London, 5 October 2012
EMA/588044/2012
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal Assessment report

Egrifta

tesamorelin

Procedure No.: EMEA/H/C/002427

Day 180 Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

This should be read in conjunction with the "Question and Answer" document on the withdrawal of the application: the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application.

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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	**Egrifta**
INN (or common name) of the active substance:	Tesamorelin
Applicant:	Ferrer International S.A. Diagonal 549, 5 planta 08029 Barcelona Spain
Applied Indication:	Indicated for the treatment of excess abdominal fat in adult HIV-infected patients with lipodystrophy
Pharmaco-therapeutic group (ATC Code):	H01AC06
Pharmaceutical form and strength:	Powder for solution for injection 2 mg

LIST OF ABBREVIATIONS

ACTG	AIDS Clinical Trial Group
ACTH	Adrenocorticotropic hormone
ADR	Adverse drug reaction
AE	Adverse event
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
ART	Antiretroviral therapy
AST	Aspartate aminotransferase
ATC	Anatomic therapeutic code
AUC	Area under the curve
AUEC	Area under the effect curve
BA	Bioavailability
BE	Bioequivalence
BIM	Body image module
BL	Baseline, the last evaluation performed prior to the first dose of study treatment
BMI	Body mass index
BOCF	Baseline observation carried forward
BP	Blood pressure
BUN	Blood urea nitrogen
CD4	Cluster of differentiation 4
CD8	Cluster of differentiation 8
CDF	Cumulative distribution function
cGH	Canine growth hormone
CHO	Chinese hamster ovary
cIGF-1	Canine insulin-like growth factor-1
CK	Creatinine kinase
Cl/F	Apparent total body clearance
CNS	Central nervous system
C_{max}	Maximum concentration
COPD	Chronic obstructive pulmonary disease
CPK	Creatine phosphokinase
CRF	Case report form
CRO	Contract research organization
CT	Computerized tomography
CV%	Percent coefficient of variation
CYP	Cytochrome P(450)
d	Day
DDI	Drug-drug interaction study
DEXA	Dual energy x-ray absorptiometry
dL	Decilitre

DPP-IV	Dipeptidyl peptidase IV
DRF	Dose range-finding
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
ELISA	Enzyme-linked immunosorbent assay
Emax	Maximum effect
ET	Early termination
FBG	Fasting blood glucose
FDA	Food and Drug Administration
FPG	Fasting plasma glucose
GAS	Global Analogue Scale
GCP	Good Clinical Practice
GD	Gestation day
GH	Growth hormone
GRF	Growth hormone-releasing factor
GHRH	Growth hormone-releasing hormone
HAART	Highly active retroviral therapy
HARS	HIV-associated adipose redistribution syndrome
HbA1c	Glycohaemoglobin
HCP	Healthcare professional
HDL-C	High-density lipoprotein cholesterol
hERG	Human ether-a-go-go
hGRF	Human growth hormone-releasing factor
HIV	Human immunodeficiency virus
HOMA-IR	Homeostasis model assessment-insulin resistance
HR	Heart rate
HRQOL	Health-related quality of life
IB	Investigator Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent ethics committee
IFG	Impaired fasting glucose
IGF-1	Insulin-like growth factor-1
IGFBP-3	Insulin-like growth factor binding protein-3
IgG	Immunoglobulin G
IGT	Impaired glucose tolerance
IM	Intramuscular
IRB	Institutional review board
ITT	Intent-to-Treat
IU	International Unit
IVRS	Interactive Voice Response System
L	Litre
LBM	Lean body mass
LCMS	Liquid chromatography mass spectroscopy

LDL-C	Low-density lipoprotein cholesterol
LH	Luteinizing hormone
LLN	Lower limit of normal
LLOQ	Lower limit of quantitation
LLT	Lipid-lowering treatment
ln	Natural logarithm
LOCF	Last observation carried forward analysis
LSM	Least-squares mean
MANCOVA	Multivariate analysis of covariance
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mg/d	Milligram per day
mL	Millilitre
MID	Minimally important difference
mmol	Millimole
MTD	Maximum tolerated dose
NC	Not calculated
NCEP	National Cholesterol Education Program
ng	Nanogram
nmol	Nanomole
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
OC	Observed case analysis
OGTT	Oral glucose tolerance test
OIS	(PHASE V) Outcomes Information System
OTC	Over-the-counter
P	Placebo
PCNA	Proliferating cell nuclear antigen
PD	Pharmacodynamic
pg	Picogram
pGH	Porcine growth hormone
PI	Protease inhibitor
PK	Pharmacokinetic
pmol	Picomole
PP	Per Protocol
P-T	placebo Main Phase, followed by tesamorelin Extension Phase
PRO	Patient-reported outcomes
PSA	Prostate-specific antigen
QOL	Quality of life
RBC	Red blood cell
rGH	Rat growth hormone
RIA	Radioimmunoassay
RMP	Risk management plan
SAE	Serious adverse event

SAP	Statistical analysis plan
SAT	Subcutaneous adipose tissue
sc	Subcutaneous
SD	Standard deviation
SDS	Standard deviation scores
SEM	Structural equation modelling
SOC	System organ class
T	Tesamorelin
TC	Total cholesterol
TEAE	Treatment-emergent adverse event
TEmax	Time to maximum effect
TG	Triglycerides
TH9507	Tesamorelin
TSH	Thyroid stimulating hormone
T-P	Tesamorelin Main Phase, followed by placebo Extension Phase
T-T	Tesamorelin in Main and Extension Phase
$T_{1/2}$	Half-life
UDPGT	Uridine diphosphate glucuronyltransferase
ULN	Upper limit of normal
ULOQ	Upper limit of quantitation
VAT	Visceral adipose tissue
Non-responder	Any patient with a change from baseline in VAT <8%
Responder	Any patient with a change from baseline in VAT ≥ 8%
WBC	White blood cell
WHO	World Health Organization
WHR	Waist : hip ratio

1. RECOMMENDATION

Based on the review of the data and the Applicant's response to the CHMP LoQ on quality, safety and efficacy, the CHMP considers that the application for Egrifta in the treatment of HIV infected patients with lipodystrophy, is not approvable since major objections still remain, which preclude a recommendation for marketing authorisation at the present time.

Questions to be posed to additional experts

N/A

Inspection issues

N/A

New active Substance status

Based on the review of the data the CHMP considers that the active substance tesamorelin contained in the medicinal product Egrifta is to be qualified as a new active substance in itself.

2. EXECUTIVE SUMMARY

2.1. Problem statement

In patients on antiretroviral therapy (ART) a condition referred to as "HIV-associated lipodystrophy" has been proposed, characterised by abnormalities in body composition and metabolism, including increased visceral adiposity (lipohypertrophy), loss of subcutaneous fat (lipoatrophy), glucose intolerance, insulin resistance, and dyslipidaemia consisting of hypercholesterolemia, elevated low-density lipoprotein cholesterol (LDL-C), hypertriglyceridaemia and possibly low high density lipoprotein cholesterol (HDL-C) levels. Recent data suggest that different pathophysiological mechanisms are involved in the development of lipohypertrophy and lipoatrophy in these patients (*Capeau et al., 2005; Brown, 2008; Domingo et al.; 2009).*

In 2008 a study in HIV patients (Fat Redistribution and Metabolic Changes in HIV Infection, FRAM) showed an association between increased VAT and triglyceride levels (with a weaker trend for increased LDL-C/lower HDL-C) as well as an association with diabetes prevalence and Framingham Risk Score for cardiovascular disease. More recent studies have suggested an association in HIV patients between VAT level and subclinical atherosclerosis, as evaluated by coronary artery CT imaging. However, no prospective data are available on the correlation between VAT in HIV patients and actual clinical endpoints such as myocardial infarction. The ongoing Data Collection on Adverse Events of Anti-HIV Drugs (DAD) study has identified an association between the use of anti-HIV medicines and the risk of cardiovascular disease, although the contribution of lipodystrophy to this is uncertain.

Currently there is no medical therapy that has been approved in the EU for the treatment of excess visceral adipose tissue (VAT) in HIV infection. Use of pharmacological doses of growth hormone (GH) indicated possible beneficial effects of reduced trunk fat and VAT and increased lean body mass (LBM) (*Wanke et al., 1999; Lo et al., 2001; Engelson et al., 2002; Kotler et al., 2004b*), but was also associated with significant side effects, including symptoms of interstitial fluid retention and

hyperglycaemia. Metformin has also been investigated in small studies. Dietary and exercise intervention may also be important in some patients, however there are no large-scale studies to look at the effect of this on VAT. Some recent studies have looked at switching antiretroviral treatments as a strategy to reduce VAT.

Background information on the condition to be treated

In general, the term "lipodystrophy syndrome (LDS)" describes a concurrence of symptoms in HIV-infected patients consisting of lipoatrophy, i.e. loss of subcutaneous fat (most evident on extremities including buttocks, and face, but naturally occurring throughout the body) and central lipohypertrophy, which may include abdominal girth, dorsocervical fat pad (buffalo neck), supraclavicular fat pad, anterior neck accumulation, chest enlargement (gynaecomastia or lipomastia), hypertrophy of the parotid areas, suprapubic fat accumulation, and single or multiple lipomata. The expression "HIV-associated adipose redistribution syndrome (HARS)", is used synonymously for "lipodystrophy syndrome". It should be noted that the overall concept of fat redistribution in HIV-infected patients is currently questioned.

Changes of body fat composition related to antiretroviral treatment were first described by *Carr et al.* in 1998 in patients exposed to protease inhibitors (PI) (*Carr A et al. AIDS 1998; 12(7): F51-8)*. Since then, lipid changes, particularly hypertriglyceridaemia, hypercholesterolaemia and accumulation of visceral fat as well as other metabolic complications, such as insulin resistance and type-2 diabetes have been attributed to this class of antiretrovirals (ARV). However, causality assignment has always been complicated by the fact that protease inhibitors were usually co-administered with another class of antiretrovirals, called nucleosidic/-tidic reverse transcriptase inhibitors (N(t)RTIs). Moreover, ARV use led to an increased life-expectancy with the HIV-infection (with the "normal aging process"), further confounding this assessment. In the early years of antiretroviral combination therapy in the Northern Hemisphere and until very recently in the Southern Hemisphere the N(t)RTI-backbone therapy did usually include at least one thymidine analogue. Of these, particularly stavudine (d4T) is known for its pronounced mitochondrial toxicity contributing significantly to the development of lipoatrophy. Data from three epidemiological studies conducted in Switzerland and Africa (Ruanda and Senegal) indicate that lipohypertrophy is also observed when PIs are not used (*Nguyen A et al HIV Med 2008; 9: 142-50*, *Multimura E et al. JAIDS 2007; 46:451-5* and *Mercier S et al. JAIDS 2009; 51:224-30).* In conclusion, it is the current view that there are differences in the potential for causing lipoatrophy/lipohypertrophy within the same drug class as well as across drug classes. Also, changes in body composition in ART treatment-naïve HIV patients have been reported.

The pathogenesis of lipodystrophy is currently regarded as multifactorial with certain host factors (older age, female gender, white race, higher body fat, less exercise, elevated TG levels, low CD4-nadir, advanced HIV-infection, hepatitis C-coinfection and genetic polymorphisms predisposing for the development of lipodystrophy), treatment effects (see preceding paragraph), and HIV-infection (HIV itself or via chronic inflammation) contributing to its development (*Baril JG et al. Can J Infect Dis Med Microbiol 2005: 16(4) 233-43, Bonnet E. HIV/AIDS – Research and Palliative Care 2010: 2; 167-178*).

The reported prevalence of lipodystrophy syndrome is highly variable, as standardized criteria for its definition are lacking, characteristics of the studied populations are not uniform and the duration of observation may vary. According to major clinical studies (conducted between 1998 and 2005) frequency varies between 2 to 84%. To put these figures into context, UN statistics in 2009 gave an adult prevalence of HIV in EU member states of 0.1 to 0.6%, depending on country.

The overall incidence tends to decrease with newer antiretroviral agents. However, with respect to lipohypertrophy it is noteworthy that abdominal adiposity (as measured by waist circumference) still seems to be a common and even increasing issue. In a cross-sectional study with more than 2000

HIV-infected patients the condition was reported in 24-53% of the women and 13-29% of the male patients starting antiretroviral therapy before 2005, and in 44-73% in women and 12-38% in men who commenced after 2005 (*Poizot-Martin I et al. EACS 2009, abstract PS11/1*). This is confirmed by a comparison of the reporting frequencies of gain in trunk fat in various studies over the past years (see table 1).

Table 1. Body Fat Changes by DEXA in Studies of Various Regimens in Treatment Naive Patients

Study	Treatments	Fat changes by DEXA from baseline by week 96 of treatment
ACTG5142	1) lopinavir/ritonavir (LPV/r) + 2 NRTI vs 2) efavirenz + 2 NRTI vs 3) lopinavir/ritonavir + efavirenz NRTI selection: d4T, zidovudine (AZT) or tenofovir df (TDF) (+ lamivudine [3TC])	Lipoatrophy (i.e. loosing > 20% limb fat according to DEXA) d4T: 42% of patients AZT: 27% tdf: 9% Trunk fat: + 2.2 kg from baseline *- Similar regardless of treatment and NRTI selection in change in trunk fat or % of patients with > 20% gain in trunk fat.*
ABCDE	d4T *vs* abacavir (ABC) + 3TC/efavirenz	Limbs: d4T -1.6 kg abc + 0.9 kg Trunk: d4T + 1.0 kg abc + 1.2 kg
Startmrk	Raltegravir *vs* efavirenz + tdf/emtricitabine (FTC)	Limbs: ral +2.4 kg (+18%) efz +1.4 kg (+17%) Trunk: ral +2.6 kg (+22%) efz +2.4 kg (+25%)
NCT00084253 McComsey	atazanavir/ritonavir [ATV/r] (300/100 qd) *vs* atazanavir (400 qd) + d4T	Limbs: atv/r -9% atv -17% Trunk: atv/r +16% atv +14% *(only % change given in publication)*
Castle	atazanavir/ritonavir (300/100 qd) *vs* lopinavir/ritonavir (800/200 mg per day) + TDF	Limbs: atv/r +27% lpv/r +15% Trunk: atv/r +34% lpv/r +16%
Gilead 934	AZT *vs* TDF + 3TC/efavirenz	Limbs: azt 5.5 kg (amount of fat week 96)* tdf 7.7 kg Trunk: d4T 8.9 kg tdf 10.4 kg * *DEXA not performed at baseline*
M03-613	lopinavir/ritonavir (lpv/r) + AZT/3TC* *vs* efavirenz +AZT/3TC *AZT/3TC stopped after 24-48 wks, then lpv/r as monotherapy.	Limbs: lpv/r +1.5 kg (+18%) efz - 0.7 kg (-9%) Trunk: lpv/r + 1.1 kg (+14%) efz + 1.1 kg (+15%)

The diagnosis of lipohypertrophy is based on patients' complaints confirmed by clinical examination. Beside psychological impairment excess abdominal fat can physically cause symptoms of distention and gastroesophageal reflux. Difficulties in exercising and sleep problems have been observed in clinical practice (*Baril JG et al. Can J Infect Dis Med Microbiol 2005: 16(4) 233-43*).

