PK) or pharmacokinetics/pharmacodynamics (PK/PD) studies in healthy and HIV infected patients, two bioavailability studies, and two drug-drug interaction studies.

PK/PD of Tesamorelin in Healthy Subjects

PK/PD of tesamorelin in healthy subjects was evaluated following single and multiple subcutaneous administrations of 1 mg and 2 mg doses in healthy volunteers. The serum growth hormone (GH) and insulin growth factor -1 (IGF-1) serum levels were used for PD evaluation. Following a single s.c. administration of tesamorelin (1 or 2 mg), the time to reach maximum plasma concentration (T_{max}) was approximately 8-9 minutes (8 min after a single 1 mg dose and 9 min following a single 2 mg dose). The mean elimination half-lives ($t_{½}$ el) were 7.8 min following a single 1 mg dose and 13.2 min following a single 2 mg dose. The apparent clearance (CL/F) was comparable between doses and days. No tesamorelin accumulation was seen following multiple dose administration at 1 mg and 2 mg dose. Dose related increase in plasma concentration was seen at 1 mg and 2 mg dose (**Figure 1**).

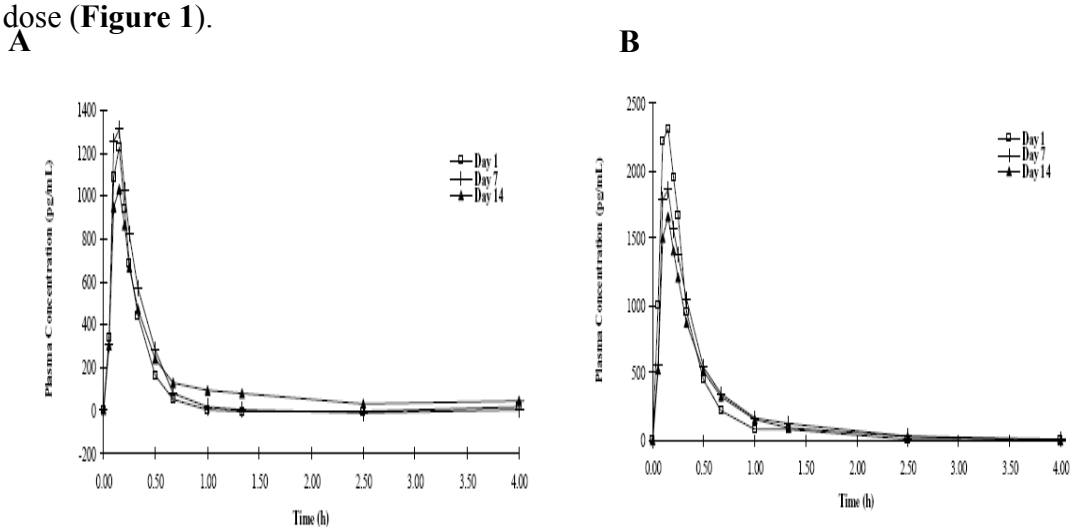


Figure 1: Mean Plasma Concentrations of tesamorelin following s.c. administration in healthy subjects A) 1 mg Dose, B) 2 mg Dose: Linear Scale*

**** Source- Copied from Sponsors electronic report for study TH9507/CTR/1016***

For both 1 mg and 2 mg doses, a decrease in C_{max} was observed on Day 14 as compared to those on Day 1 and Day 7 (**Figure 3**). Despite the decrease in C_{max} of tesamorelin, the IGF-1 increased significantly overtime and GH production was comparable after multiple administrations of tesamorelin 1 mg or 2 mg dose (pharmacodynamic markers for tesamorelin activity) (**Figure 2**).

In healthy subjects, the growth hormone levels were higher following 2 mg s.c. dose as compared to 1 mg dose. Growth hormone production, as expressed in terms of area under effect curve (AUEC), was approximately 68% higher following administration of the 2 mg dose when compared to the 1 mg dose. Similarly, baseline corrected IGF-1 levels were approximately 26% greater for the 2 mg dose when compared to the 1 mg dose. In healthy subjects IGF-1 levels increased from Day 1 to Day 7 to Day 14. The IGF-1 level seems to reach a maximum level after 13 days (**Figure 2**).

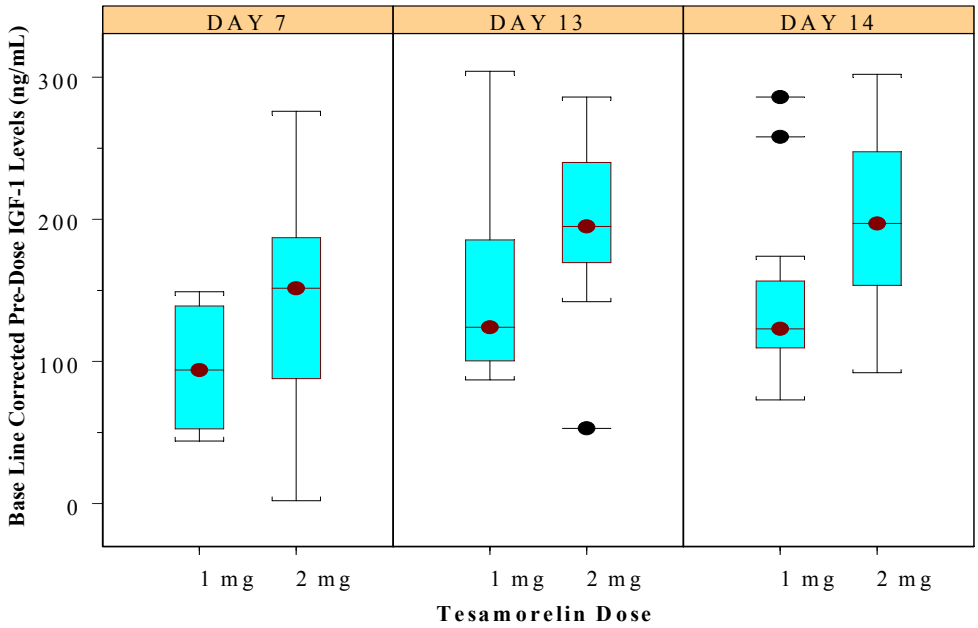


Figure 2: Tesamorelin Dose-Response (IGF-1 Levels) in Healthy Subjects (Dose: 1mg and 2 mg)

<u>PK/PD of Tesamorelin in HIV Infected Patients</u>

In HIV infected patients without lipodystrophy, the pharmacokinetic parameters after s.c. administration were similar to those in healthy subjects (**Figure 3**). In HIV infected patients, no tesamorelin accumulation was seen following multiple dose s.c. administration of EGRIFTA at 2 mg dose. In HIV infected patients, the mean T_{max} was observed approximately 10 minutes post dose following single (Day 1) and multiple (Day 14) doses with values ranging from 4 minutes to 20 minutes. The mean elimination half-life ($t_{½}$ el) was 18 min and 37 min following single and multiple s.c. injections, respectively. Similar to healthy subjects, in HIV infected patients a decrease in C_{max} was

observed on Day 14 as compared to Day 1. The decrease in C_{max} is of no clinical relevance since the IGF-1 level increases, similar to healthy subjects, significantly overtime.

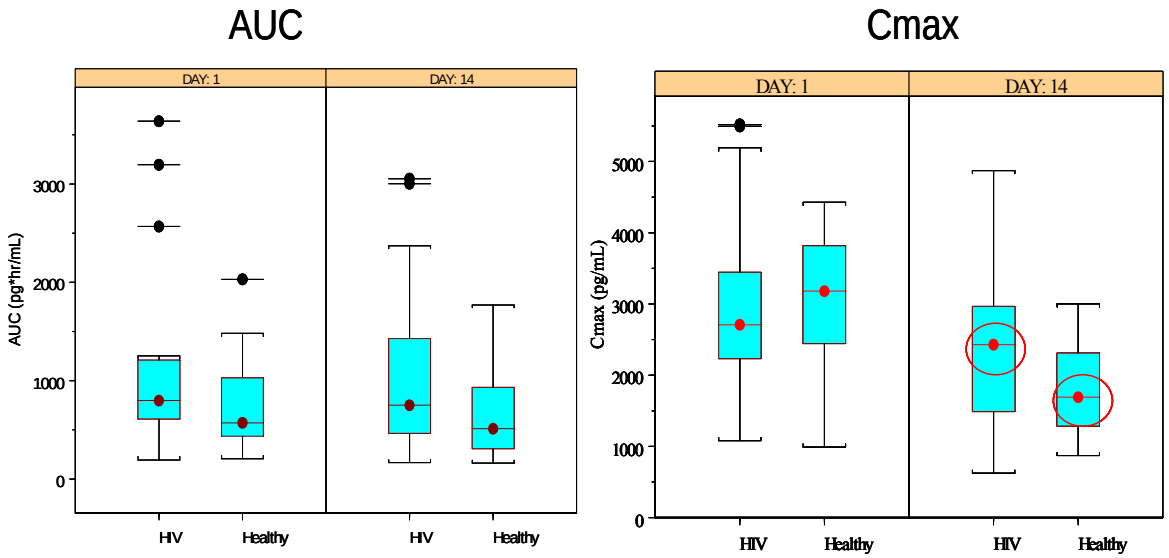


Figure 3: Tesamorelin PK in Healthy and HIV Infected Patients following 2 mg s.c. Dose

In HIV infected patients, the IGF-1 serum concentrations increased gradually after daily 2 mg tesamorelin dose from day 1 to day 14. The ratio of Day 14 to Day 1 predose IGF-1 concentration was 2.21. The increase in the IGF-1 serum concentration in HIV positive patients is comparable to the one observed in healthy volunteers (**Figure 4**)

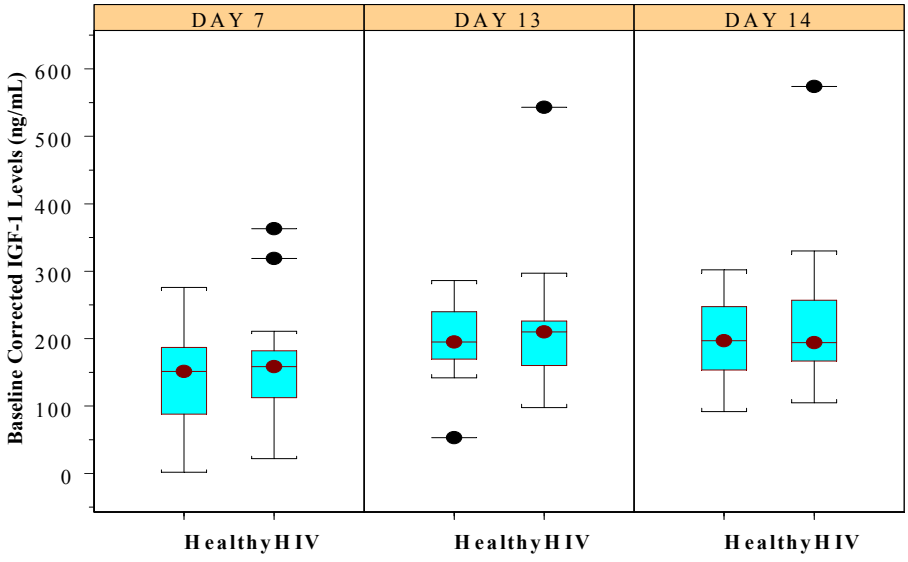


Figure 4: PD Effect (IGF-1 Levels) of Tesamorelin in Healthy and HIV Infected Patients following 2 mg Dose

Absolute Bioavailability in Healthy Subject

In healthy subjects, following intravenous administration the mean elimination half-life ($t_{½}$ el) was observed to be 7.2 min on Day 1 and 7.8 min on Day 15 of administration, respectively. The absolute bioavailability of tesamorelin after subcutaneous injection was estimated to be less than 4%.

Drug-Drug Interaction

In vivo drug-drug interaction studies showed that tesamorelin has no clinically significant impact on the metabolism of simvastatin and ritonavir.

Effect of Immunogenicity on the Pharmacokinetics of Tesamorelin

Effect of anti-tesamorelin IgG antibodies on the pharmacokinetics of tesamorelin was evaluated in Phase 3 study (Study#010). No definitive conclusion can be made on the effect of immunogenicity on PK of tesamorelin due to limited number of subjects studied and high variability in the data set. In the Phase 3 study, PK sampling was conducted in very few subjects (8 subjects studied for PK analysis) and the PK sampling scheme was not appropriate to characterize the PK of the drug. Also, the analytical method was not validated to evaluate the PK of tesamorelin in the presence of drug specific IgG antibodies. Thus, no definitive conclusion can be made on the effect of immunogenicity on PK of tesamorelin However, in the Phase 3 studies, the sponsor has demonstrated that immunogenicity has no effect on efficacy of tesamorelin in HIV infected patients with lipodystrophy. Pooled analysis of pivotal studies (main phase) showed that the percent change in VAT (primary efficacy endpoint) as a function of anti-tesamorelin antibody status was similar between antibody positive and antibody negative patients. Please refer to Dr. Ali Mohamadi's (Medical Officer) review for further details.

In conclusion, from clinical pharmacology standpoint this NDA 22-505 is acceptable provided that the mutual agreement on the labeling language can be reached between the sponsor and the Agency.

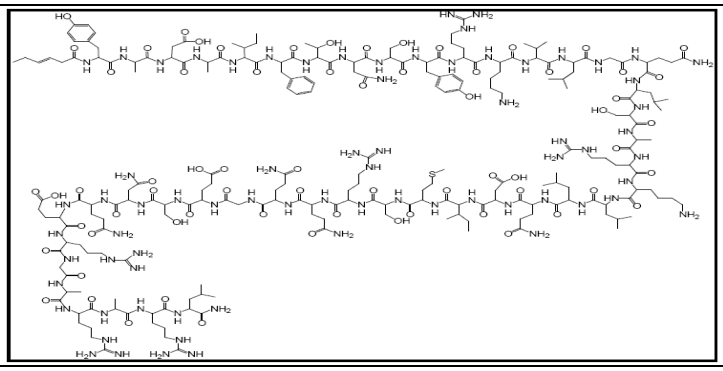
2 Question-Based Review (QBR)

2.1 General Attributes of the Drug and Drug Product

EGRIFTA™ (TH9507 or Tesamorelin) is a sterile lyophilized powder for injection. EGRIFTA is available as 1.1 mg/vial as a single unit dose for reconstitution with 1.1 mL of sterile water for Injection USP. EGRIFTA is indicated to induce and maintain a reduction of excess abdominal fat in HIV infected patients with lipodystrophy. The proposed daily dose for EGRIFTA is 2 mg administered by subcutaneous (s.c.) injection to HIV patients with lipodystrophy.

EGRIFTA is a synthetic analogue of human hypothalamic Growth Hormone-Releasing Factor (hGRF), also known as Growth Hormone-Releasing Hormone (GHRH), comprised of the 44- amino acid sequence of hGRF on which a hexenoyl moiety, a C6 chain with a double bond on position 3, has been anchored on Tyr at the N-terminal part of the molecule. The binding affinity of EGRIFTA to hGRF receptors is comparable to that of natural hGRF and has an increased stability and half-life in humans.

2.1.1 What are the highlights of the chemistry and physicochemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

	Tesamorelin
Description	white to off-white powder
Chemical Name	[N-trans-3-Hexenoyl] Human Growth Hormone Releasing Factor (1-44), Acetate
Molecular Formula	$C_{221}H_{366}N_{72}O_{67}S$. x $C_2H_4O_2$
Molecular Weight	5135.9 (free base)
Structural Formula	
Solubility	It is freely soluble in acetic acid, soluble in water and slightly soluble in methanol and PBS pH7.2

Formulation: Tesamorelin, sterile lyophilized powder, 1.1 mg/vial is available as a single unit dose for reconstitution with 1.1 ml of Sterile Water for Injection USP for a final concentration of 1 mg/mL.

Table 1: Composition of EGRIFTA

Component	Quantity (mg/vial)	Function	% Of the total unit weight*
N-[trans-3-Hexenoyl]-Human Growth Hormone-Releasing Factor (1-44) Acetate, In-house	1.1**	Active Pharmaceutical Ingredient	0.1
Mannitol USP	55 mg	Bulking agent	(b) (4)
Water for injection USP ***	--------	Solvent	--------
(b) (4)	--------	(b) (4)	--------
	--------		--------
	--------		--------

* Based on a theoretical unit filling weight of 1.1mg
** This weight is corrected for peptide content

(b) (4)

2.1.2 What is the mechanism of action and therapeutic indication?

EGRIFTA is indicated to induce and maintain a reduction of excess abdominal fat in HIV infected patients with lipodystrophy. Lipodystrophy affects a significant proportion of HIV infected patients treated with combination antiretroviral therapy (ART) and is characterized by excess visceral adipose tissue (VAT) accumulation, loss of extremity and subcutaneous fat in association with dyslipidemia and insulin resistance. Increased VAT in these patients is associated with elevated cardiovascular risk. HIV lipodystrophy is also associated with lowered growth hormone (GH) levels (basal and pulse amplitude).

EGRIFTA is a synthetic analogue of human hypothalamic Growth Hormone-Releasing Factor (hGRF), also known as Growth Hormone-Releasing Hormone (GHRH). hGRF mediates the secretion of growth hormone (GH) by binding to its receptor on pituitary somatotroph cells triggering GH synthesis and secretion. Since GH is known to be lipolytic, restoring physiological levels and patterns of GH may be beneficial in HIV patients with lipodystrophy.

In addition, GH has been shown to play an important role in the formation and the function of fat cells as well as in the overall regulation of fat metabolism whereby GH has been shown to reduce total fat mass through a combination of several actions, including inhibition of adipocyte differentiation, and stimulation of fat mobilization and oxidation. GH actions are mediated directly through the GH receptor and indirectly through the stimulation and release of insulin-like growth factor-1 (IGF-1) in the liver and other tissues.

2.1.3 What are the proposed dosage and route of administration?

The proposed daily dose for Egrifta is 2 mg administered by subcutaneous (s.c.) injection to HIV patients with lipodystrophy

2.1.4 Is any DSI (Division of Scientific Investigation) inspection requested for any of the clinical studies?

No, DSI inspection was not requested from clinical pharmacology standpoint.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Efficacy and Safety Program:

The efficacy and safety of EGRIFTA in the treatment of excess abdominal fat in HIV-infected patients with lipodystrophy is supported by three multicenter, randomized, double-blind, placebo-controlled Phase 3 trials (TH9507III/LIPO/010, TH9507-CTR-1011, and TH9507- CTR-1012). In the Phase 3 trials, the primary efficacy endpoint was the percent change from baseline in visceral adipose tissue (VAT), as assessed by computed tomography (CT) scan, after 26 weeks of treatment with EGRIFTA. In Phase 3 trials the 26-week main treatment phase (TH9507/III/LIPO/010 and TH9507-CTR-1011) was followed by a 26-week extension phase (TH9507/III/LIPO/010 Extension Phase and TH9507-CTR-1012).

The primary objective of the Phase 3 trials was to demonstrate a reduction in visceral adipose tissue (VAT), as assessed by computed tomography (CT), after 26 weeks of treatment with tesamorelin 2 mg per day as compared to placebo. The secondary efficacy endpoints included improvements in lipids (triglycerides, total cholesterol to HDL-cholesterol ratio) and patient reported outcomes (PRO) related to body image, accompanied by an increase in insulin-like growth factor-I (IGF-I) level after 26 weeks of treatment.

The Phase 3 trial was based on a Phase 2 study (TH9507/II/LIPO/008) in which subjects were randomized to receive either placebo, tesamorelin 1 mg, or tesamorelin 2 mg once daily by subcutaneous injection for 12 weeks. Study TH9507/II/LIPO/008 was a Phase 2, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of tesamorelin (1 mg or 2 mg/day) in HIV subjects with excess abdominal fat accumulation.

Clinical Pharmacology Program:

Clinical pharmacology of tesamorelin, under this submission is supported with 10 clinical pharmacology studies. Amongst these 10 studies, six studies are single or multiple doses pharmacokinetics (PK) or pharmacokinetics/pharmacodynamics (PK/PD) studies in

healthy and HIV infected patients, two bioavailability studies and two drug-drug interaction studies.

2.2.2 What are the basic pharmacokinetic and pharmacokinetic/pharmacodynamic characteristics of tesamorelin in healthy subjects?

Pharmacokinetics and pharmacodynamics of tesamorelin was evaluated in Phase 1, parallel, randomised, open-label, multiple doses study following single and multiple subcutaneous administrations of 1 mg and 2 mg doses in healthy volunteers (study # CTR-1016). The serum growth hormone (GH) and insulin growth factor -1 (IGF-1) serum levels were used for PD evaluation.

Pharmacokinetics of tesamorelin in Healthy Subjects:

Following a single s.c. administration of tesamorelin (1 or 2 mg), the time to reach maximum plasma concentration (T_{max}) was approximately 8-9 minutes (8 min after a single 1 mg dose and 9 min following a single 2 mg dose). Mean elimination half-life ($t_{½}$ el) of tesamorelin was 7.8 min following a single 1 mg dose and 13.2 min following a single 2 mg dose. The clearance (CL/F) was comparable between doses and days. No tesamorelin accumulation was seen following multiple dose administration. Dose related increase in plasma concentration was seen at 1 mg and 2 mg dose (**Figure 5**).

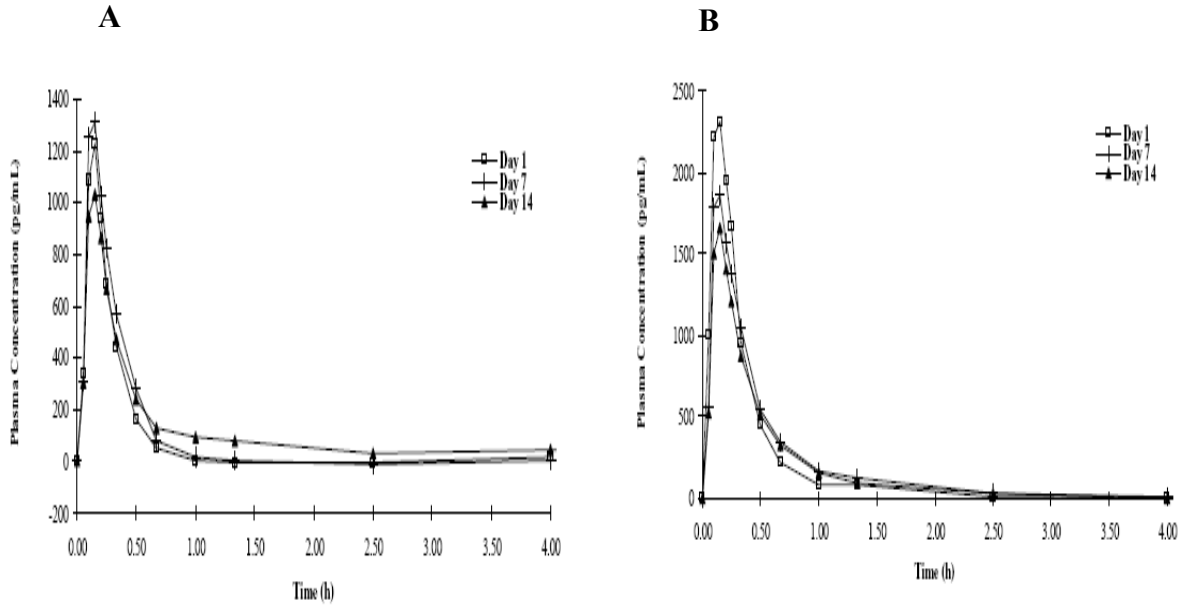


Figure 5: Mean Plasma Concentrations of tesamorelin following s.c. administration in healthy subjects A) 1 mg Dose, B) 2 mg Dose: Linear Scale*

**** Source- Copied from Sponsors electronic report for study TH9507/CTR/1016***

Descriptive statistics of pharmacokinetic parameters of tesamorelin at 1 mg dose and 2 mg dose on Day 1, Day 7, and Day 14 is presented below in **Table 2 and 3**

Table 2: Summary of pharmacokinetics parameters of tesamorelin on Day 1, Day 7, and Day 14 at 1 mg dose*.

Parameters		Day 1					Day 7					Day 14				
		Mean	SD (±)	CV (%)	Geo. Mean	Geo. Mean CV(%)	Mean	SD (±)	CV (%)	Geo. Mean	Geo. Mean CV(%)	Mean	SD (±)	CV (%)	Geo. Mean	Geo. Mean CV(%)
AUC_{0-t}	(pg·h/mL)	301.63	159.09	52.74	268.10	54.01	403.99	174.60	43.22	369.01	47.91	304.26	259.40	85.26	232.06	85.05
AUC_{0-4h}	(pg·h/mL)	323.18	166.57	51.54	289.33	52.64	380.57	153.56	40.35	353.34	42.11	363.72	292.06	80.30	289.15	79.23
AUC_{0-inf} *	(pg·h/mL)	342.43	179.17	52.32	304.47	54.23	416.35	160.40	38.52	389.45	40.09	418.13	362.46	86.69	318.16	86.19
$AUC_{t/inf}$ *	(%)	85.93	7.00	8.15	-	-	87.06	7.14	8.20	-	-	77.83	7.27	9.34	-	-
C_{max}	(pg/mL)	1338.4	461.7	34.49	1259.9	38.93	1391.6	448.8	32.25	1314.2	38.54	1021.7	407.6	39.89	959.7	36.92
T_{max}	(h)	0.138	0.033	24.32	-	-	0.129	0.026	19.93	-	-	0.153	0.061	39.92	-	-
T_{max} **	(h)	0.150	0.054	-	-	-	0.150	0.050	-	-	-	0.150	0.013	-	-	-
K_{el} *	(h^{-1})	5.3488	1.7070	31.91	-	-	4.6050	1.0631	23.09	-	-	4.5231	2.9648	65.55	-	-
$T_{½ el}$ *	(h)	0.14	0.04	31.23	-	-	0.16	0.04	27.22	-	-	0.26	0.22	86.76	-	-
Cl/F *	(L/(h·kg))	50.57	24.61	48.66	-	-	38.24	13.20	34.52	-	-	52.26	31.03	59.38	-	-
Vd/F *	(L/kg)	9.61	4.27	44.45	-	-	8.75	4.51	51.58	-	-	12.07	1.38	11.42	-	-

* For these parameters, n = 11 for Day 1, n = 10 for Day 7 and n = 9 for Day 14.
** Median and interquartile ranges are also presented.
"-" = Not applicable.

**** Source- Copied from Sponsors electronic report for study TH9507/CTR/1016***

Table 3: Summary of pharmacokinetics parameters of tesamorelin on Day 1, Day 7, and Day 14 at 2 mg dose*.

Parameters		Day 1					Day 7					Day 14				
		Mean	SD (±)	CV (%)	Geo. Mean	Geo. Mean CV(%)	Mean	SD (±)	CV (%)	Geo. Mean	Geo. Mean CV(%)	Mean	SD (±)	CV (%)	Geo. Mean	Geo. Mean CV(%)
AUC_{0-t} ‡	(pg·h/mL)	774.72	547.03	70.61	634.62	72.36	844.98	665.57	78.77	661.24	82.03	686.32	465.91	67.88	557.80	78.17
AUC_{0-4h}	(pg·h/mL)	855.69	567.49	66.32	710.70	70.57	883.73	654.72	74.09	710.19	75.90	771.91	506.27	65.59	633.78	75.88
AUC_{0-inf} *	(pg·h/mL)	860.98	605.65	70.34	706.33	72.35	954.29	752.63	78.87	750.37	80.54	828.54	611.21	73.77	665.71	78.63
$AUC_{t/inf}$ *	(%)	92.71	4.75	5.12	-	-	88.25	4.87	5.52	-	-	84.35	9.83	11.65	-	-
C_{max}	(pg/mL)	3076.4	1027.5	33.40	2874.6	43.87	2135.6	802.0	37.56	2013.2	36.55	1843.2	615.6	33.40	1744.9	36.54
T_{max}	(h)	0.147	0.052	35.05	-	-	0.150	0.048	31.78	-	-	0.150	0.043	28.43	-	-
T_{max} **	(h)	0.150	0.063	-	-	-	0.150	0.063	-	-	-	0.150	0.013	-	-	-
K_{el} §	(h^{-1})	5.3507	2.7280	50.98	-	-	3.4848	2.0662	59.29	-	-	2.9734	1.8073	60.78	-	-
$T_{½ el}$ §	(h)	0.21	0.22	108.07	-	-	0.35	0.38	107.94	-	-	0.43	0.42	98.93	-	-
Cl/F *	(L/(h·kg))	48.97	30.17	61.61	-	-	46.72	31.15	66.68	-	-	50.29	29.82	59.30	-	-
V_d/F *	(L/kg)	9.39	3.06	32.62	-	-	14.74	7.33	49.72	-	-	22.32	22.90	102.58	-	-

** Median and interquartile ranges are also presented.
"-" = Not applicable.
* For these parameters, n = 11.
‡ For this parameter, n = 12 for Day 1 and n = 11 for Day 7 and Day 14.
§ For these parameters, n = 11 for Day 1 and Day 7 and n = 12 for Day 14.

**** Source- Copied from Sponsors electronic report for study TH9507/CTR/1016***

For the 1 mg and 2 mg dose, a decrease in C_{max} was observed on Day 14 as compared to Day 1 and Day 7. The decrease in C_{max} is of no clinical relevance, since the IGF-1 increases significantly overtime, and GH production is comparable after multiple administrations of tesamorelin 1 mg and 2 mg doses.

Reviewer's Comment: For several subjects (002, 015, and 017), tesamorelin concentrations were detected at pre-dose and also at 24 hours post dose samples. The half-life of this tesamorelin is very short and thus, quantifiable pre-dose and post dose concentrations after 24 hours were not expected. Sponsor later found out that the detected pre-dose concentrations could be due to elevated background signal caused by human anti-rabbit antibodies (HARA) that essentially cross-linked the two polyclonal rabbit antibodies used in the bioanalytical method. Also, anti-tesamorelin antibodies were detected for subjects 002, 005, 008 and 012, which can potentially interfere with the analytical assay for the quantitation of tesamorelin. Reviewer did reanalysis of the PK data excluding these subjects. **Table 4** and **Table 5** represent the summary of PK parameters in healthy subjects after reanalysis of PK parameters.