Waist and hip circumference and waist-to-hip ratios have been used to evaluate fat accumulation. The most reliable means to assess lipodystrophy are imaging studies. However, they are not readily available in routine practice. Dual-energy-X-ray absorptiometry (DEXA), ultrasonography, CT, and MRI have all been used for the objective measurement of the fat composition of particular body regions or given compartments in patients with lipodystrophy. Whereas DEXA is mainly used for assessment of lipoatrophy, CT and MRI are particularly useful for measuring intra-abdominal fat mass.

The European AIDS Clinical Society (EACS) recommends monitoring for changes in body composition of HIV patients by using body mass index, waist circumference, waist-to-hip ratio, and clinical lipodystrophy in all patients at HIV diagnosis, before starting highly active antiretroviral therapy, and annually thereafter. The current EACS guideline for prevention and management of lipodystrophy (http://www.europeanaidsclinicalsociety.org/images/stories/EACS-Pdf/eacsguidelines-6.pdf) is detailed in table 2.

Table 2. Details of Current EACS Guideline for Prevention and Management of Lipodystrophy

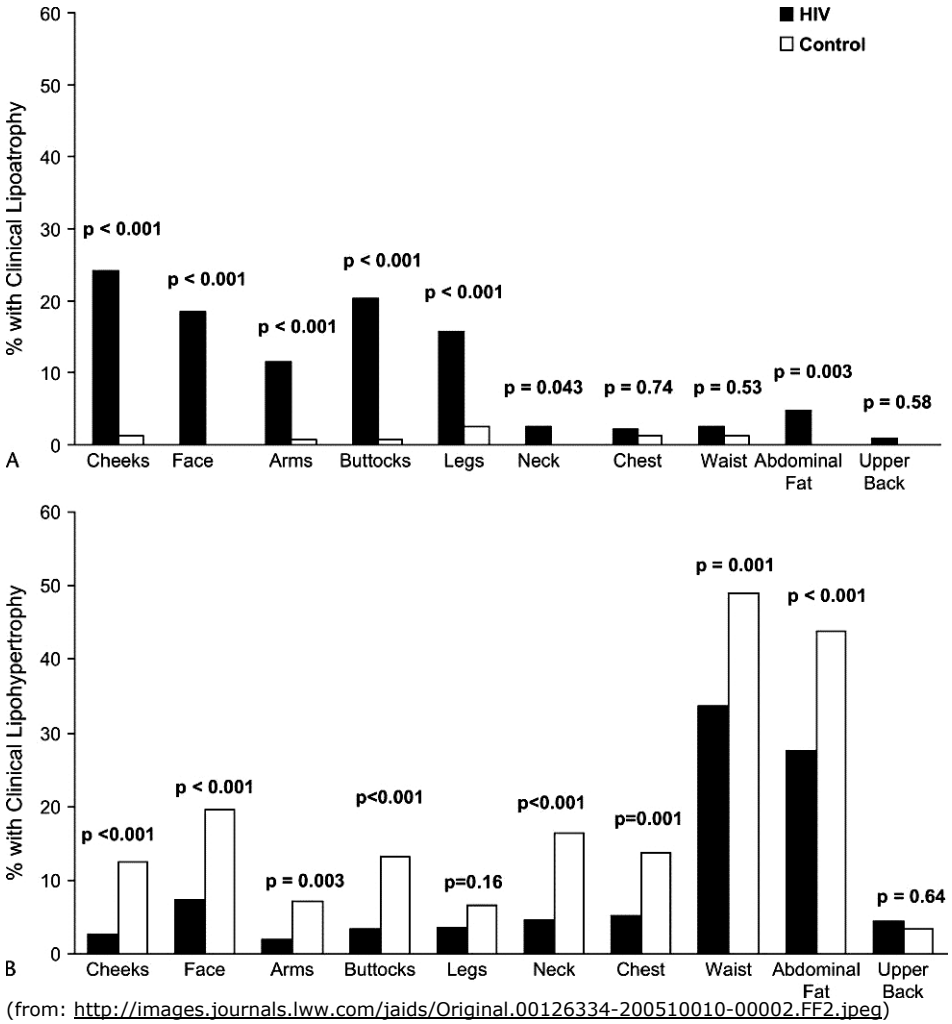
LIPOATROPHY	LIPOHYPERTROPHY
Prevention • Avoid d4T and ZDV or pre-emptively switch away from them • Regimens containing ritonavir-boosted PIs lead to more limb fat gain than regimens containing NNRTIs • Regimens not containing NRTIs lead to more fat gain than regimens containing NRTIs • CCR5 and integrase inhibitors have not been associated with lipoatrophy in registrational studies, although not in formal comparative studies **Management** • Modification of ART - Switch d4T or ZDV to ABC or TDF: • Only ART modification proven to partially restore subcutaneous fat; increase in total limb fat ~400-500 g/year • Risk of toxicity from new drug (see p. 20) - Switch to regimen not including NRTIs • Increase in total limb fat ~400-500 g/year • May increase risk of dyslipidaemia • Surgical intervention - Offered for relief of facial lipoatrophy only	**Prevention** • No proven strategy. • ATV/r has been associated with more central fat gain than EFV • Weight gain expected with effective ART reflecting "return to health" type of response • Weight reduction or avoidance of weight gain may decrease visceral adiposity • Avoid inhaled fluticasone (and potentially other inhaled corticosteroids) with ritonavir-boosted PI as it may cause Cushing syndrome or adrenal insufficiency **Management** • Diet and exercise may reduce visceral adiposity - Limited data, but possibly reduction of visceral adipose tissue and improvement in insulin sensitivity and blood lipids, especially in obesity associated with lipohypertrophy - No prospective trials in HIV-infected patients to definitely indicate degree of diet and/or exercise needed to maintain reduction in visceral fat - May worsen subcutaneous lipoatrophy • Pharmacological interventions to treat lipohypertrophy have not been proven to provide long-term effects and may introduce new complications - Growth hormone • Decreases visceral adipose tissue • May worsen subcutaneous lipoatrophy and insulin resistance - Tesamorelin [0] - Metformin • Decreases visceral adipose tissue in insulin resistant persons • May worsen subcutaneous lipoatrophy - Surgical therapy can be considered for localised lipomas/buffalo humps • Duration of effect variable

Tesamorelin (growth hormone releasing factor) was shown to reduce visceral adipose tissue volume but this effect was lost on discontinuation; the drug is not currently licensed in Europe

Critical discussion of the condition to be treated

It must be noted that the overall concept of fat redistribution in HIV-infected patients is not undisputed in the scientific community. It has been postulated, as reviewed by *Moyle et al.*, that a thinning of the arms and legs may result in the appearance of abdomen prominence, and, with increased waist circumference, extremities may appear smaller. Furthermore, central fat accumulation is common in the general population and an increase in weight, abdominal girth, and VAT is a normal component of aging in the general population. Moreover, commencement of effective antiretroviral therapy is associated with a restoration to health in the depleted compartments, including a rise in lean body mass and trunk and limb fat (*Moyle G et al. AIDS Rev 2010; 12: 3-14*). Results from a cross-sectional analysis of 425 HIV-positive and 152 control men from the FRAM-study (*Grunfeld C et al JAIDS 2005; 40: 121-31*), who were asked to report an increase or decrease over the past 5 years, showed that peripheral lipoatrophy was more frequent in HIV-positive men than in controls, central lipohypertrophy, however, was less frequent. Measurements by MRI found that the clinical syndrome of peripheral lipoatrophy in HIV-infected patients was not associated with increased VAT. Lipoatrophy was more pronounced in the lower than in the upper limbs.

Figure 1. Lipoatrophy (A) and lipohypertrophy (B) by concordance



(from: http://images.journals.lww.com/jaids/Original.00126334-200510010-00002.FF2.jpeg)

Figure 1 shows the prevalence of lipoatrophy and lipohypertrophy by concordance. Subjects who reported loss of fat and had less fat than normal on examination were designated as having clinical lipoatrophy and subjects who reported gain of fat and had more fat than normal on examination were designated as having clinical lipohypertrophy.

The factors associated with leg subcutaneous adipose tissue (SAT) and visceral adipose fat (VAT) were assessed by a multivariate model. The effects of race, smoking and physical activity all followed known patterns in the general population. Of note, age was associated with less leg SAT but more VAT in HIV-infected subjects. Duration of use of stavudine was strongly associated with less leg SAT, as was that of indinavir. However, stavudine and indinavir were not associated with more VAT. A substantial positive association with VAT was not seen for any ARV; the largest point estimate for an ARV was much smaller in magnitude than those for race, age, or physical activity. The study demonstrates that HIV-infected men who had the clinical syndrome of peripheral lipoatrophy had less adipose tissue in each peripheral and central depot than HIV-infected men without peripheral lipoatrophy. Furthermore, HIV-infected men with or without the clinical syndrome of peripheral lipoatrophy had less adipose tissue in both peripheral and central subcutaneous sites compared with control subjects. Indeed, VAT was slightly lower in HIV-infected subjects with peripheral lipoatrophy compared with HIV-infected subjects without peripheral lipoatrophy. These results argue against the proposals in other reports of a reciprocal syndrome of lipodystrophy in which peripheral fat loss is accompanied by central fat gain, including increased VAT. The finding that leg fat was much lower in HIV-infected men compared with controls, whereas upper trunk fat was relatively spared, may explain the proposed association of

peripheral lipoatrophy with central lipohypertrophy. Data obtained from a cross-sectional cohort study in HIV-infected women showed some sex-specific differences but were broadly in accordance with the data for males (*Bacchetti P et al. JAIDS 2006; 42: 562-71*). All these results argue against a single syndrome of peripheral fat loss and central fat gain.

In conclusion, it appears that after more than a decade of research there is still a considerable degree of uncertainty about HIV-lipodystrophy syndrome. Whereas the syndrome of lipoatrophy appears better defined with respect to clinical symptoms and its underlying pathology/pathomechanisms (i.e. mitochondrial toxicity), the picture is less clear for lipodystrophy syndrome and even more vague for lipohypertrophy: So far, it has not been elucidated if this syndrome is indeed caused by fat redistribution or if different entities coinciding are wrongly pooled as a syndrome. In addition, for lipohypertrophy even the existence of this disease entity is questioned, taking into account also the uncertainties with respect to its etiology, its pathogenesis and its unanimous (differential) diagnosis.

2.2. About the product

Tesamorelin (TH9507) 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 Tyr1 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.

Human GRF is a hypothalamic peptide that acts on the pituitary somatotroph cells to stimulate the synthesis and pulsatile release of endogenous GH; human data on whether tesamorelin also stimulates a pulsatile release of endogenous GH have not been provided. GH has been shown to be anabolic and lipolytic. Its actions are mediated directly through GH receptors or indirectly, primarily mediated by IGF-1 production in the liver and in peripheral tissues. When GH interacts with specific receptors on a variety of target cells, these results in a host of pharmacodynamic effects such as regulation of body composition, glucose, and lipid metabolism, bone metabolism as well as cardiac function. Of interest is the role of GH in the formation and the function of fat cells as well as in the overall regulation of fat metabolism. The intended use for tesamorelin in this application is the treatment of excess abdominal fat in adult HIV-infected patients with lipodystrophy; the applied dose is 2 mg tesamorelin sc daily. Overall, pharmacology studies have shown TH9507 to have increased potency and longer duration of action compared to normal hGRF.

2.3. The development programme/compliance with CHMP guidance/scientific advice

The proposed indication is for the treatment of excess abdominal fat in adult HIV-infected patients with lipodystrophy, at a dose of 2mg by subcutaneous injection once daily. The clinical program of Egrifta consisted of:

- 4 single dose studies in healthy volunteers (100 mcg to 2mg, two were bioequivalence studies),
- 2 multiple dose studies in healthy volunteers (1 mg or 2mg per day, up to 14 days),
- 1 multiple dose study in HIV patients without lipodystrophy (2mg per day, 14 days),
- 1 multiple dose study in healthy elderly volunteers (2mg once daily/twice daily, for 14 days),
- 2 drug interaction studies,

- A 12 week placebo-controlled phase 2 study in HIV patients with lipodystrophy evaluating 1mg vs. 2mg,
- Two similar multicentre, randomized, double-blind, placebo controlled phase 3 studies in HIV patients with lipodystrophy (each with a 26-week main treatment phase followed by a 26 week extension).

Supporting safety information is available from a small study in diabetic patients, and also from studies done in support of other indications under investigation by the applicant (COPD, insomnia, post surgery, following influenza immunisation).

The Phase 3 development program in HIV-associated lipodystrophy included three multi-centre, randomized, double-blind, placebo-controlled pivotal Phase 3 studies (TH9507/III/LIPO/010 Main and Extension Phase, TH9507-CTR-1011, and TH9507-CTR-1012). TH9507/III/LIPO/010 included sites in North America only, while TH9507-CTR-1011 included sites in North America and in Europe (Belgium, France, Spain, United Kingdom). With regard to the acceptability of data generated outside the EU (ICH E5), the theoretical expectation was that the North American population comprising the majority of the patient database would not respond differently to the EU population in which authorisation is sought. A comprehensive range of sub-population analyses was conducted and no requirement for a bridging study was identified.