Table 4: Summary of pharmacokinetics parameters of tesamorelin on Day 1, Day 7 and Day 14 at 1 mg dose*

Parameter	Day 1				Day 7				Day 14			
	Mean	CV (%)	Geo. Mean	Geo Mean (CV %)	Mean	CV (%)	Geo. Mean	Geo Mean (CV %)	Mean	CV (%)	Geo. Mean	Geo Mean (CV %)
AUC 0-t (pg*h/mL)	306.2 ±170.9	55.8	268.5	58.2	366.5 ± 152.9	41.7	337.9	45.4	333.7 ± 282	84.5	258.6	81.9
C_{max} (pg/mL)	1341.2 ±476.1	35.5	1258.8	40.5	1400.3 ±455.2	32.5	1320.7	39.7	1011.9 ±452.2	44.7	941.3	39.9
T_{max} (h)	0.13 ± 0.33	24.1			0.135 ± 0.02	17.8			0.16 ± 0.06	43.1		
$T_{1/2}$ (h)	0.135 ±0.04	30			0.159 ± 0.04	27.08			0.27 ± 0.23	85.9		
CL/F (L(h*kg)	49.12 ±25.4	51.7			38.24 ± 13.2	34.5			49.6 ± 32.6	64.6		
Vd/F (L/kg)	8.6 ±2.8	32.7			8.7 ± 4.5	51.6			11.8 ± 1.32	11.2		

**** Source- Reviewer's Reanalysis of Data***

Table 5: Summary of pharmacokinetics parameters of tesamorelin on Day 1, Day 7 and Day 14 at 2 mg dose*

Parameter	Day 1				Day 7				Day 14			
	Mean	CV (%)	Geo. Mean	Geo Mean (CV %)	Mean	CV (%)	Geo. Mean	Geo Mean (CV %)	Mean	CV (%)	Geo. Mean	Geo Mean (CV %)
AUC 0-t (pg*h/mL)	794.8 ±569	71.6	642.6	76.5	844.9 ±665.5	78.7	661.2	82.0	686.3 ±465	67.8	557.8	78.1
C_{max} (pg/mL)	3094.7 ±1075.7	34.7	2874.5	46.2	2181.6 ±824.3	37.7	2052.3	37.7	1797.5 ±623	34.7	1698.6	37.0
T_{max} (h)	0 14 ±0.05	36.8			0.14 ±0.04	32.4			0.15 ±0.04	29.8		

$T_{1/2}$ (h)	0 22 ±0.23	105.3			0.34 ±0.37	108.3			0.42 ±0.44	104.7		
CL/F (L(h*kg)	48.6 ±31.7	65.4			46.7 ±31.1	66.6			50.2 ±29.8	59.3		
Vd/F (L/kg)	9.72 ±3.0	31.0			14.7 ±7.3	49.7			22.3 ±22.8	102.5		

**** Source- Reviewer's Reanalysis of Data***

<u>Pharmacodynamics Effect of Tesamorelin on Growth Hormone in Healthy Subjects</u>

Linear plots of the mean plasma concentrations of growth hormone at 1 mg and 2 mg tesamorelin dose are presented in **Figure 6.** In healthy subjects, the growth hormone levels were higher following 2 mg s.c. dose as compared to 1 mg dose **Table 6 and 7**.

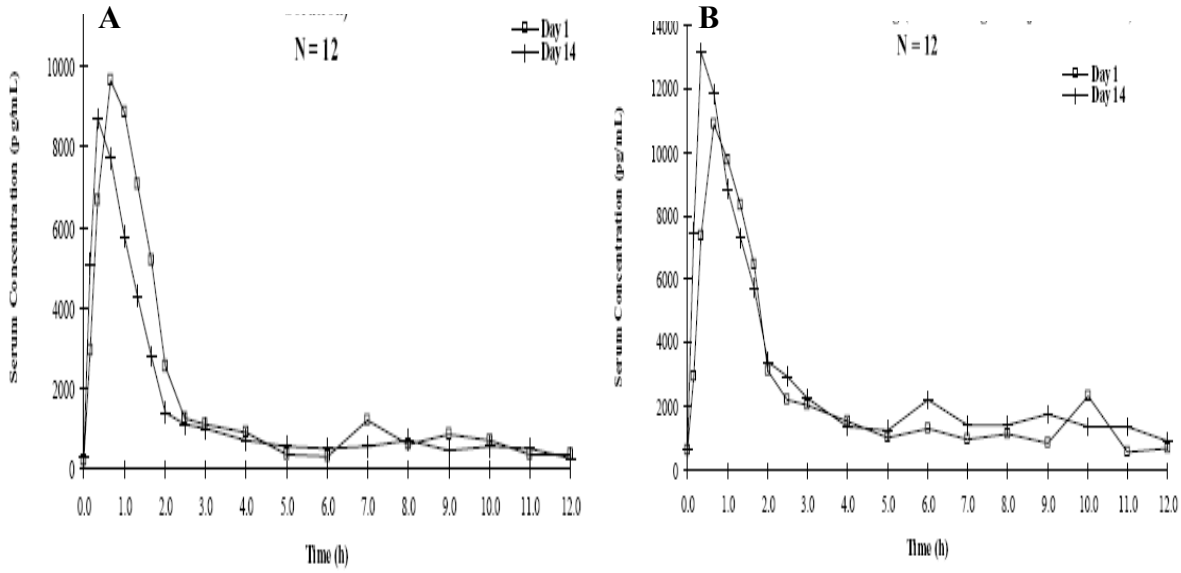


Figure 6: Mean serum growth hormone concentrations time profile in healthy subjects* (A: Dose =1 mg, B: Dose = 2 mg)

**** Source- Copied from Sponsors electronic report for study TH9507/CTR/1016***

Growth hormone production, as expressed in terms of area under effect curve (AUEC), was approximately 68% higher following administration of the 2 mg dose when compared to the 1 mg dose. The maximum growth hormone release (E_{max}) was 38% greater for the 2 mg dose than for the 1 mg dose (**Table 8**).

Table 6 : Summary of Growth Hormone PD parameters after administration of 1 mg tesamorelin

Parameters	Day 1					Day 14				
	Mean	SD (±)	CV (%)	Geo. Mean	Geo. Mean CV(%)	Mean	SD (±)	CV (%)	Geo. Mean	Geo. Mean CV(%)
AUEC (pg·h/mL)	20435.04	11890.50	58.19	17086.80	73.54	16383.93	8888.46	54.25	14455.29	56.06
E_{max} (pg/mL)	10513.86	6292.27	59.85	8793.55	72.43	9113.02	5278.60	57.92	7982.12	55.68
T_{Emax} (h)	0.807	0.221	27.41	-	-	0.417	0.151	36.27	-	-
T_{Emax}* (h)	0.667	0.333	-	-	-	0.333	0.084	-	-	-

*Medians and interquartile ranges are presented

Table 7: Summary of Growth Hormone PD parameters after administration of 2 mg tesamorelin

Parameters	Day 1					Day 14				
	Mean	SD (±)	CV (%)	Geo. Mean	Geo. Mean CV(%)	Mean	SD (±)	CV (%)	Geo. Mean	Geo. Mean CV(%)
AUEC (pg·h/mL)	28252.90	16567.15	58.64	23903.19	67.31	33126.52	15577.30	47.02	29285.50	59.84
E_{max} (pg/mL)	13156.19	9993.68	75.96	10146.28	88.29	14518.29	5904.44	40.67	13212.80	51.79
T_{Emax} (h)	1.86	2.74	147.16	-	-	0.614	0.423	68.82	-	-
T_{Emax}* (h)	0.834	0.501	-	-	-	0.342	0.429	-	-	-

*Medians and interquartile ranges are presented.

Table 8: Growth hormone ratios of treatment B (2 mg) vs treatment A (1 mg) and 90% CIs*

Parameter	Ratio (%)	90% CI	
		Lower (%)	Upper (%)
AUEC[1]	168.35	115.24	245.94
E_{max}[2]	138.20	95.25	200.51

[1] Calculated using the CS variance-covariance matrix.
[2] Calculated using the CSH variance-covariance matrix.

****Source- Copied from Sponsors electronic report for study TH9507/CTR/1016***

<u>Pharmacodynamics Effect of Tesamorelin on IGF-1 in Healthy Subjects</u>

Baseline corrected IGF-1 levels were approximately 26% greater for the 2 mg dose when compared to the 1 mg dose. In healthy subjects IGF-1 levels increased from Day 1 to Day 7 to Day 14. The IGF-1 levels seem to reach a maximum level after 13 days (**Figure 7**).

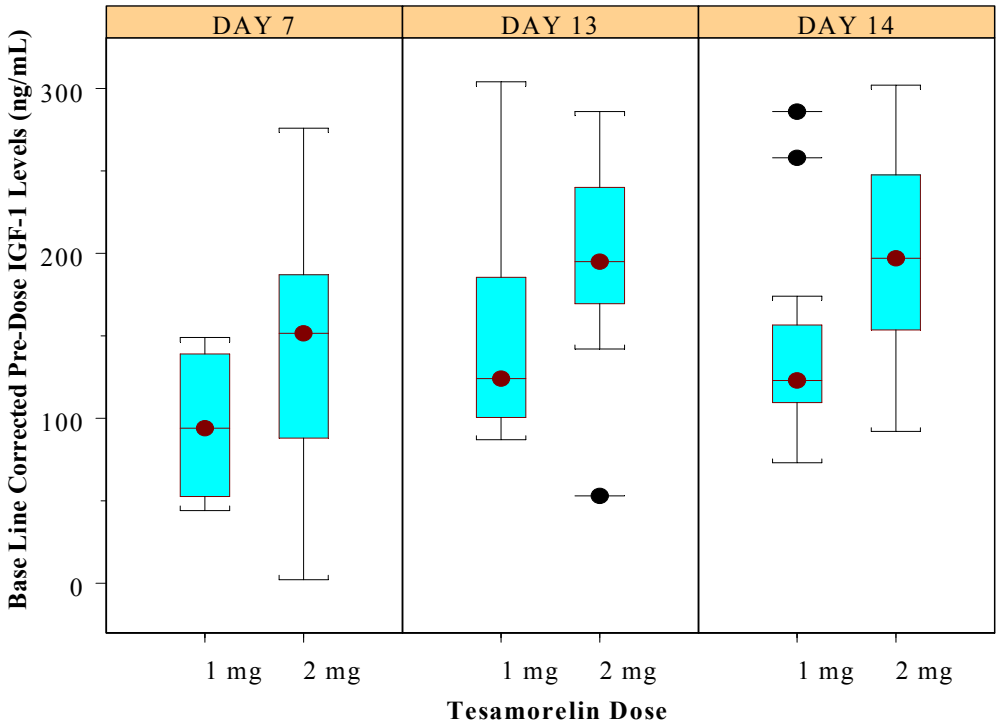


Figure 7: Tesamorelin Dose-Response (IGF-1 Levels) in Healthy Subjects (Dose: 1mg and 2 mg)

Summary of baseline adjusted IGF-1 mean pre-dose concentrations (ng/mL) for treatment A (1 mg dose) and treatment B (2mg dose) is presented in **Table 9 and 10:**

Table 9: Baseline adjusted IGF-1 mean pre-dose concentrations (ng/mL) for Treatment A (1 mg Dose)*

	Day 7	Day 13	Day 14
Mean	95	152	145
SD (±)	41	70	64
CV (%)	43.37	45.94	44.17
Geo. Mean	86	140	135
Geo. Mean CV(%)	49.38	43.38	40.31

Table 10: Baseline adjusted IGF-1 mean pre-dose concentrations (ng/mL) for Treatment B (2 mg Dose)*

	Day 7	Day 13	Day 14
Mean	139	195	200
SD (±)	75	61	66
CV (%)	53.70	31.16	33.29
Geo. Mean	96	182	189
Geo. Mean CV(%)	214.73	45.78	37.44

**Source- Copied from Sponsors electronic report for study TH9507/CTR/1016*

The IGF-1 serum concentrations increased gradually after daily administration of the 1 mg and the 2 mg tesamorelin doses. For 1 mg dose, the ratio of Day 14 to Day 1 predose IGF-1 concentration was 1.84. At 2 mg dose, the ratio of Day 14 to Day 1 was 2.14.

Table 11: Mean IGF-1 pre-dose concentration (ng/mL) at tesamorelin 2 mg dose.

	Day 1	Day 7	Day 13	Day 14
Mean	183	322	378	383
SD (±)	54	64	60	67
CV (%)	29.71	19.97	15.89	17.63
Geo. Mean	175	316	373	377
Geo. Mean CV(%)	32.16	20.93	16.52	18.78

2.2.3 What are the basic pharmacokinetic and pharmacokinetic/pharmacodynamic characteristics of tesamorelin in HIV infected patients?

Pharmacokinetics and pharmacodynamics of tesamorelin was evaluated in Phase 1, 1-way study in which HIV-positive patients received a daily s.c. injection of 2 mg tesamorelin for 14 consecutive days (study # CTR-1015).

Pharmacokinetics of Tesamorelin in HIV Infected Patients:

In HIV infected patients, no tesamorelin accumulation was seen following multiple dose s.c. administration of Egrifta at 2 mg dose. The mean T_{max} was observed approximately 10 minutes post dose following single (Day 1) and multiple (Day 14) doses with values ranging from 4 minutes to 20 minutes. The mean elimination half-life ($t_{½}$ el) was 18.6 min and 37.8 min following single and multiple s.c. injections, respectively.

Linear plots of the mean plasma concentrations of tesamorelin 2 mg dose are presented in **Figure 8**. Summary of pharmacokinetic parameters for each patient are shown in **Table 12** for Day 1 and Day 14, respectively.

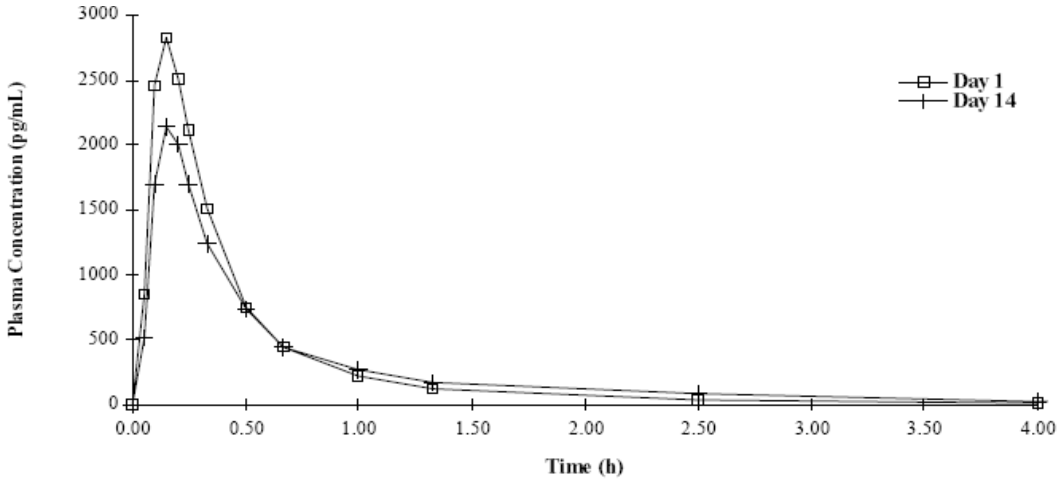


Figure 8: Mean Plasma Concentrations of tesamorelin (Dose =2 mg): Linear Scale*

**Source- Copied from Sponsors electronic report for study TH9507/CTR/1015*

Table 12: Summary of pharmacokinetics parameters of tesamorelin on Day 1, and Day 14 following 2 mg s.c. injection dose

Pharmacokinetic Parameters

Parameters		Day 1 (n = 17)					Day 14 (n = 15)				
		Mean	SD (±)	CV (%)	Geo. Mean	Geo. Mean CV(%)	Mean	SD (±)	CV (%)	Geo. Mean	Geo. Mean CV(%)
AUC_{0-t}	(pg·h/mL)	1149.55	1008.70	87.75	852.80	91.87	1117.23	953.40	85.34	794.68	108.59
AUC_{0-inf}	(pg·h/mL)	1255.40	1104.49	87.98	933.35	90.94	1312.60	1124.19	85.65	940.40	104.73
$AUC_{t/inf}$	(%)	91.44	3.62	3.96	-	-	84.73	6.39	7.54	-	-
C_{max}	(pg/mL)	3106.4	1375.3	44.27	2822.3	48.89	2333.3	1185.0	50.78	2013.2	66.52
T_{max}	(h)	0.162	0.060	37.23	-	-	0.157	0.042	26.61	-	-
T_{max}*	(h)	0.150	0.000	-	-	-	0.150	0.025	-	-	-
K_{el}	(h^{-1})	4.3214	2.7194	62.93	-	-	2.5071	1.9692	78.54	-	-
$T_{½ el}$	(h)	0.31	0.32	104.79	-	-	0.63	0.61	96.54	-	-
Cl/F	(L/(h·kg))	38.71	26.85	69.38	-	-	40.97	31.15	76.04	-	-
V_d/F	(L/kg)	10.48	6.10	58.25	-	-	20.19	9.87	48.90	-	-

* Median and interquartile ranges are also presented.
"-" = Not applicable.