Out of the 18 trials pooled for the combined safety database, 1419 subjects received at least 1 dose of tesamorelin (of any strength) and 459 subjects received placebo. 953 subjects received tesamorelin at the proposed dose of 2 mg/day; of these 564 were patients with HIV lipodystrophy. Four hundred HIV patients received tesamorelin for greater than 6 months. Two hundred twenty five were exposed for 40-52 weeks, of which 209 completed the 52 week period. Forty three HIV patients received tesamorelin for over 1 year.

The efficacy and safety has not been evaluated in subjects with renal or hepatic impairment. No patients in the proposed target population over 65 years have been exposed to tesamorelin, although some elderly subjects were enrolled in supporting studies for other indications under development.

Design and endpoints of the two pivotal Phase 3 studies were established based on recommendations of the roundtable discussion organized by the Forum for Collaborative HIV Research (*Synder, 2006*). Following these recommendations, the primary endpoint was a decrease in VAT and the minimum difference needed in order to detect a clinically relevant difference between tesamorelin and placebo was considered to be 8%.

There are no regulatory guidelines specific to the proposed indication within the EU, and there is no product currently approved in the EU for this indication. Whilst tesamorelin is not a therapeutic protein as such, two guidance documents still have some relevance – these are the guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins (EMEA/CHMP/BMWP/14327/2006) and the guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins (CHMP/EWP/89249/2004). Guidelines CPMP/EWP/3020/03 (treatment of lipid disorders) CPMP/EWP/633/02 (treatment of HIV) and CPMP/EWP/1080 (treatment of diabetes) have some relevance to the secondary efficacy and safety endpoints.

Scientific advice was received from the CHMP on 2008-03-19 (EMEA/CHMP/SAWP/351462/2007). Clinical questions surrounded the investigation of immunogenic potential, the requirement for drug-interaction and thorough QT-studies, as well as the dose selection, design, inclusion criteria and endpoints for phase 3, in particular the clinical relevance of any effect in the primary endpoint of reduction in visceral adipose tissue. Scientific advice was also received from Member States Sweden (2010-06-02) and France (2010-07-02) and from the US Food and Drug Administration. Where key areas of European advice have not been followed this is mentioned in the assessment.

2.4. General comments on compliance with GMP, GLP, GCP

No issues during assessment of the dossier give any reasons for asking for a GMP inspection prior to authorisation.

Many of the non clinical studies were conducted in Canada, which did not have a GLP Monitoring Authority for pharmaceuticals at the time of conduct of the studies. Although there is therefore no obligation to accept the data from these studies, they appear to have been conducted in a scientifically appropriate manner.

According to the applicant the clinical trials were conducted according to Good Clinical Practices as described in ICH E6 and under the principles of the Declaration of Helsinki. These trials included sites in the USA, the European Union, and Canada. A formal declaration has been provided in the dossier. All trials contain the relevant GCP related information and no trial that causes suspicions on serious violations of GCP principles has been identified during the review.

2.5. Type of application and other comments on the submitted dossier

- Legal basis

This application concerns a centralised procedure according to Regulation (EC) No 726/2004, Article 3(2) for a new active substance, submitted in accordance with Article 8(3) of Directive 2001/83/EC.

- Conditional approval

N/A

- Approval under exceptional circumstances

N/A

- Accelerated procedure

N/A

- Biosimilarity

N/A

- 1 year data exclusivity

N/A

- Significance of paediatric studies

In accordance with Article 7 of Regulation (EC) No 1901/2006, regarding the paediatric investigation plan for tesamorelin a product-specific waiver in all age subsets of the paediatric population has been agreed (Decision Number: EMEA-001029-PIP01-10), based on safety grounds related to the risks of increased growth hormone before closure of bone epiphyses. The application has been subject to a PIP compliance verification (PDCO compliance Opinion Number: EMEA-001029-PIP01-10).

3. SCIENTIFIC OVERVIEW AND DISCUSSION

The indication for Egrifta as proposed by the applicant is in the treatment of excess visceral abdominal fat in treatment experienced HIV-infected adult patients; patients should be identified by waist circumference of at least 95cm in men, and of 94 cm in women; the intended dose is 2 mg sc daily.

3.1. Quality aspects

Drug substance

Tesamorelin acetate is a synthetic peptide consisting of 44 amino acids. The structural formula is Hexenoyl-Tyr-Ala-Asp-Ala-Ile-Phe-Thr-Asn-Ser-Tyr-Arg-Lys-Val-Leu-Gly-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Met-Ser-Arg-Gln-Gln-Gly-Glu-Ser-Asn-Gln-Glu-Arg-Gly-Ala-Arg-Ala-Arg-Leu-NH_2. All amino acid are of L-configuration.

The ASMF procedure is used.

Tesamorelin is manufactured using solid phase peptide synthesis. The basic principles of the drug substance manufacturing process have been described. The batch size for the drug substance remains to be defined in the dossier.

Specifications for all solvents and reagents used in the synthesis have been provided in the dossier. Only amino acid derivatives had been utilised that are manufactured with amino acids of non-human and non-animal sources. Control of materials has been adequately described.

Control of critical steps and intermediates is part of the Closed/Restricted Part of the ASMF.

Process validation was performed utilizing three consecutive batches of the peptide.

Characterisation tests have provided confirmation of the chemical structure.

The origin of potential impurities generated during solid phase peptide synthesis has been extensively discussed. The depletion of residual reagents used during the synthesis has been adequately addressed. Residual solvents are routinely controlled by the drug substance specification.

Efforts have been made to identify impurities greater than 0.2% peak area in the drug substance. The drug substance specification comprises the parameters appearance, solubility, amino acid analysis, specific rotation, mass spectral analysis, identity, peptide purity, peptide impurities, peptide content, acetate content, trifluoroacetate content, water content, residual organic solvents, mass balance, bioburden and bacterial endotoxins. Some of the specification limits has been tightened according to batch analysis data with the responses to the list of questions. All analytical methods have been adequately described. Batch Analyses data for eleven batches have been provided.

Stability data are available for nine batches up to 72 months. No critical changes have been observed at the proposed storage temperature. The proposed re-test period of two years if stored at -20°C is acceptable.

Drug Product

Tesamorelin for injection 2 mg/vial is available as a single unit dose of sterile, lyophilized powder for reconstitution with 2.1 mL of sterile water for injection for a final concentration of 1 mg/ml. The drug product is packaged in 3 mL, 13 mm neck, type I borosilicate, clear untreated glass vials. The vials are stoppered with pre-siliconised, pre-washed, 13 mm grey bromobutyl lyophilisation stoppers. The

stoppers are capped with 13 mm avocado green, plastic flip off caps with aluminium seals. A 30-day supply of vials is packed in an opaque cardboard box containing 30 vials for one month supply.

The manufacturing of the drug product comprises manufacture of bulk product, pre-filtration, sterilising filtration, filling of vials, stopper placement, lyophilisation, stoppering, and crimping. The control of critical steps of the manufacturing as described in the dossier is acceptable.

Process validation was undertaken and has been completed. Major steps and process controls as well as results obtained for the validation batches are presented in the dossier. The manufacturing process of the drug product has been sufficiently validated. The data demonstrate that all pre-determined quality attributes and specifications are met.

All excipients (mannitol, water for injection, sodium hydroxide, hydrochloric acid and nitrogen) used in the manufacture of the drug product are of compendial grade and controlled to the current version of Ph. Eur.

The specification of the drug product comprises the parameters appearance, identity, content, impurities, uniformity of dosage units, water content, bacterial endotoxins and sterility. For the reconstituted drug product the specification parameters are completeness and clarity of solution, reconstitution time, osmolality, pH and particulate matter.

Analytical procedures used for testing the drug product are compendial (Ph. Eur.) except for the identification, assay and impurity method. Description of analytical methods has been provided. Validation data for analytical methods have been provided. The methods are suitable for their intended use. Batch analysis data are provided.

Stability data for three batches are provided. Stability studies were conducted in the proposed commercial primary packaging. Stability data of up to 24 months at 5°C, demonstrate that all batches presentation meet the proposed specifications.

A shelf-life of 36 months is proposed for tesamorelin acetate for injection, 2 mg/vial, when stored at 5°C. A photostability study was performed. The drug product is sensitive to light. However, in its marketing pack (opaque carton box) the drug product is stable with respect to light exposure. The labelling will also include a statement to store the drug product in its marketing pack until use in order to minimize its exposure to light.

Discussion on chemical, pharmaceutical and biological aspects

Overall, the development, manufacture, characterisation and control of drug substance and drug product are adequately described in the quality dossier. However, there are outstanding issues which need to be addressed prior to recommendation for marketing authorisation at the present time.

Conclusions on the chemical, pharmaceutical and biological aspects

There are outstanding issues which need to be addressed prior to recommendation for marketing authorisation at the present time.

3.2. Non clinical aspects

Pharmacology

The Applicant has performed a restricted development program to investigate the primary pharmacodynamic properties of tesamorelin in pigs or in porcine freshly isolated pituitary gland cells. Nine studies were presented.

Two in-vitro studies were performed in freshly isolated porcine anterior pituitary cells to investigate a possible cleavage of tesamorelin by proteases/peptidases and to investigate differences in tesamorelin`s ability to induce GH secretion. No such differences were noted. The Applicant's conclusion that tesamorelin is not a pro-drug under this aspect is reasonable.

Seven studies were performed in growing pigs to investigate effects of tesamorelin on serum pGH and IGF-1 concentrations and the influence of alternative formulations and different batches of tesamorelin.

Single subcutaneous doses of tesamorelin produced a dose-related (0.33 to 1 µg/kg) increase in pGH plasma concentration; hGRF(1-44)NH_2 at 27 and 81µg/kg had a similar effect to tesamorelin at 1 and 3 µg/kg.

Single intravenous doses also produced dose-dependent increases in pGH, with two or three peaks seen within an 8 hour post-dose period, which was not apparent with hGRF(1-44)NH_2.

Both subcutaneous and intravenous doses of tesamorelin (3 µg/kg) produced significantly higher pGH AUCs in growing pigs than either saline or 2.5% mannitol vehicles.

Tesamorelin produced greater increases in serum IGF-1 concentrations than hGRF(1-44)NH_2 in growing pigs following twice daily subcutaneous administration for 5 days, although the effects of tesamorelin on IGF-1 levels did not appear to be dose-related over the range tested (7.5 to 30 µg/kg), suggesting 7.5µg/kg already produced a maximal response.

In summary, a series of studies in growing pigs (barrows) has shown that tesamorelin increases pGH levels following subcutaneous and intravenous administrationand that IGF-1 levels are increased following twice daily subcutaneous dosing for 5 days. In the studies where comparison was made with hGRF(1-44)NH_2, the effects of tesamorelin were greater, that is, lower doses of tesamorelin were needed than of hGRF(1-44)NH_2 to achieve the same effect on GH levels. It might be noteworthy that the pGH response elicited by tesamorelin was in opposite to the response induced by hGRF oscillatory. The extent of the studies performed and the supportive material provided is very limited. However, the Applicant clearly showed the proof of principle.

Safety pharmacology studies investigated the possible effects of tesamorelin on the cardiovascular, respiratory and central nervous systems and included an in vitro assay in Chinese hamster ovary cells stably transfected with the human ether-a-go-go (hERG) gene. There were no effects on the cardiovascular system in conscious telemetered dogs or on the CNS or respiratory systems in rats following single subcutaneous doses of tesamorelin of up to 50mg/kg. There were no effects on the rapidly rectifying potassium current (IKr) in the hERG study at concentrations up to 800ng/mL. At the dose administered in the in vivo studies (about 50-fold higher than those used in the repeated-dose studies), and the concentration used in the hERG assay, tesamorelin concentration would greatly exceed plasma concentration at therapeutic doses. In summary, the core battery of safety pharmacology studies does not reveal significant effects on the tested organ systems.

The Applicant does not present secondary pharmacodynamic or pharmacodynamic drug interaction studies. The Applicant justifies the absence of pharmacodynamic interaction studies on the basis that the pharmacological activity of tesamorelin is well characterised, and as such, drug interactions with other compounds that affect GH or IGF-1 levels are considered to be predictable, although it is not known whether these effects would be additive or synergistic. The clinical programme excluded medications that induced or influenced the release of GH and therefore the SmPC will specify that tesamorelin should not be co-administered with GH or GRF products, GH secretagogues, IGF-1 or IGFBP-3 products. With these restrictions in the SmPC the absence of pharmacodynamic interaction studies can be considered justified. Further secondary pharmacodynamic studies are not considered necessary.

Pharmacokinetics

A limited pharmacokinetic package of studies was carried out. This is generally acceptable as tesamorelin is a peptide and conventional ADME studies are not usually required for such compounds. The pharmacokinetics of tesamorelin were assessed in rats and dogs after subcutaneous (SC) and intravenous (IV) single and repeat administration primarily as part of the preclinical toxicology studies. Along with the process of conduct of preclinical toxicology studies 3 different analytical methods were used. In the 52 week dog study the majority of the samples was processed without proven long term sample stability. Pharmacokinetics following a single dose were evaluated on day 1 of the dosing in the repeated-dose toxicity studies. As stated above, different methods of analysis were used depending on the stage of development. Irrespective of the method, the results tended to be variable and often below the limit of quantification for the assay. This, and limited time points in a number of the studies, resulted in pharmacokinetic parameters being incalculable in some instances.

In rats at SC doses ranging from 0.1 to 1.2 mg/kg b.w. C_{max} occurred mainly at the first sampling point (5 min). After single SC administration C_{max} and AUC increased in the rat roughly dose-proportional. After repeated SC administration for 26 weeks C_{max} and AUC increased up to 6.7 and 8.6 fold, respectively, indicating accumulation, with loss of dose proportionality in the high dose group. After 4 week repeated IV administration to rats no accumulation was observed.

In the dog after SC administration C_{max} was achieved mainly within the first 60 minutes. In general increases in C_{max} and AUC were dose-related but not dose-proportional. After repeated administration C_{max} and AUC increased strongly in both genders (largest increase between Day 1 and Week 13) with higher C_{max} and AUC values observed in females compared to males. C_{max} and AUC increased up to 39 times and 95 times, respectively, from Day 1 to Day 365. The Applicant initially concluded that the accumulation of tesamorelin in the dog after repeated SC administration was likely due to the presence of anti-tesamorelin antibodies. Formation of anti-tesamorelin antibodies in dogs was demonstrated (see section on toxicology).The Applicant was asked whether there was any experimental evidence available (e.g. liberation of tesamorelin from tesamorelin/antibody complexes) supporting that the demonstrated increase in exposure to tesamorelin seen in the 52 week repeated dose toxicity study in dogs (E-PCL-089) is due to binding of tesamorelin to antibodies. The Applicant confirmed that there is no experimental evidence available and concluded that the increase in exposure cannot be definitely attributed to the presence of anti-tesamorelin antibodies.

After repeated daily IV administration for 4 weeks to dogs, no accumulation was observed. Elimination phase was at higher doses slightly biphasic with mean $t_{1/2}$ of about 20 to 48 minutes. Bioavailability in dogs after SC administration was found to be low (6.3 to 21.2 %) and could not be calculated for rats, although is also likely to be low given rapid uptake and clearance in this species. Apparent volume of distribution was low in dogs and suggested distribution mainly in extracellular fluid with little tissue uptake.

Compared to the rat, exposure in the dog was at the same SC dosage level higher, particularly in terms of AUC.

In both species, elimination after a single iv injection was rapid: mean apparent terminal elimination t½ was estimated to range from 19.2 to 48.2 minutes in the dogs, but insufficient sampling precluded an estimation of the elimination kinetics in the rat.

Only one (pilot) distribution study was conducted, using ^{123}I-radiolabelled tesamorelin and related peptides using intravenous and subcutaneous administration in male Sprague-Dawley rats. Scintigraphic images obtained from 3 rats up to 100 min after IV administration of ^{123}I-tesamorelin indicated that most of the radioactivity content in the animals was found in excretory tissues such as kidney, bladder (and presumably urine contained within) and intestine including contents. The

relatively high initial liver concentrations (initial 17 % of dose, followed by a rapid decline to about 5 %) and the high levels observed in the intestine (30 – 35 %) may indicate biliary excretion and/or recirculation of the ^{123}I-label.

Tissue distribution was generally similar irrespective of the peptide administered or the route of administration, with the exception of the lung, where markedly higher levels of radioactivity after IV injection of ^{123}I-tesamorelin (compared to IV administered [^{123}I]-labelled hGRF) were detected. The possible reasons for this were not discussed by the applicant although it was stated that the conclusions from the study were tenuous given that the radioactivity did not necessarily represent intact peptide. The Applicant was asked to comment whether there are any findings in non-clinical or clinical studies which relate to a higher tissue concentration of tesamorelin compared to hGRF observed in rat lung tissue and discuss the possible consequences thereof, taking into account the finding of increased incidence of alveolar macrophages at doses of 0.6 mg/kg b.w./day and higher in the 52-week repeated dose toxicity study in dogs (E-PCL-089). In response the Applicant compiled non-clinical and clinical data focussing on tesamorelin treatment and the respiratory system. The reason for the obviously higher tissue concentration of tesamorelin compared to hGRF observed in pilot non-GLP distribution studies in rats remains unknown. A higher number of alveolar macrophages seen in dogs dosed 0.6 mg/kg b.w./day or above for 52 weeks has not been reported in other non-clinical animal studies. It is agreed that the clinical data presented by the Applicant do not raise concerns regarding adverse events on the respiratory system under tesamorelin treatment.

Plasma protein binding was not investigated. The Applicant did not investigate occurrence of metabolites in any *in-vivo* studies but performed i*n vitro* biodegradation studies with tesamorelin to evaluate stability and putative identification of peptide breakdown products. *In-vitro* human plasma $t_{1/2}$ of tesamorelin was found to be markedly greater than that one of hGRF (by a factor of about 6 to 15, depending on the experimental conditions used). In addition, tesamorelin was found to be more stable in human and dog compared to rat plasma. The slower degradation in dog plasma compared to rat plasma may contribute to the higher exposure found in dogs compared to that one seen in rats at the same mg/kg b.w. dosage levels. No degradation of tesamorelin was observed when the peptide was incubated with DPP-IV enzyme confirming directly that the resistance to DPP-IV cleavage is based on the trans 3-hexenoyl group on tesamorelin. The formation of tesamorelin fragments in plasma was found to be species dependent. Biodegradation of tesamorelin appeared to occur from the C-terminal end of the molecule. The main fragment (constituting about 10 % of total) observed after incubation of tesamorelin with human plasma was 3-hexenoyl-Tyr^{1}-Ala^{42}OH. The same fragment was observed as a minor degradation product (0.97 % of total) after incubation of tesamorelin with rat plasma but was not seen when incubating with dog plasma. The fragments 3-hexenoyl-Tyr1-Lys12OH and 3-hexenoyl-Tyr1-Arg11OH were found in the plasma incubations from all three species. Since the metabolic pathway is generally understood for peptides, further degradation of tesamorelin-related peptides is expected to occur in a short time frame to smaller peptides and individual amino acids. The Applicant does not focus on metabolism regarding the 3-hexenoic acid residue attached to Tyr^{1}. No removal of this moiety was apparently observed in human (and rat and dog) plasma. It is assumed that the 3-hexenoic acid is likely to be removed by the liver and handled like naturally occurring trans fatty acids. A further characterisation of degradation pathways of tesamorelin is not considered necessary.

Repeated SC dosing in rats for 26 weeks did not affect cytochrome b5 and CYP450 levels or the activities of CYP1A1/2, CYP2B1/2, CYP2E1 and UDPGT enzymes, but there was a statistically significant dose-dependent decrease in activity of CYP3A1/2 in males (up to 3.2 fold; not seen in females), but this is considered to be an indirect effect of tesamorelin in the rat due to treatment–related induction of GH in the rat and to be of no relevance for therapeutic use in humans.

Toxicology

The toxicological studies performed with tesamorelin included single- and repeated-dose toxicity studies in mice, rats and dogs, in-vitro and in-vivo genotoxicity studies, reproductive toxicology studies in rats and rabbits, a single dose local tolerance study in rabbits, a T-cell dependent antibody response study and an impurity qualification study in rats.

Single dose studies were conducted to ascertain maximum tolerated dose (MTD) values for subsequent studies. In single-dose IV toxicity studies MTD ranged from between 100 to 200 mg/kg b.w. in rats to likely slightly below 100 mg/kg b.w. in mice to 25 mg/kg b.w. in dogs. Findings of acute toxicity studies include local tissue damage (mouse and rat; not in the dog) and highly elevated histamine levels (only studied in the dog), which likely were causative of the clinical signs observed.

Preliminary 2-week intravenous studies and 4-week intravenous studies were conducted in rats and dogs. Subcutaneous studies were carried out in mice (13-week study), rats (13- and 26-week studies) and dogs (16- and 52-week studies). The 13-week rat and 16-week dog studies also included a 4-week recovery period.

In a 13-week repeated SC toxicity study in mice with doses of 0.3, 0.6 and 1.2 mg/kg b.w./day increased body weight, injection site irritation, slight increases in serum phosphorus and calcium were observed. Apart from injection site reaction, the findings are likely related to the pharmacological activity of the GRF analogue.

In a 4-week repeated IV toxicity study in rats with doses of 0.1, 0.3 and 0.6 mg/kg b.w./day increased body weight and food consumption, transient increase in rat GH levels, increased adrenal gland weight and slight increase in bilirubin were seen. After SC administration of the same dosage levels for 13 weeks to rats increased body weight and food consumption, injection site irritation, transient increase in rGH levels, hepatocellular vacuolation and formation of anti-tesamorelin/anti-hGRF antibodies were found. In a 26-week repeated SC toxicity study in rats with doses up to 1.2 mg/kg b.w./day increase in liver weight, increased total cholesterol, LDL and HDL, hemosiderin deposition in Kupffer cells and extramedullary erythropoiesis in (the latter effect in only 2 of 15 high dose males) and an increase in the incidence of diestrus in females were seen in addition to the effects seen in the 13-week study. With the exception of the injection site reaction and the possible effect on the estrus cycle, the findings likely represent exaggerated pharmacological effects of tesamorelin. In rats, subcutaneous dosing for 13 or 26 weeks resulted in a low immunogenic response. Any antibodies formed were likely non-neutralising, as rGH levels still increased.

Repeated IV administration to dogs in daily doses of up to 0.6 mg/kg b.w./day for up to 4 weeks was associated with increases in bodyweight, slight increases serum cholesterol and triglycerides and transient increases in canine GH; effects which are considered to represent pharmacological effects of tesamorelin. After SC administration to dogs at the same doses for 16 weeks, increases in body weight and food consumption, decreases in RBC, HB, HCT, increases in reticulocytes and platelets, increases in cholesterol/triglycerides, increase in serum phosphorus, increase in serum protein, globulin and slightly in albumin, increase in canine IGF-1, formation of anti-tesamorelin/anti-hGRF antibodies, increased liver and pituitary weights, decreased spleen weights, injection site irritation, renal tubular basophilia, and centrilobular hepatocellular vacuolation were found. According to the study documentation (E-PCL-089) dog anti-tesamorelin antibodies bind similarly to tesamorelin and to human GRF.

The toxicology written summary mentions that PAS staining in the 16-week dog study showed that the hepatocellular vacuolation was associated with glycogen accumulation. In the studies with recovery periods, the finding was reversible.

Additional findings in a 52-week repeated daily dose toxicity studies in dogs with SC administered dosages up to 1.2 mg/kg b.w./day included signs of canine acromegaly, development of insulin resistance and/or diabetes with vacuolar degeneration of the endocrine pancreas, hypertrophy of compact bone, increased incidence of alveolar macrophages, increased thyroidal c-cell complexes, pronounced spleen weight reduction without histopathological correlate, increased adrenal weight with cortical hypertrophy, pituitary hyperplasia, thickening of the skin and the wall of the digestive tract and urinary bladder, slight reduction in APTT.

The findings of canine acromegaly, including morphological changes and development of insulin resistance and/or diabetes were consistent with those reported following chronic administration of exogenous GH to dogs, and therefore attributable to prolonged exposure to supraphysiological levels of IGF-1 (and/or GH) resulting from tesamorelin administration or considered secondary to the development of insulin resistance and/or diabetes and not considered to represent a direct toxic effect of tesamorelin. Apart from all these described findings, most of which were considered to be related to the pharmacological action of tesamorelin, changes of the kidney (cortical tubular basophilia and/or medullary tubular dilatation, mononuclear cell infiltrate, vacuolar degeneration of collecting ducts), exocrine pancreas (vacuolar epithelial duct degeneration) and gall bladder (vacuolar epithelial degeneration and basophilic fibrous contents) were observed at the lowest dosage level already (0.1 mg/kg b.w.) and could not be definitively attributed to prolonged exposure to supraphysiological levels of IGF-1 (and/or GH). The Applicant suggests possible links between these changes and chronic high levels of GH/IGF-1, though direct toxicological action of tesamorelin cannot be excluded. GH has in published literature (Mc Cormick and Bradshaw, 2006) been shown to increase tubular sodium reabsorption and reduce GFR leading to kidney hypertrophy. Due to a hyperinsulinaemic condition sustained release of CCK (Weickert et al., 2008), which activates the exocrine pancreas and the gall bladder, might be involved in the effects seen in these two organs. The possibility of the involvement of the endogenous secretagogue ghrelin was also discussed.

In the 52-week repeated dose toxicity study in dogs (E-PCL-089) a reduction of spleen weights and a strong reduction of the spleen weights relative to body weights by 80 % (to about 20 % of the values of untreated controls) were seen. No histopathological correlate was reported. The Applicant was asked to elaborate on the immunotoxicological potential of tesamorelin taking into account the data generated in the repeated dose toxicity studies in rats and dogs and to comment, whether a further immunocompromising effect of tesamorelin can be excluded in already immunocompromised patients. In response the Applicant summarised the findings related to immune function in the non-clinical repeated dose studies in rats and dogs. No evidence of tesamorelin-related adverse effects on other immune system organs/tissues (apart from spleen and thymus), or on hematologic or clinical chemistry parameters was found. No evidence of adverse effects on immune function or immune system-related organs and tissues in any repeated-dose toxicity study in rats were found. Furthermore, the 28-day T-cell-dependent immunogen (keyhole limpet hemocyanin [KLH]) assay in Sprague-Dawley rats (E-PCL-159) did not reveal adverse effects on the immune function.

The striking reduction in spleen weight in dogs was already evident at the lowest dose employed (0.1 mg/kg body weight/day), therefore, no NOAEL could be established regarding this effect. On a mg/kg base, the human therapeutic dose is one third of this dose (2 mg/day; 0.03333 mg/kg body weight/day for a 60 kg individual). The Human Equivalent Dose of 0.1 mg/kg body weight/day in dogs is 0.05555 mg/kg body weight/day. This HED is just slightly larger than the human therapeutic dose (0.03333 mg/kg body weight/day). Although no obvious adverse effect on the function of the immune system could be attributed to the striking reduction of spleen weight under long-term treatment in dogs, the relevance for humans remains unknown. The Applicant is asked to include an appropriate wording regarding the finding of massively reduced spleen weight under long-term treatment in dogs

in SmPC section 5.3 Preclinical Safety Data and in the Safety Specification of the Risk Management Plan. (other concern)

The Applicant concludes that as increased IGF-1 levels were found in the 52-week dog study throughout the study, antibodies formed are of non-neutralising nature. To substantiate this view, the Applicant provides Table 15 in Module 2.6.6 and states that, despite the higher exposure to tesamorelin in the presence of antibodies, the increase in the pharmacodynamic marker (cIGF-1) over the 52 weeks of daily administration of tesamorelin was not affected by the presence of anti-drug antibodies. The argumentation of the Applicant can at present not be followed, as the way the data were compiled is not provided. Regarding the 52-week repeated dose study in dogs (E-PCL-089) at present still no conclusions regarding the exposure level to tesamorelin, the development/presence of anti-tesamorelin antibodies in dogs and the extent of the remaining pharmacodynamic effects of tesamorelin can be drawn. The Applicant is asked again to explain in detail the basis of the data shown in Table 15 of Module 2.6.6. (other concern).