**Source- Copied from Sponsors electronic report for study TH9507/CTR/1015*

Similar to healthy subjects, in HIV infected patients a decrease in C_{max} was observed on Day 14 as compared to Day 1. The decrease in C_{max} is of no clinical relevance since the IGF-1 increases significantly overtime. In HIV infected patients without lipodystrophy, the pharmacokinetic parameters after subcutaneous administration were similar to healthy subjects (**Figure 9**).

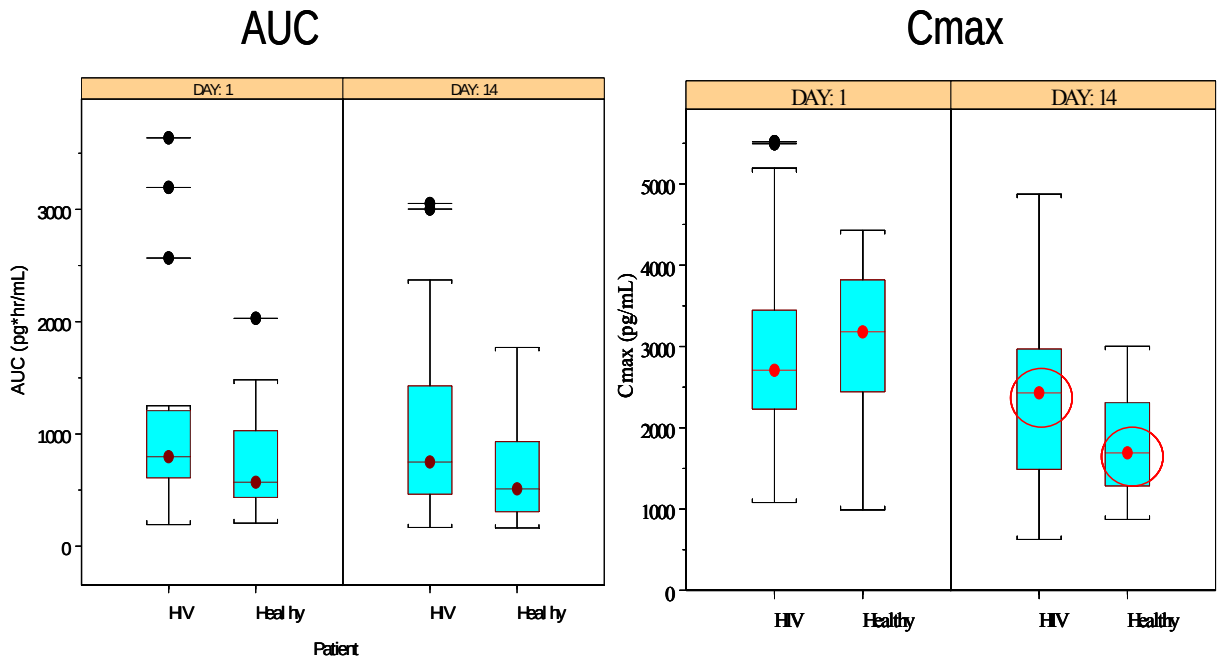


Figure 9: Tesamorelin PK in Healthy and HIV Infected Patients following 2 mg Tesamorelin Dose

<u>Pharmacodynamics Effect of Tesamorelin on IGF-1:</u>

In HIV infected patients, the IGF-1 serum concentrations increased gradually after daily 2 mg tesamorelin dose from day 1 to day 14. The ratio of Day 14 to Day 1 predose IGF-1 concentration was 2.21. The increase in the IGF-1 serum concentration in HIV positive patients is comparable to the one observed in healthy volunteers (**Figure 10**)

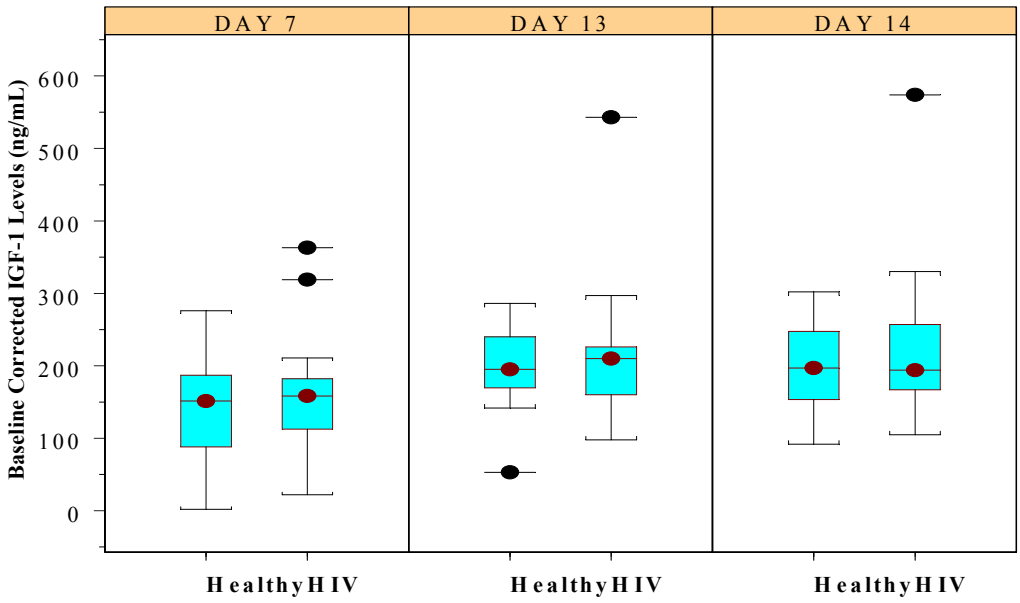


Figure 10: PD Effect (IGF-1 Levels) of Tesamorelin in Healthy and HIV Infected Patients following 2 mg Dose

2.2.4 *What is the effect of immunogenicity on the PK of tesamorelin?*

Effect of anti-tesamorelin IgG antibodies, on the pharmacokinetics of tesamorelin was evaluated in Phase 3 study. Summary of pharmacokinetic parameters is shown in **Table 13**. Due to an inadequate number of patients (8 patients), inappropriate PK sampling, and limitation of analytical method to accurately evaluate PK of tesamorelin in presence of drug specific IgG antibodies, the PK data generated is highly variable and not accurate.

Table 13: Summary of Pharmacokinetics parameters in anti-tesamorelin IgG positive patients

Pharmacokinetic Parameters of TH9507 in Patient

Visit	Study Day		AUC_{0-t} (pg·h/mL)	AUC_{0-inf} (pg·h/mL)	C_{max} (pg/mL)	T_{max} (h)	K_{el} (h^{-1})	$T_{½ el}$ (h)	Vz/F (L)	Cl/F (L/h)
2	Day 0	N	7	7	7	7	7	7	7	7
		n	7	2	7	7	2	2	2	2
		Mean	583.48	535.46	2049.6	0.133	4.8594	0.14	795.97	3912.91
		SD (±)	318.24	161.41	851.9	0.047	0.7573	0.02	118.68	1179.55
		Jack Knife SD	-	-	-	-	-	NC	-	-
		Harmonic Mean	-	-	-	-	-	0.14	-	-
		Geom. Mean	508.57	523.15	1925.7	-	-	-	791.53	3822.98
		Geom. Mean CV(%)	64.13	31.35	38.0	-	-	-	15.05	31.35
4	Week 13	N	5	5	5	5	5	5	5	5
		n	5	3	5	5	3	3	3	3
		Mean	6709.60	14430.92	2513.0	0.300	1.3342	5.38	1450.69	2461.38
		SD (±)	12442.81	21005.46	3049.6	0.225	1.9987	7.32	432.14	3832.93
		Jack Knife SD	-	-	-	-	-	9.17	-	-
		Harmonic Mean	-	-	-	-	-	0.52	-	-
		Geom. Mean	1242.70	3676.84	1622.6	-	-	-	1407.04	543.94
		Geom. Mean CV(%)	869.19	2005.69	121.0	-	-	-	31.25	2005.69
6	Week 26	N	6	6	6	6	6	6	6	6
		n	6	5	6	6	5	5	5	5
		Mean	5274.53	7089.35	1288.3	0.472	0.6946	3.17	2559.51	1521.75
		SD (±)	9780.82	11800.94	681.7	0.434	0.9269	2.89	1329.30	1501.01
		Jack Knife SD	-	-	-	-	-	3.18	-	-
		Harmonic Mean	-	-	-	-	-	1.00	-	-
		Geom. Mean	1768.17	2552.82	1125.7	-	-	-	2196.73	783.45
		Geom. Mean CV(%)	276.13	316.05	66.2	-	-	-	75.94	316.05

NC = Not calculable.

Reviewer's Comment: No definitive conclusion can be made on the effect of immunogenicity on PK of tesamorelin due to limited number of subjects studied and high variability in the data set. However, in the Phase 3 studies, the sponsor has demonstrated that immunogenicity has no effect on efficacy of tesamorelin in HIV infected patients with lipodystrophy. Pooled analysis of pivotal studies (main phase) showed that the percent change in VAT (primary efficacy endpoint) as a function of anti-tesamorelin antibody status was similar between antibody positive and antibody negative patients. Please refer to Dr. Ali Mohamadi's (Medical Officer) review for further details.

2.2.5 *Are the active moieties in the plasma appropriately identified and measured?*

Yes. Tesamorelin concentrations in plasma from HIV infected patients and healthy volunteers were quantified using sandwich ELISA method. For details see section 2.6.

2.2.6 Exposure Response

2.2.6.1 What are the characteristics of the dose-response relationships for efficacy?

Dose-response relationship was explored in a Phase 2 (008) trial. The Phase 2 trial was a multicenter, randomized, double-blind, and placebo controlled study, in which subjects were randomized to receive either subcutaneous injection of placebo, tesamorelin 1 mg, or tesamorelin 2 mg for 12 weeks.

In this trial a dose- response relationship was seen where only 2 mg daily administration of tesamorelin for 12 weeks resulted in statistically significant decreases from baseline to Week 12 in VAT.

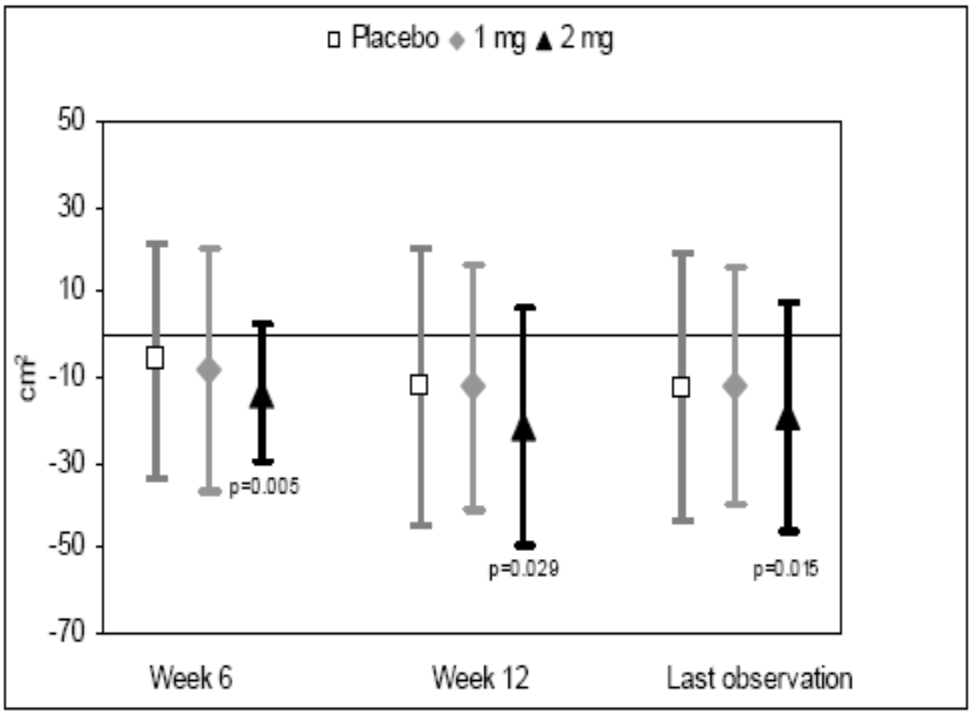


Figure 11 : Mean change from baseline in VAT (ITT population) following placebo, 1mg and 2 mg daily s.c. administration of tesamorelin*.

* *Source- Copied from Sponsors electronic report for study TH9507/II/LIPO/008*

The mean change from baseline in VAT was significant in the tesamorelin 2 mg group at Week 6 (-13.657 cm^2; p=0.0052) and at Week 12 (-21.500 cm^2; p=0.0286). Mean decreases in VAT were also observed in the tesamorelin 1 mg and placebo groups. However, neither group was significantly different from baseline, from each other nor from the tesamorelin 2 mg group (**Table 14**).

Table 14 : Statistical summary of Mean VAT (cm^2) measurement (ITT population) following placebo, 1 mg and 2 mg daily s.c. administration of tesamorelin*.

	Placebo	1 mg	2 mg	Between-group
Baseline	190.5 ± 75.7	157.8 ± 56.6	160.2 ± 53.5	0.229
Change at week 6	-5.81 ± 27.46	-8.18 ± 28.39	**-13.66 ± 15.98	0.577
Change at week 12	-12.02 ± 32.48	-11.94 ± 28.71	*-21.50 ± 27.92	0.447
Change at last observation	-12.39 ± 31.33	-11.97 ± 27.80	*-19.10 ± 26.62	0.563

Source: Post-text tables 11-13 ** p<0.05 within-group ** p<0.01 within-group*

**** Source- Copied from Sponsors electronic report for study TH9507/II/LIPO/008***

In this study, 2 mg daily dose, which was efficacious in reducing VAT, had a superior effect when compared to the 1 mg dose. Also, the daily administration of TH9507 at 2 mg dose had a consistently superior effect on IGF-1(an integrated measure of GH and a surrogate endpoint of the biological activity of tesamorelin production) when compared to the 1 mg dose. Based on these results, the sponsor investigated only one dose, 2 mg daily s.c. administration, of tesamorelin for the Phase 3 trials. Phase 3 trials have no exposure data and only 2 mg dose is used in the Phase 3 trials, so no additional exposure/dose response relationship was evaluated from Phase 3 data.

2.2.6.2 What are the characteristics of the dose-response relationships for safety?

In the Phase 2 trial, the sponsor monitored various safety variables like glucose homeostasis, lipid profiles, bone mineral density (BMD), bone formation and resorption markers were explored for dose-response relationship for safety. No dose-response relationship for safety was evident from this trial. Please refer to Dr. Ali Mohamadi's (Medical Officer) review for further safety related issues in details.

2.3 Intrinsic Factors

2.3.1 What is Effect of Age on the Pharmacokinetics and Pharmacodynamics of tesamorelin?

The effect of age on the pharmacodynamics and pharmacokinetics was investigated in a randomized, cross over, open label study following s.c. administration of tesamorelin 2 mg once (Treatment A) or 2 mg twice daily (Treatment B) for 14 days in elderly patients aged between 70 and 85 years (study #009). Twice daily (b.i.d.) subcutaneous dosing (Treatment B) with 2 mg tesamorelin for 14 days provided a greater increase in both IGF-1 levels (**Table 15**) and GH levels (**Table 16**) as compared to once daily (q.d.) dosing (Treatment A) for the same period.

Table 15 : Arithmetic Mean ±SD (Geometric Mean) IGF-1 (ng/mL) by treatment (Treatment A: Once daily s.c. injection, Treatment B: twice daily s.c. injection)

	Day			
	1	4	8	15
Treatment A	111 ± 28.2 (108)	182 ± 53.7 (174)	202 ± 68.9 (192)	232 ± 73.0 (221)
Treatment B	117 ± 29.5 (114)	253 ± 76.7 (243)	278 ± 79.8 (267)	300 ± 85.9 (285)

Table 16: Arithmetic Mean ±SD (Geometric Mean) GH AUEC (ng*h/mL) by treatment. (Treatment A: Once daily s.c. injection, Treatment B: twice daily s.c. injection)

	Day 1	Day 14
Treatment A	27.3 ± 15.9 (23.3)	35.5 ± 20.1 (30.9)
Treatment B	23.6 ± 10.9 (20.4)	40.2 ± 16.6 (37.1)

Reviewer's Comment: No pharmacokinetics results were presented in this report. The ratio of Day 1 to Day 14 of predose IGF-1 levels was approximately 2.1. This ratio is similar to that from healthy young subjects. However, the mean plasma levels of IGF-1 in elderly subjects were lower than the healthy young subjects (**Table 11**). The clinical impact of low IGF-1 levels on safety and efficacy in elderly subjects is not known. In Phase 3 safety and efficacy clinical trials, no subjects above 65 years of age were enrolled.

2.4 Extrinsic Factors

2.4.1 Drug-Drug Interaction

2.4.1.1 What is the Effect of Tesamorelin on the PK of Simvastatin?

The effect of tesamorelin on the pharmacokinetic of simvastatin was evaluated in a randomized, open-label, two-period, two-sequence, two treatment, two-group crossover, drug-drug interaction study in healthy volunteers under fasting conditions (study # CTR-1019). There were 2 treatment arms in this study. For Treatment A, a single s.c. injection of tesamorelin, as a 2 mL x 1 mg/mL (2 mg) was administered once daily for 7 consecutive days along with a single oral dose of simvastatin co-administered as a 1 x 80

mg tablet on Day 6. For Treatment B, no study drug was administered on Days 1 to 5 and 7. On Day 6, a single oral dose of simvastatin (1 x 80 mg tablet) was administered.

In this study, it was shown that there is no clinically significant impact of tesamorelin on the PK profile of simvastatin. For simvastatin, the estimated ratios of LSM and corresponding 90% CIs for AUC_{0-t}, AUC_{0-inf} and C_{max} were contained within the acceptance range of 80-125%. For the metabolite simvastatin acid, the lower CI for AUC_{0-inf} (78.6%) fell outside of the acceptance range (**Table 17**). This decrease in metabolite exposure is not expected to have any clinical implication.

Table 17: Statistical Summary of Pharmacokinetic Parameters for Simvastatin and Simvastatin Acid

	Geometric Mean Ratio (%) Tesamorelin+Simvastatin/Simvastatin		90 % Confidence Interval	
	Simvastatin	Simvastatin Acid	Simvastatin	Simvastatin Acid
AUC(0-t)	92.2	86.3	83.5-101.9	80.2-92.7
AUC(0-inf)	91.7	85.2	83.0-101.3	78.6-92.4
Cmax	105.3	99.0	94.6-117.1	91.4-106.7

Reviewer's Comment: In this study, fifty-eight (58) healthy adult subjects were enrolled and dosing was conducted in two groups: Group 1 consisted of Subjects 001-029 and Group 2 consisted of Subjects 030-058. The dosing interval between two groups was approximately 10 days. Sponsor's analysis of PK data based on two groups showed different results in Group 1 and Group 2, as shown in **Table 18**.

Table 18: Summary of ANOVA of simvastatin and simvastatin acid for each group

	Group 1		Group 2	
	A/B Ratio (%)	90% CI (%)	A/B Ratio (%)	90% CI (%)
Simvastatin				
AUC_{0-t}	81.0	70.5 – 92.9	105.4	92.1 – 120.7
AUC_{0-inf}	80.6	70.4 – 92.3	104.6	91.2 – 119.9
C_{max}	94.5	80.1 – 111.4	117.6	103.1 – 134.2
Simvastatin acid				
AUC_{0-t}	77.6	70.9 – 84.9	96.8	87.2 – 107.4
AUC_{0-inf}	76.3	68.6 – 84.8	94.9	84.6 – 106.5
C_{max}	94.4	85.0 – 104.8	104.3	93.6 – 116.2

Sponsor investigated into the causes that could have possibly contributed to the group effect. However, no major differences were identified between the two groups with respect to demographics (e.g. gender, race, and body mass index) and meals served. Thus, due to the absence of a clinically-based reason for the group effect, this reviewer also agrees with the sponsor's pooled analysis of PK data from the two groups. Pooled analysis showed no clinically significant impact of tesamorelin on the pharmacokinetics of simvastatin.

2.4.1.2 What is the Effect of Tesamorelin on the PK of Ritonavir ?

The effect of tesamorelin on the pharmacokinetic of ritonavir was evaluated in a single centre, randomised, open-label, two-period, two-treatment crossover study in thirty two healthy volunteers (study# CTR-1020). The subjects were given a single dose of ritonavir with and without prior subcutaneous administration of tesamorelin once daily for 7 days. In treatment A daily s.c. injection of Tesamorelin (2 mg) was administered from Day 1 to 7 and a single dose of ritonavir 100 mg was administered on Day 6 after standard breakfast. Treatment B a single dose of ritonavir 100 mg was administered on Day 6 after standard breakfast

The mean concentration versus time profiles for ritonavir for both Treatments A (tesamorelin + ritonavir) and B (ritonavir) are presented in **Figure 12.**

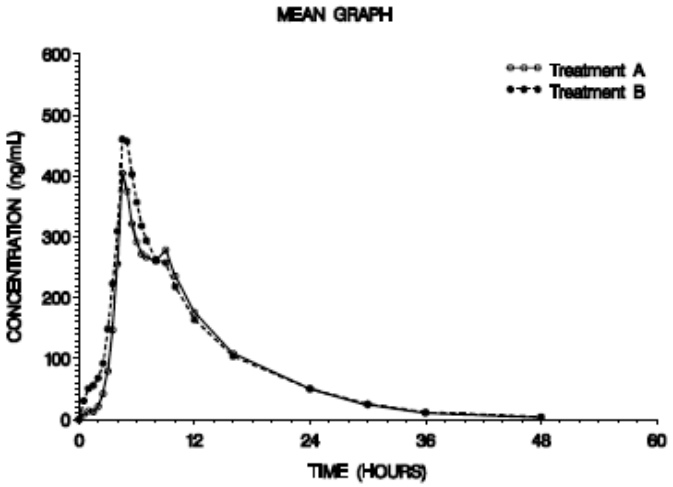


Figure 12: Mean Plasma Concentrations time profile of ritonavir: Linear Scale

Statistical analysis of the PK parameters calculated from plasma concentrations of ritonavir showed that the acceptance limits of 80-125% for the ratio and 90% CI of Treatment A/Treatment B were met for $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$. However, for C_{max}, the lower CI was 74.80%, which is outside of the acceptance limits (**Table 19**).

Table 19: Statistical Summary of Pharmacokinetic Parameters for ritonavir

	Geometric Means[a]		A/B Ratio (%)	90% CIs	
	Treatment A	Treatment B		Lower (%)	Upper (%)
AUC_{0-t} (ng·h/mL)	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)	404.2	452.7	89.3	74.8	106.6

[a] Calculated by exponentiating the LSM from a model using a log-transformed response
Reference: Appendix 16.1.9 (Appendix 8.3.2)

Reviewer's Comment: The literature suggests that human growth hormone may modulate cytochrome P450 (CYP) enzyme activity and expression. Since tesamorelin induces the secretion of GH, the potential impact of tesamorelin on CYP3A4 activity was investigated in the drug-drug interaction studies.
In this study, after multiple dose administration of tesamorelin, the ritonavir mean exposure and 90% CI was within limits of 80-125% for treatment with and without tesamorelin. However, for C_{max}, the lower CI was 74.80%, which is outside of the 80%-125% range. This lowering of C_{max} will not be of any clinical significance since ritonavir is commonly used as adjunct therapy to boost the effect of other HIV protease inhibitors. No definitive conclusion on the effect of tesamorelin on CYP3A4 activity can be drawn since ritonavir itself is a very strong inhibitor for CYP3A4. Thus the slight decrease in AUC and C_{max} observed in this study could be due to self-inhibitor effect of ritonavir on its own pharmacokinetics.

2.5 General Biopharmaceutics

2.5.1 What is bioavailability of Egrifta following s.c. administration?

The absolute bioavailability of Egrifta was evaluated from a Phase 1, parallel, randomized, open-label, two periods, single-dose study after a single s.c. (2 mg) (Treatment A) or i.v (Treatment B) injection (200 µg), given on two different occasions separated by a 14-day washout period in healthy forty four healthy subjects (Study #1017). In healthy subjects, following intravenous administration the mean elimination half-life ($t_{½}$ el) was observed to be 0.12 h on Day 1 and 0.13 h on Day 15 of administration, respectively. The absolute bioavailability of tesamorelin after subcutaneous injection was estimated to less than 4%. Summary of PK parameters following s.c. and i.v. administration is shown in **Table 20** and **Table 21**, respectively.

Table 20: Summary of the PK Parameters for Treatment A (2 mg S.C. injection) for Period 1 (Day 1) and for Period 2 (Day 15)

Parameters		Period 1 (Day 1)					Period 2 (Day 15)				
		Mean	SD (±)	CV (%)	Geo. Mean	Geo. Mean CV (%)	Mean	SD (±)	CV (%)	Geo. Mean	Geo. Mean CV (%)
AUC_{0-t}	(pg·h/mL)	880.80	344.07	39.06	824.05	38.21	907.61	569.71	62.77	744.44	74.39
AUC_{0-inf}*	(pg·h/mL)	957.90	404.80	42.26	888.96	40.17	935.97	589.35	62.97	777.20	70.39
$AUC_{t/inf}$*	(%)	92.79	4.07	4.38	-	-	91.24	4.30	4.71	-	-
C_{max}	(pg/mL)	3171.8	969.6	30.57	3049.0	28.82	2903.0	1244.7	42.88	2670.2	44.68
T_{max}	(h)	0.128	0.030	23.38	-	-	0.119	0.025	21.05	-	-
T_{max}**	(h)	0.133	0.050	-	-	-	0.100	0.050	-	-	-
K_{el}*	(h^{-1})	4.1441	1.7735	42.80	-	-	4.3910	2.2901	52.16	-	-
$T_{½ el}$*	(h)	0.26	0.32	121.80	-	-	0.25	0.22	89.05	-	-
Cl/F*	(L/(h·kg))	36.49	13.28	36.38	-	-	47.77	29.43	61.60	-	-
V_d/F*	(L/kg)	10.38	5.96	57.38	-	-	12.31	7.10	57.64	-	-

* For these parameters, n = 15 for Period 2 (Day 15).
** Median and interquartile ranges are also presented.
"-" = Not applicable.

Table 21: Summary of the PK Parameters for Treatment B (200 µg I.V. Injection) for Period 1 (Day 1) and for Period 2 (Day 15)

Parameters		Period 1 (Day 1)					Period 2 (Day 15)				
		Mean	SD (±)	CV (%)	Geo. Mean	Geo. Mean CV (%)	Mean	SD (±)	CV (%)	Geo. Mean	Geo. Mean CV (%)
AUC_{0-t}	(pg·h/mL)	2354.27	418.08	17.76	2301.94	18.74	2662.58	591.84	22.23	2614.40	18.64
AUC_{0-inf}	(pg·h/mL)	2394.00	419.25	17.51	2339.24	18.50	2701.62	591.34	21.89	2653.91	18.44
$AUC_{t/inf}$	(%)	98.30	0.53	0.54	-	-	98.51	0.40	0.40	-	-
C_{max}	(pg/mL)	19644.1	4194.5	21.35	19461.5	21.08	23644.5	10759.0	45.50	22438.10	29.08
T_{max}	(h)	0.051	0.004	7.14	-	-	0.050	0.000	0.00	-	-
T_{max}*	(h)	0.050	0.000	-	-	-	0.050	0.000	-	-	-
K_{el}	(h^{-1})	5.7903	0.8877	15.33	-	-	5.6413	0.9940	17.62	-	-
$T_{½ el}$	(h)	0.12	0.02	14.84	-	-	0.13	0.03	23.05	-	-
Cl	(L/(h·kg))	1.25	0.34	26.78	-	-	1.09	0.20	18.51	-	-
V_d	(L/kg)	0.22	0.06	26.38	-	-	0.20	0.06	30.36	-	-

* Median and interquartile ranges are also presented.
"-" = Not applicable.

2.6 Analytical

2.6.1 How are the active moieties identified and measured in the plasma/serum?

Concentrations of tesamorelin in plasma samples from healthy volunteer and HIV infected patients were measured using validated sandwich ELISA method.

2.6.2 What bioanalytical methods are used to assess concentrations?

In this application, the PK data collected in the early Phase 1 studies (study # 10-98, 002, and 009) in healthy volunteers were analysed using radioimmunoassay (RIA) methods that detected tesamorelin immunoreactive fragments, especially at later time points (i.e., the elimination phase), in addition to the intact peptide. Due to the limitations of the initial RIA method used in the early Phase 1 studies the sponsor developed a new PK program, following the development and validation of an enzyme-linked immunosorbent assay (ELISA) for tesamorelin.

Tesamorelin concentrations in plasma from HIV infected patients and healthy volunteers were quantified using validated sandwich ELISA method (Validation Reports: #E-PCL-177, E-PCL-272 and E-PCL-273). The ELISA method developed uses antibody raised in rabbits against N- and C- terminal epitopes of tesamorelin. The sponsor's cross reactivity analysis suggested that the antibodies are specific for intact tesamorelin with negligent cross reactivity for endogenous hGRF (4%) and also negligible cross reactivity for other biodegradation product of tesamorelin. A brief summary of the assay characteristics is shown below in **Table 22.**

Table 22: Assay Validation Results for Tesamorelin

	Tesamorelin
Standard Curve Range	150 pg/mL- 6000 pg/mL
QC Sample Concentrations	400, 1500, 4500 pg/mL
Precision (%CV) (HIV Positive Human Plasma)	Intra-Assay: 6.0 % to 16.8 % Inter- Assay: 8.4 % to 13.7 %
Accuracy (%) (HIV Positive Human Plasma)	Intra- Assay: 86.3 % to 115.2 % Inter- Assay: 93.6 % to 105.3 %
Precision (%CV) (Normal Human Plasma)	Intra- Assay: 2.3 % to 11.7 % Inter- Assay: 5.2 % to 11.4 %
Accuracy (%)(Normal Human Plasma)	Intra- Assay: 86.7 % to 109.6% Inter- Assay: 88.1% to 104.3%
Dilution Linearity	53,333 fold in HIV positive plasma matrix 26,667 fold in normal plasma matrix
Reference Standard	TH9507 Lot No: FHEXGRF0201 (98.95% purity)
Specificity	No Interference
Stability	Room Temperature Stability: Approx 2 hours in normal plasma and approx 3 hours in HIV positive plasma. Stability at 4°C and on Ice: Approx 3 hours in both HIV and normal plasma matrix Freeze/ Thaw Stability: 3 FT Cycle at -80°C Long Term Matrix Stability: 91 Days at -80°C in stabilized normal plasma and 171 days at -80°C in HIV positive plasma[¥]

¥***Note: Data presented is based on the validation report (E-PCL-177).***

Reviewer's Comment: The sponsor later tested the potential interference of anti-tesamorelin immunoglobulin G (IgG) antibodies on the quantification of tesamorelin using ELISA. Results indicated that anti-tesamorelin IgG antibodies can potentially interfere with the analytical assay for the quantitation of tesamorelin. Depending on the nature of the antibodies, interference occurs at low titers and thus this reviewer excluded subjects with positive antibody status when evaluating PK results.