The Applicant bases the calculation of exposure ratios between animals and humans on the high dose (1.2 mg/kg b.w.) exposure values of the 26-week rat SC study [E-PCL-105], on the low dose (0.1 mg/kg b.w.) exposure values of the 52-week dog SC study [E-PCL-089] and on the high dose (0.6 mg/kg b.w.) exposure values of the 4-week IV dog study [E-PCL-293]. Mean exposure in rats after single administration is therefore considered to represent at least 5.6 and 4.3 fold multiples of C_{max} and AUC compared to exposure after single dose in humans at the intended therapeutic dosage. After chronic (26-week) administration in rats compared to 7 day treatment in humans exposure ratios of a minimum of 27 are calculated by the Applicant. If due to possibly tesamorelin-associated effects on the estrus cycle which were observed particularly in female mid and high-dose rats the exposure level at the low dose (SC 0.1 mg/kg b.w./day) was taken as a basis for calculation of exposure margins this would result after single administration in a factor of about 1.1 to 1.2 fold for both, C_{max} and AUC.

In regard to the 52-week SC study in dogs the Applicant points out that whereas mean exposure after single 0.1 mg/kg dose in dogs was approximately equivalent to that in humans administered a single 2 mg dose of tesamorelin, following chronic administration to dogs, mean C_{max} and AUC in the dog increased to at least ca. 52-fold and 135-fold, respectively, those in humans given a 2 mg dose for 7 days. In the 4-week IV repeated dose toxicity dog study E-PCL-293 C_{max} and AUC values remained rather unaffected during the 4-week treatment period with the mean exposure (C_{max} and AUC) being at least 150-fold the human exposure at a dose of 2 mg/day for 7 days. On the contrary, during the 52-week SC dog study E-PCL-089 C_{max} and AUC values increased massively with maximum increases of C_{max} and AUC values of 39 times and 95 times those values of Day 1. The Applicant was asked to provide evidence that exposure in humans remains comparable during short and long term therapeutic administration and to demonstrate that the identification of exposure multiples between animals and humans as provided by the Applicant based on data derived from long-term use in animals and from short-term use in humans is valid. In response the Applicant pointed out that the most important marker of pharmacodynamic activity and safety is considered to be IGF-1. From Week 26 onward, all dogs in all tesamorelin-treated groups had IGF-1 levels beyond 3SDS (standard deviation scores – an established measure of increase in IGF-1), whereas in humans only approximately 35% of subjects treated with tesamorelin had IGF-1 levels exceeded 3SDS at 26 weeks and this number did not increase with continued treatment for 52 weeks in humans. By Week 13, mean IGF-1 SDS values were >8 for all tesamorelin-treated groups in the 52-week dog study and tesamorelin-related adverse effects in dogs occurred following chronic exposure to dose levels producing IGF-1 SDS >8. The Applicant concludes that these data demonstrate a margin of at least 2.6-fold based on IGF-1 SDS values (8SDS vs. 3SDS). Although it is considered a major shortcoming, that the Applicant is unable to provide exposure data to therapeutically intended tesamorelin doses in humans beyond 14 days of treatment, the argumentation of the Applicant appears to be reasonable. The Applicant did not provide

the calculation of IGF-1 standard deviation scores for the 52-week dog study (E-PCL-089) and is, therefore, asked to provide the missing information in detail (other concern).

Tesamorelin was not genotoxic in a standard battery of genotoxicity tests. No treatment-related effects were observed on proliferating cell nuclear antigen (PCNA) in any tissues in the 13-week sc rat study, nor in selected tissues in the 26-week study. In this latter study, there were also no differences in the proliferative responses of spleen cells to Concanavalin A, which is a known mitogen.

Life time carcinogenicity studies were not performed. Additional life time rodent bioassays would be of limited value for the assessment of the carcinogenic potential of tesamorelin due to the technical limitations (weight gain in treated rats or severe injection site reaction in mice) and the already existing rodent bioassays for recombinant rat-GH in rat and mouse-GH in mouse and recombinant human IGF-1 in rat which did not expose relevant carcinogenic effects.

The reproductive and developmental toxicity of tesamorelin was evaluated in a fertility and embryo-fetal development study in rats, embryofetal development studies in rabbits and peri- and post-natal development study in rats. Doses for reproductive studies in rats and rabbits were selected based on dose finding studies.

In the fertility and embryo-fetal development study in rats tesamorelin did not induce adverse effects on male and female fertility. No treatment-related effects were noted up to the highest dose of 0.6 mg/kg, except dose dependent increases in the tesamorelin groups for body weight, body weight gain and improved food conversion efficiency. The increased numbers of corpora lutea and increased pre-implantation losses (both not significant) were considered to be of no toxicological significance since the number of live fetuses was similar between control and treated animals. There may be a correlation between the increase in corpora lutea and the increased incidence of diestrus in the 26-week subcutaneous injection toxicity study in rats (E-PCL-105(77201)).

The fetal weights for the 0.6 mg/kg/day group were significantly increased. Effects on the fetal skeleton were indicative of advanced ossification, which, along with increased fetal weight, was considered attributable to the maternal effects on body weight and food intake, although a direct pharmacological effect on embryo-fetal development could not be excluded

When pregnant rabbits were treated with tesamorelin no effects were seen on body weights, body weight gains, corrected body weights, corrected body weight gains and food consumption, except for the high dose group in study E-PCL-228, where a lower group mean food consumption was noted. There was no evidence of maternal toxicity, embryo lethality, fetotoxicity or teratogenicity in the studies.

Exposure to tesamorelin from implantation to weaning in the rat did not induce maternal toxicity. Viability, growth, mating and fertility in the offspring were not affected by daily treatment with tesamorelin. Increase in body weight and body weight gain is associated with the expected pharmacology of tesamorelin.

An effect on pup structural development in the form of a slight increase in the incidence of litters developing hydrocephaly was noted after application of tesamorelin during the lactation period at 1.2 mg/kg/d. Given the occurrence in 2 litters the possibility of an effect of tesamorelin must be considered since this exceeds slightly the historical control data range of offspring.

Tesamorelin was not quantifiable in serum from pups. The concentration of tesamorelin in milk of lactating rats was not tested. Behavioural and reproductive development of the F1 adult generation and the viability and growth of the F2 generation pups were unaffected by tesamorelin administration.

Overall tesamorelin produced no important developmental or reproductive toxicity in rats or rabbits, with the exception of a slightly increased incidence of litters with hydrocephaly following administration

of 1.2 mg/kg/day to the dams. The overall developmental and reproductive NOAEL was 0.6 mg/kg/day in rats. The NOAEL for embryo-fetal development in the rabbit was 2 mg/kg/day. Based on a comparison of steady-state AUCs, exposure at these NOAELs was 2.3-fold(rat) and 564-fold (rabbit) greater than the AUC observed in humans given a 2 mg dose daily for 7 days.

Egrifta (Tesamorelin Ferrer) is contraindicated in pregnancy and lactation.

The proposed indication is for adult patients and the absence of juvenile toxicity studies is acceptable.

The effect of single SC injection of tesamorelin on the back of male Japanese White Rabbits was macroscopically and microscopically assessed 2 days (n=3) and 14 days (n=3) post injection. The conclusion of the Applicant, that there was no evidence of tesamorelin causing SC local irritation can only in partially be agreed to. The local toxicity testing employed single injection only. Repeated dose toxicity studies in animals clearly showed the local irritant effect of SC administered tesamorelin. The vehicle in the repeated-dose studies was 5 % mannitol in water for injection. Mannitol is the excipient in the proposed product and it is noted that injection site reactions have also been seen in the clinic. This is addressed in the product labelling by warning that the injection sites be rotated. Further experimental studies in animals are not considered necessary.

Daily SC administration of 1.2 mg tesamorelin/kg b.w./day to rats for 28 days did not reveal evidence of adverse effects on T-cell dependent antibody response to IV injected keyhole limpet hemocyanin.

In order to qualify impurities/degradants in tesamorelin the Applicant conducted a 4-week toxicity study in rats with daily SC administration of 4 mg/kg b.w. of control tesamorelin and stressed tesamorelin. Apart from a slightly more pronounced injection site reaction associated with the stressed form of tesamorelin, both preparation are considered toxicologically equivalent. Bacterial reverse mutation (in *Salmonella typhimurium* and *Escherichia coli*) and chromosome aberration (in CHO cells) assays were conducted on impurities TH5111 and TH7117. These *in vitro* genotoxicity studies were negative and therefore neither impurity is considered genotoxic.

The Applicant proposes following EMA´s request tightened specification limits for impurities TH05111 and for total related substances of ≤ 1.5% at release and ≤ 2.5% at the end of shelf life and ≤ 4.0% at release and ≤ 5.0% at the end of shelf life, respectively. The specification limit for impurity TH07117 has been tightened to ≤ 1.0%, which is below the ICH threshold of qualification. On a body surface area basis the margins of safety are 14 and 18 for impurity TH05111 and for total related substances, respectively, which is considered acceptable.

Ecotoxicity / environmental risk assessment

Not applicable because tesamorelin is essentially a peptide.

Discussion on non-clinical aspects

The non-clinical pharmacology and pharmacokinetic studies are limited in number. The pharmacology studies demonstrate tesamorelin is not a prodrug, and that it increases circulating levels of growth hormone (GH) and insulin-like growth factor-1 (IGF-1) in growing pigs, and at lower doses than hGRF.

Safety pharmacology studies were appropriate and do not suggest that there are likely to be any issues at therapeutic doses.

Pharmacodynamic interaction studies were not conducted and their absence was justified.

Classic ADME studies are not usually required for proteins and peptides and a more limited pharmacokinetic programme was presented. The analytical methodology to measure tesamorelin in the toxicology species changed throughout the programme, as more accurate methods were developed.

However, limited sampling, inter-individual variability and values near LLOQ prevented estimation of PK parameters in some studies.

Absorption was rapid in rats and dogs following subcutaneous administration. Exposure increased either in proportion or slightly less than proportional to dose. Bioavailability and volume of distribution were low in dogs.

Tissue distribution of radiolabelled tesamorelin appeared to be generally similar to that one of radiolabelled hGRF irrespective of SC or IV route of administration, with the exception of the lung, where markedly higher levels of radioactivity after IV injection of ^{123}I-tesamorelin (compared to IV administered [^{123}I]-labelled hGRF) were detected. Available non-clinical and clinical data do not raise concerns regarding adverse events on the respiratory system.

In vivo metabolism was not studied; *in vitro* and *ex vivo* studies showed more rapid degradation of tesamorelin in rat plasma than in dog or human plasma. Repeated dosing in rats did not affect cytochrome b5 and CYP450 levels or the activities of CYP1A1/2, CYP2B1/2, CYP2E1 and UDPGT enzymes, but there was a dose-dependent decrease in activity of CYP3A1/2 in males only.

Excretion was not specifically studied; a pilot distribution study in rats showed distribution to organs of excretion, although it is not clear whether the ^{123}I label would have represented intact tesamorelin or smaller fragments.

In repeated-dose toxicity studies in rats and dogs, most findings were related to the pharmacology of tesamorelin *via* increased GH levels and included increased body weight and food consumption, alterations in serum cholesterol/lipid/glucose levels and hepatocellular vacuolation. The latter finding is considered a metabolic rather than a toxic effect.

Injection site reactions were also noted in the s.c. studies. Injection site reactions have also been noted in the clinic and the product labelling advises that different sites be used.

In the 52-week dog study, additional findings were a condition suggestive of canine agromegaly and histopathological findings in the kidney, gall bladder and exocrine pancreas, which could also be potentially related to the action of GH rather than a direct toxic effect of tesamorelin. Furthermore, a reduction of spleen weights and a strong reduction of the spleen weights relative to body weights were seen, obviously without histopathological correlate. An amendment of SmPC section 5.3 and of the Safety Specification of the Risk Management Plan is sought.

Exposure to tesamorelin increased strongly on repeated dosing particularly in dogs. Development of anti-tesamorelin antibodies was as well particularly seen in dogs. Regarding the 52-week repeated dose study in dogs the relationship of the exposure level to tesamorelin, the development/presence of anti-tesamorelin antibodies in dogs and the extent of the remaining pharmacodynamic effects of tesamorelin needs clarification. There is no experimental evidence available supporting that the demonstrated increase in exposure to tesamorelin seen in the 52 week repeated dose toxicity study in dogs is due to binding of tesamorelin to antibodies. No data on tesamorelin exposure in humans beyond 14 days of treatment are available. With respect to IGF-1 Standard Deviation Scores (established measure of increase in IGF-1), which increase in dogs during the 52-weeks of the study, but which remain at a certain level in humans throughout 52 week of treatment, support the assumption that an accumulation of tesamorelin as seen in the 52-week dog study is not necessarily likely to occur in humans. These data support a margin of at least 2.6-fold based on IGF-1 SDS values (SDS seen in dogs vs. SDS seen in humans). The Applicant is requested provide the calculation of IGF-1 standard deviation scores in dogs.

Carcinogenicity studies were not conducted. Their absence was justified based on a number of considerations including product-specific information, literature review and technical limitations. These

arguments are accepted and it is concluded that although there is a potential risk of cancer in these patients, further non-clinical studies are unlikely to be useful and careful monitoring of patients would be more appropriate.

In reproductive toxicity studies, the only finding was a slightly increased incidence of litters with hydrocephaly following administration of 1.2 mg/kg/day to rat dams; exposure at GD 17 was similar to that in humans given 2 mg/day for 7 days. The product is contraindicated in pregnancy and lactation.

Other studies were carried out to qualify impurities and to demonstrate that tesamorelin is not immunotoxic. The proposed specification limits for observed impurities are considered qualified.

An environmental risk assessment was not conducted as tesamorelin is a peptide and exempt from such studies. This is acceptable.

Conclusion on non-clinical aspects

From preclinical point of view there are issues which need to be addressed prior to recommendation for marketing authorisation at the present time.

Clinical aspects

• *Tabular overview of clinical studies*

Table 3. Overview of Clinical Efficacy Trials

Study ID **No. of Ctrs./ Location** **Study Dates (Start–Completion)**	**No. of Subjects Randomized / Completed / Dropouts** **Design / Control**	**Primary Endpoint(s)** **Route and Regimen**	**Sex (M/F)** **Mean Age (Range)** **Race**	**Principal Inclusion Criteria**	**Other Assessments**
TH9507/III/LIPO/010 (main) 43/ US, Canada 30 Jun 2005-30 Apr 2007 followed by 26-week Extension	Placebo: 137/115/22 Tesamorelin 2 mg/day: 273[a]/211/62 26-week, randomized, double-blind, placebo-controlled, parallel-group	Percent change from baseline to Week 26 in VAT Placebo sc, Tesamorelin 2 mg/day sc	410 (352/58) 47.7 y (28-65) 308(75%) Caucasian, 2 (<1%) Asian, 59 (14%) Black, 34 (8%), Hispanic, 7 (2%) Other	HIV-associated lipodystrophy subjects 18-65 years of age, inclusive, on stable ART regimen for at least 8 weeks with a CD4 cell count > 100 cells/mm^3, a viral load < 10,000 copies/mL, and a BMI > 20 kg/m^2	Belly appearance distress score, TG,TC:HDL-C ratio, non-HDL-C, IGF-1, trunk fat, total fat, limb fat, SAT, LBM, anthropometric measurements, TC, HDL-C
TH9507/III/LIPO/010 (extension) 43/ US, Canada 30 Jun 2005-30 Apr 2007 preceded by a 26-	T-T: 155/129/25 T-P: 52[c]/40/10 P-T: 115[d]/87/24 26-week, randomized, double-blind,	52-Week safety Tesamorelin 2 mg-Tesamorelin 2 mg Tesamorelin 2 mg-Placebo Placebo-Tesamorelin 2 mg	315 (275/40) 47.9 y (29-65) 244(77%) Caucasian, 2 (1%) Asian, 39 (12%) Black, 25 (8%)	Subjects who completed TH9507/III/LIPO/010 (main) with a FBG ≤ 150 mg/dL	VAT, belly appearance distress score, TG, TC:HDL-C ratio, non-HDL-C, IGF-1, trunk fat, total fat, limb

week Main Phase	placebo-controlled, parallel-group		Hispanic, 5 (2%) Other		fat, SAT, LBM, anthropometric measurements, TC, HDL-C
TH9507-CTR-1011 48[e]/ US, Canada, Europe (UK, France, Spain, Belgium) 28 Feb 2007- 15 Apr 2008	Placebo: 126[f]/92/34 Tesamorelin 2 mg[g]/day: 270 /202/68 26-week, randomized, double-blind, placebo-controlled, parallel-group	Percent change from baseline to Week 26 in VAT Placebo sc, Tesamorelin 2 mg/day sc	396 (333/63) 47.7 y (27-65) 305(77%) Caucasian, 3 (1%) Asian, 46 (12%) Black, 35 (9%), Hispanic, 7 (2%) Other[g]	HIV-associated lipodystrophy subjects 18-65 years of age, inclusive, on stable ART regimen for at least 8 weeks with a CD4 cell count > 100 cells/mm^3, a viral load < 10,000 copies/mL, and a BMI > 20 kg/m^2	Belly appearance distress score, TG, TC:HDL-C ratio, non-HDL-C, trunk fat, total fat, limb fat, SAT, LBM, IGF-1, anthropometric measurements, TC, HDL-C
TH9507-CTR-1012 40h/ US, Canada, Europe (UK, France, Spain, Belgium) 30 Aug 2007- 22 Oct 2008	T-T: 92/80/12 T-P: 86i/63/22 P-T: 86/72/14 26-week, extension, randomized, double-blind, placebo-controlled, parallel-group	52-Week safety Tesamorelin 2 mg-Tesamorelin 2 mg Tesamorelin 2 mg-Placebo Placebo-Tesamorelin 2 mg	263 (234/29) 48.3 y (29-65) 218 (83%) Caucasian, 2 (1%) Asian, 21 (8%) Black, 19 (7%) Hispanic, 3 (1%) Other[g]	Subjects who completed TH9507-CTR-1011 with a FBG ≤ 150 mg/dL	VAT, belly appearance distress score, triglycerides, TC:HDL-C ratio, non-HDL-C, trunk fat, total fat, limb fat, LBM, SAT, IGF-1, anthropometric measurements, TC, HDL-C

TH9507/II/LIPO/008 7/ US, Canada 12 May 2003- 23 Feb 2004	Placebo: 21/16/5 Tesamorelin 1 mg/day: 19/17/2 Tesamorelin 2 mg/day: 21/15/6 12-week, randomized, double-blind, placebo-controlled, parallel-group	Change from baseline in VAT (at Week 6,Week 12, and last observation), Change from baseline in the trunk-to-limb fat ratio (at Week 6, Week 12, and last observation) Placebo sc, Tesamorelin 1 mg/day sc, Tesamorelin 2 mg/day sc	61(54/7) 45.7 y (32-60) 50(82%) Caucasian, 0 Asian, 4 (7%) Black, 6 (10%) Hispanic, 1 (2%) Other	HIV-associated lipodystrophy subjects as assessed by a waist circumference ≥ 95 cm (M) and 94 cm (F) and a waist-to-hip ratio ≥ 0.94 (M) and 0.88 (F), 18-65 years of age, inclusive, on stable HAART regimen for at least 8 weeks with a CD4 cell count > 100 cells/mm^3, a viral load < 10,000 copies/mL, and a BMI > 20 kg/m^2	TC:HDL-C ratio, non-HDL-C, TG, trunk fat, IGF-1, LBM, SAT, TC, HDL-C, non-HDL-C

CD4 = Cluster of differentiation 4; CT = computed tomography; BMI = body mass index; F = female; HAART = Highly Active Antiretroviral Therapy; IGF-1 = insulin-like growth factor-1; LBM = lean body mass; M = male; SAT: subcutaneous adipose tissue.

aTwo additional subjects (tesamorelin 2 mg) were randomized but never received study drug.

bOne additional subject was randomized but never received study drug.

cTwo additional subjects were randomized but never received study drug.

dFour additional subjects were randomized but never received study drug.

eTwo of the 48 sites withdrew participation after enrolling subjects.

fEight additional subjects (5 tesamorelin 2 mg and 3 placebo) were randomized but never received study drug.

gIncluded American Indian/Alaska Native and Native Hawaiian/Other Pacific Islander.

hOne of the 40 sites withdrew participation after enrolling subjects. iOne additional subject was randomized but never received study drug.

Pharmacokinetics

The tesamorelin formulation was selected on the basis of preclinical pharmacology studies. Data from seven PK and two DDI studies in man have been provided; six of the PK studies were conducted in healthy volunteers and one in HIV patients. Four of the PK studies were single-dose and three multiple-dose studies (dose range 0.02 to 2 mg). The bioanalytical methods used in the core studies appear to be adequately validated; pharmacokinetic data from earlier trials however are of limited value for the PK assessment, since the assays used for tesamorelin were not validated and lacked selectivity. A preplanned population PK analysis in the pivotal Phase 3 trial TH9507/III/LIPO/010 has not been performed and PK data are limited to 14 days of continuous exposure. Validated PK data for tesamorelin are limited to 1 and 2 mg sc daily exposure. Pharmacokinetic data analyses and statistical analyses are described in the individual study synopses and are appropriate.

PK parameters following sc administration in the core study TH9507-CTR-1016 in healthy volunteers are summarised in table 4.

Table 4. Pharmacokinetic Parameters (N=12) for Tesamorelin 2 mg in Healthy Volunteers

Parameters		Day 1					Day 14				
		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	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	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	828.54	611.21	73.77	665.71	78.63
$AUC_{t/inf}$ *	(%)	92.71	4.75	5.12	-	-	84.35	9.83	11.65	-	-
C_{max}	(pg/mL)	3076.4	1027.5	33.40	2874.6	43.87	1843.2	615.6	33.40	1744.9	36.54
T_{max}	(h)	0.147	0.052	35.05	-	-	0.150	0.043	28.43	-	-
T_{max} **	(h)	0.150	0.063	-	-	-	0.150	0.013	-	-	-
K_{el} §	(h^{-1})	5.3507	2.7280	50.98	-	-	2.9734	1.8073	60.78	-	-
$T_{½ el}$ §	(h)	0.21	0.22	108.07	-	-	0.43	0.42	98.93	-	-
Cl/F *	(L/(h•kg))	48.97	30.17	61.61	-	-	50.29	29.82	59.30	-	-
V_d/F *	(L/kg)	9.39	3.06	32.62	-	-	22.32	22.90	102.58	-	-

Reference: Module 2.7.2, Table 8

* For these parameters, N=11.

** Median and interquartile ranges are also presented.

"-" = Not applicable.

‡ For this parameter, N=12 for Day 1 and N=11 for Day 14.

§ For these parameters, N=11 for Day 1 and N=12 for Day 14.

Absolute bioavailability of tesamorelin was estimated to be low, with less than 4%. No bioequivalence data have been provided for this application which is acceptable since the intended marketing formulation is identical to that used for the relevant clinical studies. As tesamorelin is administered sc no studies were performed to evaluate the effect of food on tesamorelin PK which is considered acceptable. The volume of distribution appears to increase with consecutive tesamorelin sc injections and dose dependent. Plasma protein binding studies have not been performed, since tesamorelin is a cationic peptide that is expected to have a high degree of non-specific binding to plasma proteins. Elimination half life of tesamorelin is rapid and appears to increase with continuous dosing. Classic preclinical distribution, metabolism and excretion studies have not been performed as the metabolic pathway is generally understood for peptides, with tesamorelin expected to undergo degradation to small peptides and individual amino acids. However the applicant is still requested to discuss this issue further. In vitro biodegradation studies suggest that tesamorelin is more stable than its endogenous counterpart, hGRF, in human plasma.

The potential for genetic polymorphism in DPP-IV to affect the pharmacokinetics of tesamorelin is low, as based on ex-vivo studies, tesamorelin is more resistant to DPP-IV mediated degradation compared to endogenous GHRH, such that metabolism is more mediated by other endogenous proteases.

The limited data on dose proportionality do not allow a definite conclusion. Nevertheless no further relevant information for the current application is expected from an extended investigation of dose proportionality and thus no additional data are requested. From the limited data available Cmax and AUC appear to increase proportionally with the tesamorelin doses of 1 and 2 mg. Information on whether tesamorelin exhibits time dependant pharmacokinetics is also insufficient. Data including those in the target population are limited to 14 days of continuous exposure.

The applicant provided a brief discussion on the available pharmacokinetic data and a post-hoc Population PK and PD analysis. From the latter the applicant concludes that although PK data are only available for up to 14 days of exposure these are stable from both a dose and a time perspective and that accumulation is minimal. Furthermore the applicant argues that PD, efficacy and safety data do

not indicate accumulation. While in the context of the preclinical findings in dogs it is unfortunate that no PK data over a longer time period have been obtained, it is agreed that the available PD, efficacy, and safety data do not suggest an accumulation and thus no further PK data are requested. However, the preclinical aspects regarding accumulation of tesamorelin in the dog study at 52 weeks have so far not sufficiently been elucidated. Thus, this aspect has to be adequately reflected in the RMP.

Pharmacokinetics in the target population is summarised in the table, they are derived from the Phase 1 Study TH9507-CTR-1015 in HIV-infected patients. PK parameters were comparable between healthy volunteers and HIV patients. In both populations, a decrease in AUC_{0-t} and, to a greater extent in C_{max} was observed after 14 days of administration of 2 mg tesamorelin comparatively to Day 1. However, this period effect characterized by a decrease in C_{max} and AUC_{0-t} seems to not be reflected in IGF-1 production. Data from the preplanned population analysis in the pivotal trial TH9507/III/LIPO/010 during the first 26 weeks of exposure to assess pharmacokinetics in the target population have not been provided and it remains open whether this is due only to an unexpected low number of data from patients on tesamorelin or at least in part also to an inadequate handling and analysis of blood samples.

Table 5. Pharmacokinetic Parameters for Tesamorelin 2 mg in HIV-infected Patients

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	1149.5	1008.70	87.75	852.8	91.87	1117.2	953.40	85.34	794.6	108.59
AUC_{0-inf}	(pg·h/mL	1255.4	1104.49	87.98	933.3	90.94	1312.6	1124.19	85.65	940.4	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.	48.89	2333.3	1185.0	50.78	2013.	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	104.7	-	-	0.63	0.61	96.54	-	-
Cl/F	(L/(hr·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	-	-

Reference: Module 2.7.2, Table 18.

* Median and interquartile ranges are also presented.

"-" = Not applicable.

The inter-individual variability is high, especially for AUC, and the intra-individual variability is considered moderate.

Regarding pharmacokinetics in special populations the discussion provided is still too limited. The applicant is requested to provide more detailed information on PK parameters of tesamorelin in special populations and discuss these adequately.

The absence of i*n vitro* pharmacokinetic drug interaction studies is considered acceptable. However, as growth hormone had been shown *in vitro* to increase the clearance of CYP 3A4 substrates, the applicant performed 2 studies to investigate the effect of tesamorelin on the PK profile of simvastatin and ritonavir. An approximate 10% reduction was seen in simvastatin AUC following dosing with tesamorelin for 7 days, and ritonavir AUC and C_{max} were reduced by around 10%. These data indicate that metabolism of simvastatin appears not to be clinically significantly influenced by tesamorelin administration. Regarding ritonavir the predefined acceptance criteria were met for AUC, but for C_{max} were slightly outside the CI; all point estimates were around 90%.

Regarding products that influence the release of growth hormone, the applicant has not discussed the concomitant administration of other substances which may influence the release of growth hormone as part of their secondary pharmacology – e.g. levodopa and propranolol. As treatment may reduce glucose intolerance, the potential interaction with anti-diabetic drugs or other drugs causing hyperglycaemia also needs to be considered. Further discussion and an amendment of the SmPC are required.

Regarding exposure relevant for the safety evaluation mean (SD) C_{max} and $AUC_{0\text{-}inf}$ on day 14 of 2 mg once daily sc continuously for 14 days were 1843.2 pg/mL (615.6) and 828.54 pg·h/mL (611.21) in healthy volunteers and 2333.3 pg/mL (1185.0) and 1312.60 pg·h/mL (1124.19) in HIV patients.

Pharmacodynamics

Pharmacodynamic parameters measured as GH or IGF-1 response were determined in healthy volunteers and HIV patients in six Phase 1 studies (see table below). In studies TH9507-CTR-1016 and TH9507-CTR-1015 PD parameters were estimated after both single and multiple doses of 1 or 2 mg/day, and in study TH9507/I/PKPD/009 after both 2 mg once and twice daily. In Phase 2 and Phase 3 clinical studies IGF-1 was used as a surrogate endpoint of the biological activity of tesamorelin.