3 DETAILED LABELING RECOMMENDATION

The following are the labeling recommendations relevant to clinical pharmacology for NDA 22505. The ~~red strikeout font~~ is used to show the proposed text to be deleted and underline blue font to show text to be included or comments communicated to the sponsor.

HIGHLIGHTS OF PRESCRIBING INFORMATION
DRUG INTERACTIONS

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

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4 APPENDIX

4.1 OCP FILING MEMO

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	22-505	Brand Name	EGRIFTA
OCP Division (I, II, III, IV, V)	DCP II	Generic Name	TESAMORELIN ACETATE
Medical Division	DMEP	Drug Class	
OCP Reviewer	Ritesh Jain, Ph.D.	Indication(s)	To induce and maintain a reduction of excess abdominal fat in HIV-infected patients with lipodystrophy
OCP Team Leader	Wei Qiu, Ph.D. (Acting)	Dosage Form	Lyophilized powder containing 1.1 mg of tesamorelin acetate and 55 mg of mannitol.
Pharmacometrics Reviewer		Dosing Regimen	2 mg subcutaneous injection, once daily
Date of Submission	05/29/2009	Route of Administration	Subcutaneous
Estimated Due Date of OCP Review	02/05/2010	Sponsor	Theratechnologies, Inc
Medical Division Due Date	03/05/2010	Priority Classification	S
PDUFA Due Date	03/29/2010		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1		Study: TH9507-CTR-1014
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				

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In-vivo effects on primary drug:				
In-vivo effects of primary drug:	X	2		Studies: TH9507-CTR-1019, TH9507-CTR-1020
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:	X	5		Studies: TH9507-CTR-1013, TH9507-CTR-1015, TH9507-CTR-1016, TH9507/I/HV/002, TH9507/I/PKPD/009
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability	X	2		Studies: TH9507-CTR-1017, TCHUV 10-98
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		10		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			√	Sponsor used the same formulation in their pivotal clinical trial as to be marketed formulation
2	Has the applicant provided metabolism and drug-drug interaction information?	√			Studies TH9507-CTR-1019, TH9507-CTR-1020 are submitted to evaluate the effect of Tesamorelin on Ritonavir and Simvastatin PK

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3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	√			**Studies: TH9507-CTR-1017, TCHUV 10-98**
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	√			
5	Has a rationale for dose selection been submitted?	√			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	√			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	√			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	√			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	√			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			√	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	√			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	√			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	√			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	√			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			√	Deferral

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16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			√	Deferral
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	√			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	√			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			√	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
__YES_____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Ritesh Jain	07/17/2009
Reviewing Clinical Pharmacologist	Date
Wei Qiu (Acting)	07/17/2009
Team Leader/Supervisor	Date

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Filing Memo (Internal Memo)

1. Background

Tesamorelin (TH9507), a stabilized analogue of human hypothalamic growth hormone-releasing factor (hGRF)/growth hormone-releasing hormone (GHRH), is proposed as a treatment to induce and maintain a reduction of excess abdominal fat in human immunodeficiency virus (HIV) - infected patients with lipodystrophy. Tesamorelin is comprised of the 44-amino acid sequence of hGRF on which a hexenoyl moiety, a C6 chain with a double bond on position 3, has been anchored on Tyr1 at the N-terminal part of the molecule. With the addition of this hydrophobic side chain, resistance to enzymatic degradation in human plasma is increased.

The recommended daily dose, after reconstitution, is 2 mg administered by subcutaneous (sc) injection.

2. Clinical Pharmacology Studies:

In the Clinical Pharmacology Program sponsor has submitted a total of 10 studies. Amongst these 10 studies, six studies were single or multiple dose PK/ PK-PD studies, two bioavailability studies and two drug-drug interaction studies.

The PK data collected in the early Phase 1 studies in healthy volunteers were generated using radioimmunoassay (RIA) methods that most likely detected tesamorelin immunoreactive fragments, especially at later time points (i.e., the elimination phase), in addition to the intact peptide. Due to the limitations of the initial RIA method used in the early Phase 1 studies (TCHUV 10-98 and TH9507/I/HV/002) the sponsor developed a new PK/PD (pharmacodynamic) program, following the development and validation of an enzyme-linked immunosorbent assay (ELISA) for tesamorelin. This PK/PD program comprises the core of the tesamorelin clinical pharmacology program. The following studies are done using ELISA and will be reviewed in this application.

Core studies:

PK/PK-PD Studies

- The TH9507-CTR-1016: a 14-day PK/PD study in healthy volunteers comparing 1 mg and 2 mg sc doses of tesamorelin;
- The TH9507-CTR-1017: a 14-day PK study comparing sc versus intravenous (i.v.) single dose administration of tesamorelin in healthy volunteers;
- The TH9507-CTR-1015: a 14-day PK study of a 2 mg sc dose of tesamorelin in HIV infected patients.

Drug-Drug Interaction Studies

In addition to the aforementioned PK/PD studies, two drug-drug interaction clinical studies were undertaken during the clinical development program of Tesamorelin and will be reviewed.

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- The (TH9507-CTR-1019): potential impact of tesamorelin on PK profile of ritonavir.
- The (TH9507-CTR-1020): potential impact of tesamorelin on PK profile of simvastatin.

In addition to the core studies two supplemental studies were also submitted. These studies will also be reviewed.

Supplemental studies

- The TH9507-CTR-1014: a pilot PK study of a single 2 mg sc dose of tesamorelin from 2 different tesamorelin lots conducted in healthy volunteers; and,

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In addition to these seven studies (five that constitute the core of tesamorelin's clinical pharmacology program and two that are supplemental studies); three other studies (see below) were conducted during the earlier stages of the clinical development program of tesamorelin. They were primarily aimed at evaluating the PD response, establishing dose response curves and obtaining preliminary PK data. These studies were:

- The TCHUV 10-98: a first-in-man, single-dose dose-ranging PK/PD/bioavailability study in healthy volunteers.
- The TH9507/I/HV/002: a 7-day dose-ranging PK/PD study in healthy volunteers.
- The TH9507/I/PKPD/009: a 14-day study in which a 2 mg once daily (qd) dose was compared to a 2 mg twice daily (bid) dosing of tesamorelin.

The PK data for these studies was obtained using the RIA method mentioned above. Due to the limitations of this method, this data is considered as preliminary, supportive data only. Also the effect of immunogenicity on the PK of tesamorelin was studied in phase 3 trial (Study TH9507/III/LIPO/010) on few subjects. This data will also be reviewed.

3. Phase 3 Studies

This program included three multicentre, randomized, double-blind, placebo-controlled pivotal Phase 3 studies

- ✓ Study TH9507/III/LIPO/010
- ✓ Study TH9507-CTR-1011
- ✓ Study TH9507-CTR-1012

The primary endpoint of the studies was to demonstrate a reduction in visceral adipose tissue (VAT), as assessed by computed tomography (CT), after 26 weeks of treatment with tesamorelin 2 mg per day as compared to placebo. The secondary efficacy endpoints included improvement in blood lipids (triglycerides, total cholesterol: high density lipoprotein-cholesterol [HDL-C] ratio), improvement in PRO related to body image, and increase in insulin-like growth factor-1 (IGF-1) levels. Belly appearance distress, belly size estimation and belly profile assessment, the main PRO secondary endpoints, were measured using a validated PRO questionnaire, the Body Image Impact Module (BIIM). Other study

parameters included trunk fat, total fat, lean body mass, limb fat, and non-HDL-C. The extension phases were designed to assess long-term safety and explore duration of effects following end of treatment.

Potential Key Review Questions

- ✓ What are the PK and PK/PD characteristics of Tesamorelin in healthy and HIV infected patients?
- ✓ What is effect of tesamorelin on pharmacokinetics of ritonavir and simvastatin?
- ✓ What is the absolute bioavailability of Tesamorelin?
- ✓ What is the dose-response relationship for the Phase 3 dose selection?
- ✓ What is the effect of immunogenicity on the pharmacokinetics of tesamorelin?

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

ATTACHMENT

Table 1 Core Clinical Pharmacology Studies: Pharmacokinetic Studies in Healthy Subjects and HIV-Patients Using a Validated ELISA Method

Study ID Location Year	Type Duration Design Control type Analytical method	Subjects (M/F) Type Age (range)	Dose/route	C_{max} (pg/mL)	T_{max} (h)	AUC_{0-t} (pg·h/mL)	AUC_{0-inf} (pg·h/mL)	$T_{½ el}$ (h)
				Arithmetic Means				
TH9507-CTR-1017 Canada 2008	BA/PK/Safety Single-dose Randomized Open P - ELISA	44 (26/18) Healthy volunteers 36 y (18-64)	*Period 1* 2 mg sc 200 µg iv *Period 2* 2 mg sc 200 µg iv	3172 19644 2903 23645	0.128 0.051 0.119 0.050	881 2354 908 2663	958 2394 936 2702	0.26 0.12 0.25 0.13
TH9507-CTR-1016 Canada 2008	PK/PD/Safety Multiple-dose (14 days) Randomized Open P - ELISA	24 (24/0) Healthy volunteers 52 y (45-60)	*Day 1* 1 mg sc daily 2 mg sc daily *Day 7* 1 mg sc daily 2 mg sc daily *Day 14* 1 mg sc daily 2 mg sc daily	1338 3076 1392 2136 1022 1843	0.138 0.147 0.129 0.150 0.153 0.150	302 775 404 845 304 686	342 861 416 954 418 829	0.14 0.21 0.16 0.35 0.26 0.43

Study ID Location Year	Type Duration Design Control type Analytical method	Subjects (M/F) Type Age (range)	Dose/route	C_{max} (pg/mL)	T_{max} (h)	AUC_{0-t} (pg·h/mL)	AUC_{0-inf} (pg·h/mL)	$T_{½ el}$ (h)
				Arithmetic Means				
TH9507-CTR-1015 Canada 2008	PK/PD/Safety Multiple-dose (14 days) Open Single Group ELISA	18 (14/4) HIV-positive patients 40 y (26-58)	*Day 1* 2 mg sc daily *Day 14* 2 mg sc daily	3106 2333	0.162 0.157	1150 1117	1255 1313	0.31 0.63

PD: pharmacodynamics; PK: pharmacokinetics; P: parallel-group; X: cross-over; ELISA: Enzyme-linked immunosorbent assay

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

Table 2 Supplemental Clinical Pharmacology Studies: Pharmacokinetic/Bioequivalence Studies in Healthy Subjects Using a Validated ELISA method

Study ID Location Year	Type Duration Design Control type Analytical method	Subjects (M/F) Type Age (range)	Dose/route	C_{max} (pg/mL)	T_{max} (h)	AUC_{0-t} (pg·h/mL)	AUC_{0-inf} (pg·h/mL)	$T_{½ el}$ (h)
				Arithmetic Means				
TH9507-CTR-1014 Canada 2006	PK/Safety Single-dose Randomized Open X - ELISA	12 (4/8) Healthy volunteers 52 y (25-62)	2 mg sc Lot SM390	3681	0.151	1312	1405	0.31
			2 mg sc Lot SL263	4278	0.138	1429	1514	0.28
TH9507-CTR-1013 Canada 2006-2007	BE/PK/PD/Safety Single-dose Randomized Open X - ELISA	88 (76/12) Healthy volunteers 40 y (18-65)	2 mg sc[1]	3910	0.158	1202	1255	0.22

BE: bioequivalence; PD: pharmacodynamics; PK: pharmacokinetics; X: cross-over; ELISA: Enzyme-linked immunosorbent assay

Table 3 Drug-Drug Interaction Pharmacokinetic Studies

Study ID Location Year	Type Duration Design Control type Analytical method	Subjects (M/F) Type Age (range)	Substrate/interacting drug	Substrate (Simvastatin or Ritonavir) C_{max} (ng/mL)	AUC_{0-t} (ng·h/mL)	C_{max} ratio (A/B) ($CI_{90\%}$)	AUC_{0-t} ratio (A/B) ($CI_{90\%}$)
				Geometric Means			
TH9507-CTR-1019 Canada 2008	PK/DDI/Safety Multiple-dose (7 days) Randomized Open X - LC/MS/MS for simvastatin and simvastatin acid	58 (54/4) Healthy volunteers 41 y (20-60)	***Simvastatin*** Treatment A: tesamorelin 2 mg sc daily x 7 days; 80 mg simvastatin on Day 6	16.35	93.15	105.3% (94.6-117.1)	92.2% (83.5-101.9)
			Treatment B: no tesamorelin days 1-7; 80 mg simvastatin on Day 6	15.35	100.54		
			Simvastatin acid Treatment A : tesamorelin 2 mg sc daily x 7 days; 80 mg simvastatin on day 6	4.22	36.60	99.0% (91.9-106.7)	86.3% (80.2-92.7)
			Treatment B: no tesamorelin days 1-7; 80 mg simvastatin on Day 6	4.24	42.12		
TH9507-CTR-1020 Canada 2008	PK/DDI/Safety Multiple-dose (7 days) Randomized Open X - LC/MS/MS for ritonavir	32 (24/8) Healthy volunteers 43 y (19-63)	***Ritonavir*** Treatment A: tesamorelin 2 mg sc daily x 7 days; 100 mg ritonavir on day 6	403.9	3325.1	89.3% (74.8-106.6)	90.8% (83.8-98.3)
			Treatment B: no tesamorelin days 1-7; 100 mg ritonavir on Day 6	450.4	3678.3		

PK: pharmacokinetics; X: cross-over; LC/MS/MS: Liquid chromatography/mass spectrometry/mass spectrometry

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Table 4 Early Clinical Pharmacology Studies Providing Additional Information: Pharmacokinetic Studies in Healthy Subjects Using a RIA Method

Study ID Location Year	Type Duration Design Control type Analytical method	Subjects (M/F) Type Age (range)	Dose/route	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-t} (ng·h/mL)	AUC_{0-inf} (ng·h/mL)	$T_{½ el}$ (h)
				Arithmetic Means				
TCHUV 10-98	BA/PK/PD/Safety	6 (6/0)	100 µg sc (N=1)	0.42	0.10	0.09	0.17	0.3
	Single-dose	Healthy volunteers	200 µg sc (N=1)	0.81	0.10	0.22	0.24	0.1
Switzerland	Randomized DB (one Open arm) X	24 y (21-28)	400 µg sc (N=2)	0.70	0.21	0.39	0.52	0.4
1999	PC		1500 µg sc (N=3)	1.72	0.24	0.89	0.96	0.4
	RIA		200 µg *iv* (N=6)	19.6	-	2.2	2.3	0.2
TH9507/1/HV/002	PK/PD/Safety	39 (39/0)	***First dose***					
	Multiple-dose (7 days)	Healthy volunteers	0.5 mg sc daily	2.31	0.14	1.40	2.22	4.53
Canada	Randomized DB (one Open arm) P	54 y (50-60)	0.5 mg sc bid	1.89	0.14	1.69	2.35	3.71
2001	PC		1.0 mg sc daily	4.12	0.23	3.79	4.25	1.95
	RIA		2.0 mg sc daily	7.67	0.24	5.79	6.70	3.31
			Last dose					
			0.5 mg sc daily	1.86	0.19	1.76	2.39	4.25
			0.5 mg sc bid	3.56	0.20	2.12	2.54	2.55
			1.0 mg sc daily	4.74	0.19	3.77	4.09	1.94
			2.0 mg sc daily	8.88	0.20	6.37	6.94	2.43

BA: bioavailability; PD: pharmacodynamics; PK: pharmacokinetics; DB: double-blind; PC: placebo-controlled; P: parallel-group; X: cross-over; RIA: radioimmunoassay

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Table 5 Summary of Pharmacodynamic Studies - Growth Hormone