Regarding the mechanism of action although data indicate that administration of GH to HIV-infected patients with lipodystrophy results in reduced visceral adipose tissue and trunk fat, no adequate data have been provided that a selective decrease in visceral adipose tissue in this proposed patient population results in an improvement in cardiovascular morbidity or mortality.

For the primary pharmacodynamic parameter growth hormone the applicant provided a concentration-time profile of mean GH concentration from core study TH9507-CTR-1016; although blood samples were taken every 20 min for the first two hours, every 30 min for the third hour, and every hour thereafter, the GH concentration-time profiles do not indicate a pulsatile pattern of GH secretion.

Since, according to the applicant, the rationale for using tesamorelin instead of rGH in the proposed indication is the induction of a more physiological pulsatile GH secretion, the applicant should either demonstrate the asserted pulsatile GH secretion with tesamorelin applications using a PD trial with adequate blood sampling intervals or should clearly state that this has not been demonstrated.

Regarding the primary pharmacodynamic parameter IGF-1 the applicant generally states that the increased levels associated with tesamorelin treatment remained within the physiological range of young adults. However, the study participants had a mean age of about 50 years and the reference values for IGF-1 at this age are around half those in young adults.

No ethnic differences in response are evident on the limited data available. No further information on genetic differences in PD response is provided, however the literature regarding GH does not indicate genetic differences in the PD response

Discussion on clinical pharmacology

Absolute bioavailability of tesamorelin was estimated to be low (< 4%). The volume of distribution appears to increase with consecutive tesamorelin sc injections and dose dependant. Plasma protein binding studies have not been performed, which is considered acceptable since tesamorelin is a cationic peptide that is expected to have a high degree of non-specific binding to plasma proteins. Elimination half life of tesamorelin is rapid and appears to increase with continuous dosing. Classic preclinical distribution, metabolism, and excretion studies have not been performed and no clinical data on tesamorelin excretion and metabolism have been provided,

The metabolic pathway is generally understood for peptides, with tesamorelin expected to undergo degradation to small peptides and individual amino acids. However the applicant is still requested to discuss this issue further

In vitro biodegradation studies have demonstrated that tesamorelin is more stable in human plasma than hGRF. The limited data on dose proportionality do not allow a definite conclusion, but no information relevant for the current application is expected from an extended investigation of dose proportionality and thus no additional data are requested. From the limited data available C_{max} and AUC appear to increase proportionally with tesamorelin doses of 1 and 2 mg. The inter-individual variability is high, especially for AUC; the intra-individual variability is considered moderate. Information on whether tesamorelin exhibits time dependant pharmacokinetics is also insufficient.

Pharmacokinetics in the target population are derived from a Phase 1 Study in HIV-infected patients; PK parameters were comparable to those from healthy volunteers. In both populations, a decrease in AUC_{0-t} and, to a greater extent in C_{max} was observed after 14 days of administration of 2 mg tesamorelin comparatively to Day 1. However, this period effect seems to not be reflected in IGF-1 production. Data from the preplanned population PK analysis have not been provided and it remains open whether this is due only to an unexpected low number of data from patients on tesamorelin or at least in part also to an inadequate handling and analysis of blood samples.

Regarding pharmacokinetics in special populations the discussion is still limited. Regarding the effect of gender, ethnicity, weight and age, the applicant only focuses on the fact that tesamorelin is not a CYP substrate, which is again too simplistic. The available PK data by gender, ethnicity and weight should be presented as requested. Regarding the elderly, the applicant might comment on any PK data in the elderly across its wider tesamorelin program.

The absence of i*n vitro* pharmacokinetic drug interaction studies is considered acceptable. Regarding *in vivo* DDI the provided data indicate that metabolism of simvastatin is not influenced by tesamorelin administration. Regarding DDI with ritonavir the predefined acceptance criteria for bioequivalence / no influence were met for AUC, but for C_{max} were slightly outside the CI and all point estimates were around 90%.

Regarding products that influence the release of growth hormone, the applicant has not discussed the concomitant administration of other substances which may influence the release of growth hormone as part of their secondary pharmacology, as well as the potential interaction with anti-diabetic drugs or other drugs causing hyperglycaemia (treatment may reduce glucose intolerance). Further discussion and an amendment of the SmPC are required.

Pharmacodynamic parameters measured as GH or IGF-1 response were determined in healthy volunteers and HIV patients in Phase 1 studies and in Phase 2 and 3 clinical studies IGF-1 was used as a surrogate PD endpoint of the biological activity of tesamorelin. Regarding the mechanism of action although data indicate that administration of GH to HIV-infected patients with lipodystrophy results in reduced VAT and trunk fat, no adequate data have been provided that a selective decrease in VAT in this patient population results in an improvement in cardiovascular morbidity or mortality.

For the primary pharmacodynamic parameter GH the applicant provided concentration-time profiles of mean GH concentration; although blood samples were taken every 20 min for the first two hours, every 30 min for the third hour, and every hour thereafter, the GH concentration-time profiles do not indicate a pulsatile pattern. Since, according to the applicant, the rationale for using tesamorelin instead of GH in the proposed indication is the induction of a more physiological pulsatile GH secretion, either demonstration of the asserted pulsatile GH secretion with tesamorelin applications is requested or the applicant should clearly state that this has not been demonstrated. Regarding the primary pharmacodynamic parameter IGF-1 the applicant generally states that the increased levels associated

with tesamorelin treatment remained within the physiological range of young adults. However, the study participants had a mean age of about 50 years and the reference values for IGF-1 at this age are around half those in young adults.

Conclusions on clinical pharmacology

The clinical pharmacology data are still not considered sufficient. Regarding pharmacokinetics in special populations the available PK data by gender, ethnicity and weight should be presented as requested and regarding the elderly, the applicant might comment on any PK data in the elderly across its wider tesamorelin program.

Regarding the mechanism of action although data indicate that administration of GH to HIV-infected patients with lipodystrophy results in reduced VAT and trunk fat, no adequate data have been provided that a selective decrease in VAT in this patient population results in an improvement in cardiovascular morbidity or mortality.

For the primary pharmacodynamic parameter GH the applicant is requested to either demonstrate the asserted pulsatile GH secretion with tesamorelin applications or clearly state that this has not been demonstrated.

The applicant should also provide further discussion regarding products that influence the release of growth hormone as part of their secondary pharmacology, as well as the potential interaction with anti-diabetic drugs or other drugs causing hyperglycaemia.

Clinical efficacy

The first clinical pharmacology studies in humans were primarily aimed at evaluating the PD response, to establish dose response curves and to obtain preliminary PK data.

In the Phase 2 study TH9507/II/LIPO/008 in HIV-infected patients with excess abdominal fat in which subjects were randomized to either placebo, tesamorelin 1 mg or 2 mg for 12 weeks administration of tesamorelin 1 and 2 mg sc daily for 12 weeks was associated with significant increases from baseline in IGF-1 levels (52.5% vs. 65.8% for 1 mg vs. 2 mg tesamorelin; p = 0.13). In addition to inducing a higher increase in IGF-1 levels, the 2 mg dose resulted in a greater decrease in VAT (-12.0, -11.9, -21.5 cm2 for placebo, 1 mg, 2 mg, respectively; p = 0.03 vs. baseline for 2 mg). Consistent with this observation, a dose-related decrease in trunk fat was observed (-0.5 kg and -1.1 kg for 1 and 2 mg, respectively; p-value non significant 1 mg vs. placebo, p = 0.014 for 2 mg vs. placebo). Other effects of the 2 mg tesamorelin dose included no significant changes in limb fat and SAT, an increase in LBM (-0.5 kg, 0.7 kg, and 1.7 kg for placebo, tesamorelin 1 mg, 2 mg, respectively; p = 0.002 for tesamorelin 2 mg vs. placebo), and a reduction in TG levels and the TC/HDL-C ratio.

Based on these results as well as the overall clinical pharmacology of tesamorelin, the applicant selected the 2 mg dose for the Phase 3 clinical program. The provided dose finding data are considered rather limited. The dose finding has primarily been orientated at the PD parameter IGF-1. However, pharmacodynamic as well as the safety data cast considerable doubt on whether the chosen dose of 2 mg tesamorelin sc per day is appropriate regarding safety.

There are two pivotal phase III studies. Study LIPO/010 and the later study CTR-1011 both had a 26-week main study period and were randomised double-blind comparisons of tesamorelin 2 mg once daily versus placebo in HIV patients with excess abdominal fat. Tesamorelin 2mg or matched placebo were given by subcutaneous injection in the abdomen every morning.

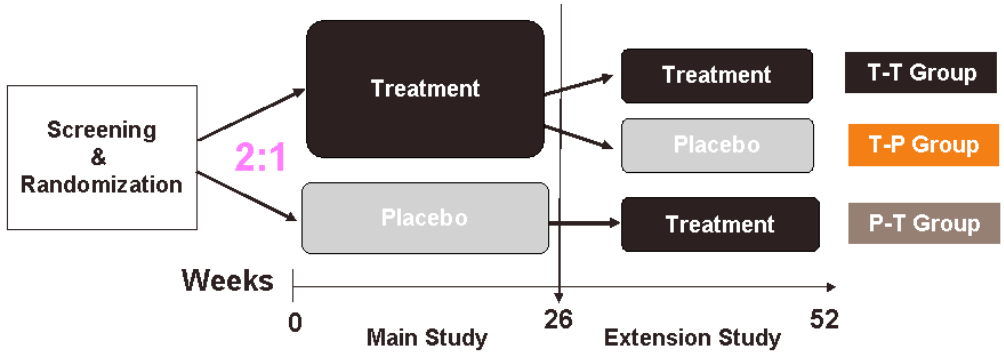
Both studies had an extension phase, in which some patients remained on tesamorelin, some patients on tesamorelin switched to placebo, and patients on placebo switched to tesamorelin.

For study CTR-1011 the extension phase was given a separate protocol number of CTR-1012, the report of study LIPO/010 covers both the main and extension phases.

The studies had the same treatment arms, primary endpoint and schedule of assessments, with some differences in secondary endpoints and the design of the extension phase. As the studies are so similar the common design features are summarised below, with any significant differences highlighted

Both studies had a main phase in which subjects were randomised 2:1 for tesamorelin 2 mg vs. placebo. In both studies, patients completing the main study and with fasting blood glucose of ≤ 150 mg/dL could enter a 26 week extension phase. In study LIPO/010 patients who received tesamorelin in the main phase were randomized in a 3:1 ratio to receive tesamorelin or placebo respectively in the extension phase, whereas patients who received placebo in the main phase were automatically switched to receive tesamorelin in the extension phase. In study CTR-1012 (the extension phase of study CTR-1011) the design was the same; except that patients who received tesamorelin in the main phase were randomized in a 1:1 ratio to receive either tesamorelin or placebo in the extension phase (see Figure 2).

Figure 2. Design of phase III studies.



Dose-response studies and main clinical studies

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 6. Summary of Efficacy for trial TH9507/III/LIPO/010

Title: A Phase 3 Multicenter, Double-blind, Randomized, Placebo-controlled Study Assessing the Efficacy and Safety of a 2 mg Dose of TH9507, a Growth Hormone Releasing Factor Analog, in HIV Patients with Excess of Abdominal Fat Accumulation		
Study identifier	TH9507/III/LIPO/010	
Design	Multicenter, Double-blind, Randomized, Placebo-controlled, with a main phase randomized in a 2:1 ratio (tesamorelin versus placebo) and an extension phase where patients initially receiving tesamorelin re-randomized in a 3:1 ratio and patients initially receiving placebo were switched to tesamorelin.	
	Duration of main phase:	26 Weeks
	Duration of Run-in phase:	not applicable
	Duration of Extension phase:	26 Weeks
Hypothesis	Superiority	

Treatments groups	Main Phase : Active	2 mg tesamorelin, 26 weeks, 275 randomized
	Main Phase: Placebo	Placebo, 26 weeks, 137 randomized
	Extension phase	Of the 211 patients who received tesamorelin and completed the main phase, 207 patients were randomized into the extension phase; 3 patients did not receive any study treatment. Tesamorelin- Tesamorelin (T-T): 154 Tesamorelin- placebo (T-P): 50 Of the 115 patients who received placebo and completed the main phase, 111 patients switched from placebo to tesamorelin (P-T)
Endpoints and definitions	Primary Efficacy Endpoint	Percent change in VAT from baseline to Week 26 in the tesamorelin group compared to the placebo group. The minimum difference needed in order to detect a clinically relevant difference between tesamorelin and placebo was 8%.
	Ranked Secondary Efficacy Endpoints:	Changes from baseline to Week 26 in Patient Reported Outcome (PRO), specifically, belly appearance distress, triglycerides level, and total cholesterol:HDL-C ratio.
	Other Secondary Efficacy Endpoints:	Changes from baseline to Week 26 in IGF-1 serum level and further PRO related to body image (e.g. belly size evaluation and belly profile).
Database lock	August 17, 2007	

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat: 26 Weeks		
Descriptive statistics and estimate variability	Treatment group	Tesamorelin	Placebo
	Number of subject	273	137
	% Change in VAT After 26 Weeks	N=272 -15.1 %	N=136 +5%
	PRO Belly Distress	N=272 11.6	6.2
	Triglycerides (mg/dL) Change from baseline to Week 26	-50.3	+9.01
	Total Cholesterol : HDL-C Ratio Change from baseline to Week 26	-0.311	+0.212

Effect estimate per comparison	% Change VAT	Comparison groups	Tesamorelin –Placebo (estimate from ANCOVA)
		% Change in VAT	-20
		95% CI	[-24, -15]
		P-value	<0.001
	Change in PRO Belly Appearance Distress	Comparison groups	Tesamorelin –Placebo (estimate from ANCOVA)
		Change	-5.4
		95% CI	N/A
		Primary analysis p-value (ANCOVA) Supportive analysis: p-value (Ranked ANCOVA)	0.076 0.028
	Change in Triglycerides (mg/dL) Week 26 Change from Baseline	Comparison groups	Tesamorelin –Placebo (estimate from ANCOVA)
		Change	-59.31
		95% CI*	NR
		p-value	<0.001
	Change in Total Cholesterol : HDL-C Ratio	Comparison groups	Tesamorelin –Placebo (estimate from ANCOVA)
		Change in Total Cholesterol : HDL-C Ratio	-0.523
		95 % CI*	N/A
		p-value	<0.001

Table 7. Summary of Efficacy for trial TH9507/III/LIPO/1011-1012

Title: **TH9507-CTR-1011** A Multicentre, Double-Blind, Randomized, Placebo-Controlled Study Assessing the Efficacy and Safety of a 2 mg Dose of TH9507, a Growth Hormone Releasing Factor Analog, in HIV Patients with Excess Abdominal Fat Accumulation **TH9507-CTR-1012** A Multicentre, Double-blind, Randomized, Placebo-Controlled Extension Study Assessing the Efficacy and Long-Term Safety of a 2 mg dose of TH9507, a Growth Hormone-Releasing Factor Analog, in HIV Subjects with Excess Abdominal Fat Accumulation		
Study identifier	TH9507-CTR-1011 , TH9507-CTR-1012	
Design	Multicentre, Double-blind, Randomized, Placebo-controlled, with a main phase randomized in a 2:1 ratio (tesamorelin versus placebo) (TH9507 CTR-1011) and an extension phase where subjects initially receiving tesamorelin re-randomized in a 1:1 ratio and subjects initially receiving placebo were switched to tesamorelin (TH9507 CTR 1012).	
	Duration of main phase:	26 Weeks
	Duration of Run-in phase:	not applicable
	Duration of Extension phase:	26 Weeks
Hypothesis	Superiority	
Treatments groups	Main Phase : 404 randomized	2 mg tesamorelin, 26 weeks, 275 randomized
	Main Phase: Placebo	Placebo, 26 weeks, 129 randomized
	Extension phase	Of the 202 patients who received tesamorelin and completed the main phase, 178 were randomized; 92 patients were randomized to receive tesamorelin (T-T) and 86 were randomized to receive placebo (T-P). Of the 92 who received placebo and completed the main phase, 86 were switched to tesamorelin (P-T).