Study ID Location Year	Type Duration Design Control type Analytical method	Subjects (M/F) Type Age (range)	Dose/route	E_{max} (ng/mL)	T_{Emax} (h)	AUEC (ng·h/mL)
				Arithmetic Means ± SD		
TH9507-CTR-1013 Canada 2006-2007	BE/PK/PD/Safety Single-dose Randomized Open X - ELISA	88 (76/12) Healthy volunteers 40 y (18-65)	2 mg sc[2]	12.9 ± 12.3	2.4 ± 2.9	32.4 ± 21.3
TH9507-CTR-1016 Canada 2008	PK/PD/Safety Multiple-dose (14 days) Randomized Open P - ELISA	24 (24/0) Healthy volunteers 52 y (45-60)	*Day 1* 1 mg sc daily 2 mg sc daily *Day 14* 1 mg sc daily 2 mg sc daily	10.5 ± 6.3 13.2 ± 10.0 9.1 ± 5.3 14.5 ± 5.9	0.8 ± 0.2 1.9 ± 2.7 0.4 ± 0.2 0.6 ± 0.4	20.4 ± 11.9 28.3 ± 16.6 16.4 ± 8.9 33.1 ± 15.6
TH9507/I/PKPD/009 Canada 2003	PK/PD/Safety Multiple-dose (14 days) Randomized Open X - RIA	24 (12/12) Healthy volunteers 73 y (70-77)	*Day 1* 2 mg sc daily 2 mg sc bid *Day 14* 2 mg sc daily 2 mg sc bid	12.4 ± 8.7 9.9 ± 5.3 16.0 ± 11.6 16.6 ± 11.0	na na na na	27.3 ± 15.9 23.6 ± 10.9 35.5 ± 20.1 40.2 ± 16.6
Earlier studies						
TCHUV 10-98 Switzerland 1999	BA/PK/PD/Safety Single-dose Randomized DB (one Open arm) X PC IRMA	6 (6/0) Healthy volunteers 24 y (21-28)	Saline (N=6) 20 µg sc (N=6) 40 µg sc (N=6) 100 µg sc (N=6) 200 µg sc (N=6) 400 µg sc (N=6) 1500 µg sc (N=6) 200 µg iv (N=6)	2.3 ± 1.8 2.7 ± 2.4 2.4 ± 3.0 2.7 ± 1.9 7.1 ± 5.3 4.8 ± 2.9 12.7 ± 11.5 16.3 ± 15.7	3.8 ± 1.8 3.4 ± 1.3 1.5 ± 1.2 1.3 ± 1.2 1.2 ± 1.0 1.0 ± 0.8 1.2 ± 0.5 1.5 ± 0.3	3.4 ± 2.5 4.1 ± 3.4 3.9 ± 4.5 4.3 ± 2.4 9.6 ± 6.0 6.9 ± 3.4 22.3 ± 18.9 33.9 ± 26.3

(b) (4)

Study ID Location Year	Type Duration Design Control type Analytical method	Subjects (M/F) Type Age (range)	Dose/route	E_{max} (ng/mL)	T_{Emax} (h)	AUEC (ng·h/mL)
				Arithmetic Means ± SD		
TH9507/I/HV/002 Canada 2001	PK/PD/Safety Multiple-dose (7 days) Randomized DB (one Open arm) P PC ICMA	39 (39/0) Healthy volunteers 54 (50-60)	*Day 1* placebo 0.5 mg sc daily 0.5 mg sc bid 1 mg sc daily 2 mg sc daily *Day 7* placebo 0.5 mg sc daily 0.5 mg sc bid 1 mg sc daily 2 mg sc daily	1.8 ± 1.0 6.1 ± 5.4 8.7 ± 5.4 11.6 ± 7.5 11.4 ± 6.4 0.5 ± 0.4 4.9 ± 3.5 7.0 ± 4.3 6.9 ± 3.4 6.8 ± 3.0	2.1 ± 1.0 0.8 ± 0.4 1.0 ± 0.6 1.3 ± 0.6 2.0 ± 3.3 4.2 ± 3.6 0.6 ± 0.2 0.5 ± 0.2 0.6 ± 0.2 0.9 ± 0.9	4.0 ± 1.8 13.3 ± 13.5 19.3 ± 10.2 27.0 ± 13.5 26.6 ± 16.1 0.9 ± 0.5 9.0 ± 6.0 16.6 ± 11.4 18.8 ± 7.1 19.3 ± 6.2

BA: bioavailability; BE: bioequivalence; PD: pharmacodynamics; PK: pharmacokinetics; DB: double-blind; PC: placebo-controlled; P: parallel-group; X: cross-over; ELISA: Enzyme-linked immunosorbent assay; RIA: radioimmunoassay; IRMA: Immunoradiometric assay; ICMA: immunochemiluminometric assay
na: Not available

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Table 6 Summary of Pharmacodynamic Studies - IGF-1 (ng/mL) and IGFBP-3 (mg/L) mean pre-dose concentration

Study ID Location Year	Type Duration Design Control type Analytical method	Subjects (M/F) Type Age (range)	Dose/route	Time point	IGF-1 ng/mL	IGFBP-3 mg/L
					Arithmetic Means ± SD	
TH9507-CTR-1016 Canada 2008	PK/PD/Safety Multiple-dose (14 days) Randomized Open P - RIA	24 (24/0) Healthy volunteers 52 y (45-60)	1 mg sc daily 2 mg sc daily	Day 1	167 ± 34 183 ± 54	- -
			1 mg sc daily 2 mg sc daily	Day 7	262 ± 68 322 ± 64	- -
			1 mg sc daily 2 mg sc daily	Day 13	320 ± 97 378 ± 60	- -
			1 mg sc daily 2 mg sc daily	Day 14	313 ± 92 383 ± 67	- -
TH9507-CTR-1015 Canada 2008	PK/PD/Safety Multiple-dose (14 days) Open - RIA	18 (14/4) HIV-positive patients 40 y (26-58)	2 mg sc daily	Day 1 Day 7 Day 13 Day 14	176 ± 71 329 ± 105 370 ± 136 380 ± 143	- - - -
TH9507/I/PKPD/009 Canada 2003	PK/PD/Safety Multiple-dose (14 days) Randomized Open X - RIA	24 (12/12) Healthy volunteers 73 y (70-77)	2 mg sc daily 2 mg sc bid	Day 1	111 ± 28 117 ± 30	2.86 ± 0.81 2.92 ± 0.65
			2 mg sc daily 2 mg sc bid	Day 4	182 ± 54 253 ± 77	3.55 ± 0.95 3.52 ± 0.82
			2 mg sc daily 2 mg sc bid	Day 8	202 ± 69 278 ± 80	3.80 ± 0.94 3.95 ± 0.77
			2 mg sc daily 2 mg sc bid	Day 15	232 ± 73 300 ± 86	3.86 ± 0.93 4.16 ± 1.11
Earlier studies						
TH9507/I/HV/002 Canada 2001	PK/PD/Safety Multiple-dose (7 days) Randomized DB (one Open arm) P PC RIA	39 (39/0) Healthy volunteers 54 y (50-60)	Placebo 0.5 mg sc daily 0.5 mg sc bid 1.0 mg sc daily 2.0 mg sc daily	Day 1	163 ± 37 156 ± 28 141 ± 40 163 ± 51 140 ± 26	- - - - -

Study ID Location Year	Type Duration Design Control type Analytical method	Subjects (M/F) Type Age (range)	Dose/route	Time point	IGF-1 ng/mL	IGFBP-3 mg/L
					Arithmetic Means ± SD	
			Placebo 0.5 mg sc daily 0.5 mg sc bid 1.0 mg sc daily 2.0 mg sc daily	Day 7	174 ± 35 218 ± 66 270 ± 52 286 ± 25 284 ± 55	- - - - -

BA: bioavailability; BE: bioequivalence; PD: pharmacodynamics; PK: pharmacokinetics; DB: double-blind; PC: placebo-controlled; P: parallel-group; X: cross-over; RIA: radioimmunoassay; -: Not measured

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22505	ORIG-1	THERATECHNOLOGIES INC	Egrifta

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RITESH JAIN
07/29/2010

SALLY Y CHOE
08/02/2010

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**22-505**	**Brand Name**	**EGRIFTA**
OCP Division (I, II, III, IV, V)	**DCP II**	**Generic Name**	**TESAMORELIN ACETATE**
Medical Division	**DMEP**	**Drug Class**	
OCP Reviewer	**Ritesh Jain, Ph.D.**	**Indication(s)**	**To induce and maintain a reduction of excess abdominal fat in HIV-infected patients with lipodystrophy**
OCP Team Leader	**Wei Qiu, Ph.D. (Acting)**	**Dosage Form**	**Lyophilized powder containing 1.1 mg of tesamorelin acetate and 55 mg of mannitol.**
Pharmacometrics Reviewer		**Dosing Regimen**	**2 mg subcutaneous injection, once daily**
Date of Submission	**05/29/2009**	**Route of Administration**	**Subcutaneous**
Estimated Due Date of OCP Review	**02/05/2010**	**Sponsor**	**Theratechnologies, Inc**
Medical Division Due Date	**03/05/2010**	**Priority Classification**	**S**
PDUFA Due Date	**03/29/2010**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**X**	**1**		**Study: TH9507-CTR-1014**
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				

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In-vivo effects on primary drug:				
In-vivo effects of primary drug:	**X**	**2**		**Studies: TH9507-CTR-1019, TH9507-CTR-1020**
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:	**X**	**5**		**Studies: TH9507-CTR-1013, TH9507-CTR-1015, TH9507-CTR-1016, TH9507/I/HV/002, TH9507/I/PKPD/009**
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability	**X**	**2**		**Studies: TH9507-CTR-1017, TCHUV 10-98**
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**10**		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			√	Sponsor used the same formulation in their pivotal clinical trial as to be marketed formulation
2	Has the applicant provided metabolism and drug-drug interaction information?	√			Studies TH9507-CTR-1019, TH9507-CTR-1020 are submitted to evaluate the effect of Tesamorelin on Ritonavir and Simvastatin PK

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3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	√			**Studies: TH9507-CTR-1017, TCHUV 10-98**
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	√			
5	Has a rationale for dose selection been submitted?	√			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	√			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	√			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	√			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	√			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			√	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	√			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	√			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	√			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	√			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			√	Deferral

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			√	Deferral
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	√			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	√			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			√	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
__YES_____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Ritesh Jain	07/17/2009
Reviewing Clinical Pharmacologist	Date
Wei Qiu (Acting)	07/17/2009
Team Leader/Supervisor	Date

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Filing Memo (Internal Memo)

1. Background

Tesamorelin (TH9507), a stabilized analogue of human hypothalamic growth hormone-releasing factor (hGRF)/growth hormone-releasing hormone (GHRH), is proposed as a treatment to induce and maintain a reduction of excess abdominal fat in human immunodeficiency virus (HIV) - infected patients with lipodystrophy. Tesamorelin is comprised of the 44-amino acid sequence of hGRF on which a hexenoyl moiety, a C6 chain with a double bond on position 3, has been anchored on Tyr1 at the N-terminal part of the molecule. With the addition of this hydrophobic side chain, resistance to enzymatic degradation in human plasma is increased.

The recommended daily dose, after reconstitution, is 2 mg administered by subcutaneous (sc) injection.

2. Clinical Pharmacology Studies:

In the Clinical Pharmacology Program sponsor has submitted a total of 10 studies. Amongst these 10 studies, six studies were single or multiple dose PK/ PK-PD studies, two bioavailability studies and two drug-drug interaction studies.

The PK data collected in the early Phase 1 studies in healthy volunteers were generated using radioimmunoassay (RIA) methods that most likely detected tesamorelin immunoreactive fragments, especially at later time points (i.e., the elimination phase), in addition to the intact peptide. Due to the limitations of the initial RIA method used in the early Phase 1 studies (TCHUV 10-98 and TH9507/I/HV/002) the sponsor developed a new PK/PD (pharmacodynamic) program, following the development and validation of an enzyme-linked immunosorbent assay (ELISA) for tesamorelin. This PK/PD program comprises the core of the tesamorelin clinical pharmacology program. The following studies are done using ELISA and will be reviewed in this application.

Core studies:

PK/PK-PD Studies

- The TH9507-CTR-1016: a 14-day PK/PD study in healthy volunteers comparing 1 mg and 2 mg sc doses of tesamorelin;
- The TH9507-CTR-1017: a 14-day PK study comparing sc versus intravenous (i.v.) single dose administration of tesamorelin in healthy volunteers;
- The TH9507-CTR-1015: a 14-day PK study of a 2 mg sc dose of tesamorelin in HIV infected patients.

Drug-Drug Interaction Studies

In addition to the aforementioned PK/PD studies, two drug-drug interaction clinical studies were undertaken during the clinical development program of Tesamorelin and will be reviewed.

- The (TH9507-CTR-1019): potential impact of tesamorelin on PK profile of ritonavir.
- The (TH9507-CTR-1020): potential impact of tesamorelin on PK profile of simvastatin.

In addition to the core studies two supplemental studies were also submitted. These studies will also be reviewed.

Supplemental studies

- The TH9507-CTR-1014: a pilot PK study of a single 2 mg sc dose of tesamorelin from 2 different tesamorelin lots conducted in healthy volunteers; and,
- The TH9507-CTR-1013: a single-dose PK/PD and bioequivalence study conducted in healthy volunteers comparing the proposed 1 mg/mL formulation (b) (4) (b) (4).

In addition to these seven studies (five that constitute the core of tesamorelin's clinical pharmacology program and two that are supplemental studies); three other studies (see below) were conducted during the earlier stages of the clinical development program of tesamorelin. They were primarily aimed at evaluating the PD response, establishing dose response curves and obtaining preliminary PK data. These studies were:

- The TCHUV 10-98: a first-in-man, single-dose dose-ranging PK/PD/bioavailability study in healthy volunteers.
- The TH9507/I/HV/002: a 7-day dose-ranging PK/PD study in healthy volunteers.
- The TH9507/I/PKPD/009: a 14-day study in which a 2 mg once daily (qd) dose was compared to a 2 mg twice daily (bid) dosing of tesamorelin.

The PK data for these studies was obtained using the RIA method mentioned above. Due to the limitations of this method, this data is considered as preliminary, supportive data only. Also the effect of immunogenicity on the PK of tesamorelin was studied in phase 3 trial (Study TH9507/III/LIPO/010) on few subjects. This data will also be reviewed.

3. Phase 3 Studies

This program included three multicentre, randomized, double-blind, placebo-controlled pivotal Phase 3 studies

- ✓ Study TH9507/III/LIPO/010
- ✓ Study TH9507-CTR-1011
- ✓ Study TH9507-CTR-1012

The primary endpoint of the studies was to demonstrate a reduction in visceral adipose tissue (VAT), as assessed by computed tomography (CT), after 26 weeks of treatment with tesamorelin 2 mg per day as compared to placebo. The secondary efficacy endpoints included improvement in blood lipids (triglycerides, total cholesterol: high density lipoprotein-cholesterol [HDL-C] ratio), improvement in PRO related to body image, and increase in insulin-like growth factor-1 (IGF-1) levels. Belly appearance distress, belly size estimation and belly profile assessment, the main PRO secondary endpoints, were measured using a validated PRO questionnaire, the Body Image Impact Module (BIIM). Other study

parameters included trunk fat, total fat, lean body mass, limb fat, and non-HDL-C. The extension phases were designed to assess long-term safety and explore duration of effects following end of treatment.

Potential Key Review Questions

- ✓ What are the PK and PK/PD characteristics of Tesamorelin in healthy and HIV infected patients?
- ✓ What is effect of tesamorelin on pharmacokinetics of ritonavir and simvastatin?
- ✓ What is the absolute bioavailability of Tesamorelin?
- ✓ What is the dose-response relationship for the Phase 3 dose selection?
- ✓ What is the effect of immunogenicity on the pharmacokinetics of tesamorelin?

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ATTACHMENT

Table 1 Core Clinical Pharmacology Studies: Pharmacokinetic Studies in Healthy Subjects and HIV-Patients Using a Validated ELISA Method

Study ID Location Year	Type Duration Design Control type Analytical method	Subjects (M/F) Type Age (range)	Dose/route	C_{max} (pg/mL)	T_{max} (h)	AUC_{0-t} (pg·h/mL)	AUC_{0-inf} (pg·h/mL)	$T_{½ el}$ (h)
				Arithmetic Means				
TH9507-CTR-1017	BA/PK/Safety	44 (26/18)	*Period 1*					
	Single-dose	Healthy volunteers	2 mg sc	3172	0.128	881	958	0.26
Canada	Randomized Open P	36 y (18-64)	200 µg iv	19644	0.051	2354	2394	0.12
2008	-							
	ELISA		*Period 2*					
			2 mg sc	2903	0.119	908	936	0.25
			200 µg iv	23645	0.050	2663	2702	0.13
TH9507-CTR-1016	PK/PD/Safety	24 (24/0)	*Day 1*					
	Multiple-dose (14 days)	Healthy volunteers	1 mg sc daily	1338	0.138	302	342	0.14
Canada	Randomized Open P	52 y (45-60)	2 mg sc daily	3076	0.147	775	861	0.21
2008	-		*Day 7*					
	ELISA		1 mg sc daily	1392	0.129	404	416	0.16
			2 mg sc daily	2136	0.150	845	954	0.35
			Day 14					
			1 mg sc daily	1022	0.153	304	418	0.26
			2 mg sc daily	1843	0.150	686	829	0.43

Study ID Location Year	Type Duration Design Control type Analytical method	Subjects (M/F) Type Age (range)	Dose/route	C_{max} (pg/mL)	T_{max} (h)	AUC_{0-t} (pg·h/mL)	AUC_{0-inf} (pg·h/mL)	$T_{½ el}$ (h)
				Arithmetic Means				
TH9507-CTR-1015	PK/PD/Safety	18 (14/4)	*Day 1*					
	Multiple-dose (14 days)	HIV-positive patients	2 mg sc daily	3106	0.162	1150	1255	0.31
Canada	Open	40 y (26-58)						
2008	Single Group		*Day 14*					
	ELISA		2 mg sc daily	2333	0.157	1117	1313	0.63

PD: pharmacodynamics; PK: pharmacokinetics; P: parallel-group; X: cross-over; ELISA: Enzyme-linked immunosorbent assay

Table 2 Supplemental Clinical Pharmacology Studies: Pharmacokinetic/Bioequivalence Studies in Healthy Subjects Using a Validated ELISA method

Study ID Location Year	Type Duration Design Control type Analytical method	Subjects (M/F) Type Age (range)	Dose/route	C_{max} (pg/mL)	T_{max} (h)	AUC_{0-t} (pg·h/mL)	AUC_{0-inf} (pg·h/mL)	$T_{½ el}$ (h)
				Arithmetic Means				
TH9507-CTR-1014 Canada 2006	PK/Safety Single-dose Randomized Open X - ELISA	12 (4/8) Healthy volunteers 52 y (25-62)	2 mg sc Lot 5M390	3681	0.151	1312	1405	0.31
			2 mg sc Lot 5L263	4278	0.138	1429	1514	0.28
TH9507-CTR-1013 Canada 2006-2007	BE/PK/PD/Safety Single-dose Randomized Open X - ELISA	88 (76/12) Healthy volunteers 40 y (18-65)	2 mg sc[1]	3910	0.158	1202	1255	0.22

BE: bioequivalence; PD: pharmacodynamics; PK: pharmacokinetics; X: cross-over; ELISA: Enzyme-linked immunosorbent assay

Table 3 Drug-Drug Interaction Pharmacokinetic Studies

Study ID Location Year	Type Duration Design Control type Analytical method	Subjects (M/F) Type Age (range)	Substrate/interacting drug	Substrate (Simvastatin or Ritonavir) C_{max} (ng/mL)	AUC_{0-t} (ng·h/mL)	C_{max} ratio (A/B) ($CI_{90\%}$)	AUC_{0-t} ratio (A/B) ($CI_{90\%}$)
				Geometric Means			
TH9507-CTR-1019 Canada 2008	PK/DDI/Safety Multiple-dose (7 days) Randomized Open X - LC/MS/MS for simvastatin and simvastatin acid	58 (54/4) Healthy volunteers 41 y (20-60)	***Simvastatin***				
			Treatment A: tesamorelin 2 mg sc daily x 7 days; 80 mg simvastatin on Day 6	16.35	93.15	105.3% (94.6-117.1)	92.2% (83.5-101.9)
			Treatment B: no tesamorelin days 1-7; 80 mg simvastatin on Day 6	15.35	100.54		
			Simvastatin acid				
			Treatment A : tesamorelin 2 mg sc daily x 7 days; 80 mg simvastatin on day 6	4.22	36.60	99.0% (91.9-106.7)	86.3% (80.2-92.7)
			Treatment B: no tesamorelin days 1-7; 80 mg simvastatin on Day 6	4.24	42.12		
TH9507-CTR-1020 Canada 2008	PK/DDI/Safety Multiple-dose (7 days) Randomized Open X - LC/MS/MS for ritonavir	32 (24/8) Healthy volunteers 43 y (19-63)	***Ritonavir***				
			Treatment A: tesamorelin 2 mg sc daily x 7 days; 100 mg ritonavir on day 6	403.9	3325.1	89.3% (74.8-106.6)	90.8% (83.8-98.3)
			Treatment B: no tesamorelin days 1-7; 100 mg ritonavir on Day 6	450.4	3678.3		

PK: pharmacokinetics; X: cross-over; LC/MS/MS: Liquid chromatography/mass spectrometry/mass spectrometry

Table 4 Early Clinical Pharmacology Studies Providing Additional Information: Pharmacokinetic Studies in Healthy Subjects Using a RIA Method

Study ID Location Year	Type Duration Design Control type Analytical method	Subjects (M/F) Type Age (range)	Dose/route	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-t} (ng·h/mL)	AUC_{0-inf} (ng·h/mL)	$T_{½ el}$ (h)
				Arithmetic Means				
TCHUV 10-98	BA/PK/PD/Safety	6 (6/0)	100 µg sc (N=1)	0.42	0.10	0.09	0.17	0.3
	Single-dose	Healthy volunteers	200 µg sc (N=1)	0.81	0.10	0.22	0.24	0.1
Switzerland	Randomized DB (one Open arm) X	24 y (21-28)	400 µg sc (N=2)	0.70	0.21	0.39	0.52	0.4
1999	PC		1500 µg sc (N=3)	1.72	0.24	0.89	0.96	0.4
	RIA		200 µg iv (N=6)	19.6	-	2.2	2.3	0.2
TH9507/I/HV/002	PK/PD/Safety	39 (39/0)	***First dose***					
	Multiple-dose (7 days)	Healthy volunteers	0.5 mg sc daily	2.31	0.14	1.40	2.22	4.53
Canada	Randomized DB (one Open arm) P	54 y (50-60)	0.5 mg sc bid	1.89	0.14	1.69	2.35	3.71
2001	PC		1.0 mg sc daily	4.12	0.23	3.79	4.25	1.95
	RIA		2.0 mg sc daily	7.67	0.24	5.79	6.70	3.31
			Last dose					
			0.5 mg sc daily	1.86	0.19	1.76	2.39	4.25
			0.5 mg sc bid	3.56	0.20	2.12	2.54	2.55
			1.0 mg sc daily	4.74	0.19	3.77	4.09	1.94
			2.0 mg sc daily	8.88	0.20	6.37	6.94	2.43

BA: bioavailability; PD: pharmacodynamics; PK: pharmacokinetics; DB: double-blind; PC: placebo-controlled; P: parallel-group; X: cross-over; RIA: radioimmunoassay

Table 5 Summary of Pharmacodynamic Studies - Growth Hormone

Study ID Location Year	Type Duration Design Control type Analytical method	Subjects (M/F) Type Age (range)	Dose/route	E_{max} (ng/mL)	T_{Emax} (h)	AUEC (ng·h/mL)
				Arithmetic Means ± SD		
TH9507-CTR-1013 Canada 2006-2007	BE/PK/PD/Safety Single-dose Randomized Open X - ELISA	88 (76/12) Healthy volunteers 40 y (18-65)	2 mg sc[2]	12.9 ± 12.3	2.4 ± 2.9	32.4 ± 21.3
TH9507-CTR-1016 Canada 2008	PK/PD/Safety Multiple-dose (14 days) Randomized Open P - ELISA	24 (24/0) Healthy volunteers 52 y (45-60)	*Day 1* 1 mg sc daily 2 mg sc daily *Day 14* 1 mg sc daily 2 mg sc daily	 10.5 ± 6.3 13.2 ± 10.0 9.1 ± 5.3 14.5 ± 5.9	 0.8 ± 0.2 1.9 ± 2.7 0.4 ± 0.2 0.6 ± 0.4	 20.4 ± 11.9 28.3 ± 16.6 16.4 ± 8.9 33.1 ± 15.6
TH9507/I/PKPD/009 Canada 2003	PK/PD/Safety Multiple-dose (14 days) Randomized Open X - RIA	24 (12/12) Healthy volunteers 73 y (70-77)	*Day 1* 2 mg sc daily 2 mg sc bid *Day 14* 2 mg sc daily 2 mg sc bid	 12.4 ± 8.7 9.9 ± 5.3 16.0 ± 11.6 16.6 ± 11.0	 na na na na	 27.3 ± 15.9 23.6 ± 10.9 35.5 ± 20.1 40.2 ± 16.6
Earlier studies						
TCHUV 10-98 Switzerland 1999	BA/PK/PD/Safety Single-dose Randomized DB (one Open arm) X PC IRMA	6 (6/0) Healthy volunteers 24 y (21-28)	Saline (N=6) 20 µg sc (N=6) 40 µg sc (N=6) 100 µg sc (N=6) 200 µg sc (N=6) 400 µg sc (N=6) 1500 µg sc (N=6) 200 µg iv (N=6)	2.3 ± 1.8 2.7 ± 2.4 2.4 ± 3.0 2.7 ± 1.9 7.1 ± 5.3 4.8 ± 2.9 12.7 ± 11.5 16.3 ± 15.7	3.8 ± 1.8 3.4 ± 1.3 1.5 ± 1.2 1.3 ± 1.2 1.2 ± 1.0 1.0 ± 0.8 1.2 ± 0.5 1.5 ± 0.3	3.4 ± 2.5 4.1 ± 3.4 3.9 ± 4.5 4.3 ± 2.4 9.6 ± 6.0 6.9 ± 3.4 22.3 ± 18.9 33.9 ± 26.3

(b) (4)

Study ID Location Year	Type Duration Design Control type Analytical method	Subjects (M/F) Type Age (range)	Dose/route	E_{max} (ng/mL)	T_{Emax} (h)	AUEC (ng·h/mL)
				Arithmetic Means ± SD		
TH9507/I/HV/002 Canada 2001	PK/PD/Safety Multiple-dose (7 days) Randomized DB (one Open arm) P PC ICMA	39 (39/0) Healthy volunteers 54 (50-60)	*Day 1* placebo 0.5 mg sc daily 0.5 mg sc bid 1 mg sc daily 2 mg sc daily *Day 7* placebo 0.5 mg sc daily 0.5 mg sc bid 1 mg sc daily 2 mg sc daily	 1.8 ± 1.0 6.1 ± 5.4 8.7 ± 5.4 11.6 ± 7.5 11.4 ± 6.4 0.5 ± 0.4 4.9 ± 3.5 7.0 ± 4.3 6.9 ± 3.4 6.8 ± 3.0	 2.1 ± 1.0 0.8 ± 0.4 1.0 ± 0.6 1.3 ± 0.6 2.0 ± 3.3 4.2 ± 3.6 0.6 ± 0.2 0.5 ± 0.2 0.6 ± 0.2 0.9 ± 0.9	 4.0 ± 1.8 13.3 ± 13.5 19.3 ± 10.2 27.0 ± 13.5 26.6 ± 16.1 0.9 ± 0.5 9.0 ± 6.0 16.6 ± 11.4 18.8 ± 7.1 19.3 ± 6.2

BA: bioavailability; BE: bioequivalence; PD: pharmacodynamics; PK: pharmacokinetics; DB: double-blind; PC: placebo-controlled; P: parallel-group; X: cross-over; ELISA: Enzyme-linked immunosorbent assay; RIA: radioimmunoassay; IRMA: Immunoradiometric assay; ICMA: immunochemiluminometric assay
na: Not available

Table 6 Summary of Pharmacodynamic Studies - IGF-1 (ng/mL) and IGFBP-3 (mg/L) mean pre-dose concentration

Study ID Location Year	Type Duration Design Control type Analytical method	Subjects (M/F) Type Age (range)	Dose/route	Time point	IGF-1 ng/mL	IGFBP-3 mg/L
					Arithmetic Means ± SD	
TH9507-CTR-1016	PK/PD/Safety	24 (24/0)	1 mg sc daily	Day 1	167 ± 34	-
	Multiple-dose (14 days)	Healthy volunteers	2 mg sc daily		183 ± 54	-
Canada	Randomized Open P	52 y (45-60)	1 mg sc daily	Day 7	262 ± 68	-
2008	-		2 mg sc daily		322 ± 64	-
	RIA		1 mg sc daily	Day 13	320 ± 97	-
			2 mg sc daily		378 ± 60	-
			1 mg sc daily	Day 14	313 ± 92	-
			2 mg sc daily		383 ± 67	-
TH9507-CTR-1015	PK/PD/Safety	18 (14/4)	2 mg sc daily	Day 1	176 ± 71	-
	Multiple-dose (14 days)	HIV-positive patients		Day 7	329 ± 105	-
Canada	Open	40 y (26-58)		Day 13	370 ± 136	-
2008	-			Day 14	380 ± 143	-
	RIA					
TH9507/I/PKPD/009	PK/PD/Safety	24 (12/12)	2 mg sc daily	Day 1	111 ± 28	2.86 ± 0.81
	Multiple-dose (14 days)	Healthy volunteers	2 mg sc bid		117 ± 30	2.92 ± 0.65
Canada	Randomized Open X	73 y (70-77)	2 mg sc daily	Day 4	182 ± 54	3.55 ± 0.95
2003	-		2 mg sc bid		253 ± 77	3.52 ± 0.82
	RIA		2 mg sc daily	Day 8	202 ± 69	3.80 ± 0.94
			2 mg sc bid		278 ± 80	3.95 ± 0.77
			2 mg sc daily	Day 15	232 ± 73	3.86 ± 0.93
			2 mg sc bid		300 ± 86	4.16 ± 1.11
Earlier studies						
TH9507/I/HV/002	PK/PD/Safety	39 (39/0)	Placebo	Day 1	163 ± 37	-
	Multiple-dose (7 days)	Healthy volunteers	0.5 mg sc daily		156 ± 28	-
Canada	Randomized DB (one Open arm) P	54 y (50-60)	0.5 mg sc bid		141 ± 40	-
2001	PC		1.0 mg sc daily		163 ± 51	-
	RIA		2.0 mg sc daily		140 ± 26	-

Study ID Location Year	Type Duration Design Control type Analytical method	Subjects (M/F) Type Age (range)	Dose/route	Time point	IGF-1 ng/mL	IGFBP-3 mg/L
					Arithmetic Means ± SD	
			Placebo	Day 7	174 ± 35	-
			0.5 mg sc daily		218 ± 66	-
			0.5 mg sc bid		270 ± 52	-
			1.0 mg sc daily		286 ± 25	-
			2.0 mg sc daily		284 ± 55	-

BA: bioavailability; BE: bioequivalence; PD: pharmacodynamics; PK: pharmacokinetics; DB: double-blind; PC: placebo-controlled; P: parallel-group; X: cross-over; RIA: radioimmunoassay; -: Not measured

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