Endpoints and definitions	Primary Efficacy Endpoint	TH9507-CTR-1011 The primary objective was to evaluate the reduction in visceral adipose tissue (VAT) after 26 weeks of treatment with 2 mg/day tesamorelin compared to placebo. TH9507-CTR-1012 • To assess the 52-week safety of 2 mg daily doses of tesamorelin; • To assess the duration of effect on visceral adipose tissue (VAT), trunk fat and lipid profile; • To collect data on efficacy after a 52-week treatment with 2 mg/day tesamorelin.
	Ranked Secondary Efficacy Endpoints	TH9507-CTR-1011 Changes from baseline to Week 26 in Patient Reported Outcome (PRO), specifically, belly appearance distress, triglycerides level, and total cholesterol:HDL-C ratio.
	Other Secondary Efficacy Endpoints	(1) to evaluate changes from baseline to Week 26 in IGF-1 serum level and further PRO related to body image (e.g. belly size evaluation and belly profile).and (2) to evaluate the safety of tesamorelin 2 mg/day as compared to placebo after 26 weeks of treatment.
Database lock	November 24, 2008	

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat: 26 Weeks		
Descriptive statistics and estimate variability	Treatment group	Tesamorelin	Placebo
	Number of subject	268	126
	% Change in VAT After 26 Weeks	-10.9	-0.621
	PRO Belly Appearance Distress	N=269 8.4	5.2
	Triglycerides (mg/dL) Change from baseline Week 26	N=270 -22.1	3.44
	Total Cholesterol : HDL-C Ratio Change from baseline Week 26	N=270 -0.0505	0.146

Effect estimate per comparison	% Change VAT	Comparison groups	Tesamorelin –Placebo (estimate from ANCOVA)
		% Change in VAT	-12%
		95% CI	[-16, -7]
		P-value	<0.001
	Change in PRO Belly Appearance Distress	Comparison groups	Tesamorelin –Placebo (estimate from ANCOVA)
		Change	-3.1
		95% CI	N/A
		Primary analysis: p-value (Ranked ANCOVA) Supportive analysis: p-value (ANCOVA)	0.022 0.083
	Change in Triglycerides (mg/dL) Week 26 Change from Baseline	Comparison groups	Tesamorelin –Placebo (estimate from ANCOVA)
		Change	-25.54
		95% CI	N/A
		p-value	0.102
	Change in Total Cholesterol : HDL-C Ratio	Comparison groups	Tesamorelin –Placebo (estimate from ANCOVA)
		Change in Total Cholesterol : HDL-C Ratio	-0.1965
		95 % CI	N/A
		p-value	0.097

Main studies

The primary objective of the main 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 use of placebo as the only comparator in the pivotal studies is appropriate as there is no licensed drug treatment in the proposed indication. The applicant has not considered the inclusion of a treatment arm involving patients switching to a HAART regimen with less propensity to visceral fat accumulation (this was highlighted in previous CHMP advice to the applicant), but given the absence of strong evidence that a switch could be beneficial in managing a side effect (lipohypertrophy) of an efficient HAART treatment, it could have been difficult to justify taking the risk of potentially affecting the virological status of the tesamorelin study subjects.

The applicant has provided some arguments as to why diet and exercise were not included in a comparator arm, but has not considered the consequences of having no inclusion criteria based on failure to improve with intensive diet and exercise. This is an important outstanding issue in the benefit/risk balance.

Whereas increased VAT is well-recognized to be related to insulin resistance and to contribute to an increased cardiovascular risk, a selective reduction in visceral adipose tissue, not accompanied by other metabolic improvements, has so far not been shown to translate into a clinically meaningful effect, e.g. reduction in cardiovascular morbidity or mortality. It is not clear if a single slice CT scan, as used in the pivotal studies for the assessment of abdominal adiposity results in precise values. According to a study by *Ellis KJ et al*, significant errors in the adiposity estimates can not be excluded and therefore multi-slice protocols should be preferred. A decrease by at least 8% was determined to be the minimum difference needed to detect a difference between placebo and tesamorelin. The underlying rationale for this threshold has not been presented and becomes neither clear from review

of literature data. Hence, it appears arbitrary and lacks the proof of clinical relevance. So the secondary efficacy endpoints are pivotal to the assessment.

The secondary efficacy objectives included improvement in blood lipids (triglycerides, total cholesterol:high density lipoprotein-cholesterol [HDL-C] ratio), improvement in Patient reported Outcomes (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 PRO questionnaire, the Body Image Impact Module (BIIM), a specific tool, exclusively developed for the condition investigated (i.e. HIV-associated adipose redistribution syndrome and more specifically visceral fat accumulation in HIV-infected patients). Validation of this tool has been reported.

Other study parameters included trunk fat, total fat, lean body mass, limb fat, anthropometric measures (e.g. hip-waist ratio), LDL-C and non-HDL-C.

For labelling purposes a gatekeeper approach was applied (see "secondary endpoints").

The extension phases were designed to assess long-term safety and explore durability of effects with continuous therapy and the duration of effects following end of treatment.

The main efficacy analysis was done at 6 months, which is considered the absolute minimum for the proposed indication, especially as any therapy would be required long term. Whilst there was a 6 month extension period in both pivotal studies, there is no comparator of patients staying on placebo for 1 year to better define the spontaneous course of lipohypertrophy and the placebo-subtracted effect. As noted below, the placebo response was in fact different between the 2 pivotal studies. Whilst there was no decline in any of the efficacy results after a year of tesamorelin treatment, the continuing acceptance of once-daily subcutaneous injections might have affected adversely the quality of life comparison to placebo, had a comparison at 1 year been done. Again, this was highlighted in previous CHMP scientific advice.

The main phase of the 2 pivotal studies included 550 subjects receiving tesamorelin and 266 receiving placebo. Taking into account the relatively low prevalence of the proposed indication this is adequate.

A number of protocol amendments were implemented, but none were considered to have affected the outcome of the studies.

Main Phase (0-26 Weeks)

Study TH9507-CTR-1011 and the Main Phase (first 26 weeks) of Study TH9507/III/LIPO/010 were both multicenter, randomized, parallel, double-blind, placebo-controlled studies to evaluate the efficacy and safety of tesamorelin (2 mg/day) in HIV infected subjects with excess abdominal fat.

The study population was subjects aged 18-65 with stable ART regimen and controlled CD4 count/ viral load, considered by the investigator to have abdominal fat accumulation due to HIV-associated lipodystrophy syndrome, with waist circumference ≥95 cm and waist: hip ratio ≥0.94 (males) or values of ≥ 94 cm and waist/hip ratio ≥ 0.88 respectively in females.

The threshold values for waist circumference and waist: hip ratios were chosen based on correlation with a VAT area of 130 cm2 (in subjects without HIV). In turn the applicant considers that a VAT level of 130 cm2 is associated with alterations in glucose, insulin and lipoprotein profile.

The applicant has not discussed how the inclusion criteria for waist circumference and waist:hip ratio correlate with VAT in the target population of HIV patients. Also, the applicant has not shown how these values correlate with cardiovascular risk in the target population. Furthermore, whilst the proposed indication is for the treatment of excess abdominal fat in HIV patient with lipodystrophy, there is no consensus definition of HIV-associated lipodystrophy, or what constitutes "excess"

abdominal fat in this condition. Neither from the inclusion criteria nor from the patients' baseline characteristics it is clear, how/if it was objectively differentiated between lipohypertrophy and obesity in HIV-infected patients.

Assessment may be difficult in practice as central fat accumulation is common in the general population, increasing with age. Finally, it is not clear how reliably waist circumference and WHR will be measured in routine clinical practice. Together, these issues raise a serious concern over the generalisability of the study results.

Notable exclusion criteria included ALT or AST ≥3 x ULN, serum creatinine >133 µmol/l, fasting blood glucose ≥8.33 mmol/l, fasting triglycerides >11.3 mmol/l, active malignancy and (with some exceptions) history of malignancy. Only patients with impaired glucose tolerance or diet-controlled type 2 diabetes were included in the phase III studies. The applicant has done a separate study in a limited number of diabetic patients. Restrictions were applied with respect to some medications, such as antihyperlipaemic agents, testosterone and other steroids, weight-loss agents of GH-related products. Additional exclusion criteria for the extension phases were history of non-compliance to medical regimen, and FBG >8.33 ml/L at week 26.

The exclusion of patients with renal and hepatic impairment has not been adequately addressed by the applicant and is still not fully reflected in the proposed SmPC. In particular the exclusion of patients with ALT/AST>3x ULN would exclude a significant number of HIV patients.

In both groups, the main reasons for early study discontinuation were adverse event (40.0% tesamorelin and 32.1% placebo) and consent withdrawal (33.1% tesamorelin and 33.9% placebo).

The overall early discontinuation rate was higher in Study TH9507-CTR-1011 (25.2%) than in Study TH9507/III/LIPO/010 (22.7%). The difference was largely driven by the higher discontinuation rate among placebo subjects in Study TH9507-CTR-1011 (27.0%) compared to Study TH9507/III/LIPO/010 (16.1%).

Of note, a greater proportion of tesamorelin than placebo subjects discontinued due to adverse event (41.9% vs. 27.3% of subjects who discontinued) and lack of compliance (12.9% vs. 0% of subjects who discontinued) from Study TH9507/III/LIPO/010. No notable difference between treatment groups was observed in the distribution of primary reasons for early study discontinuation in Study TH9507-CTR-1011 (table 10). This imbalance may point at an insufficient blinding of the trials – a concern, supported also by other indices, as further detailed in table 8.

Table 8. Subject Disposition - Main Phase ITT Population

	Study TH9507/III/LIPO/010		Study TH9507-CTR-1011		Combined results	
	Tesamorelin 2 mg/day (N=273)	Placebo (N=137)	Tesamorelin 2 mg/day (N=270)	Placebo (N=126)	Tesamorelin 2 mg/day (N=543)	Placebo (N=263)
Randomized subjects, N	275	137	275	129	550	266
ITT population[a] n (%)	273 (99.3)	137 (100.00)	270 (98.2)	126 (97.7)	543 (98.7)	263 (98.9)
Per protocol population[a] n (%)	208 (75.6)	105 (76.6)	194 (70.5)	92 (71.3)	402 (73.1)	197 (74.1)
Number of subjects who completed the main study[b] (first 6 months) n (%)						
Yes n (%)	211 (77.3)	115 (83.9)	202 (74.8)	92 (73.0)	413 (76.1)	207 (78.7)
No n (%)	62 (22.7)	22 (16.1)	68 (25.2)	34 (27.0)	130 (23.9)	56 (21.3)
Primary reason for discontinuation[c] n (%)						
Adverse event n (%)	26 (41.9)	4 (18.2)	26 (38.2)	12 (35.3)	52 (40.0)	18 (32.1)
Lack of compliance with protocol requirements and/or procedures n (%)	8 (12.9)	0	5 (7.4)	1 (2.9)	13 (10.0)	1(1.8)
Withdrawal of consent n (%)	19 (30.6)	12 (54.5)	24 (35.3)	7 (20.6)	43 (33.1)	19 (33.9)
Lost to follow-up n (%)	7 (11.3)	2 (9.1)	5 (7.4)	7 (20.6)	12 (9.2)	9 (16.1)
Others n (%)	1 (1.6)	4 (18.2)	8 (11.8)	7 (20.6)	9 (6.9)	9 (16.1)
P-value[d]					0.296	
P-value[e]					0.137/0.047	

a Percentages are based on the number of randomized subjects.

b Percentages are based on the number of subjects in ITT population.

c Percentages are based on the number of subjects who have discontinued prior to the end of the study

d From generalized linear model, to test the rates of primary reason for discontinuation between treatment groups, with treatment groups and Study included.

e From generalized linear model, to test the rates of primary reason for discontinuation between treatment groups, with treatment group, Study and Study-by-Treatment Group included. Treatment group/Study-by-treatment group p-values.

In the Main Phase studies, the tesamorelin and placebo groups showed similar demographics at baseline. The majority of individuals in these studies were male and White/Caucasian. The tesamorelin and placebo groups were also similar with respect to the various body measurements, such as weight, BMI, waist and hip circumferences, and waist:hip ratio (see table 9).

Table 9. Subject Demographics at Baseline - Main Phase ITT Population

	Study TH9507/III/LIPO/010		Study TH9507-CTR-1011		Combined Results	
	Tesamorelin 2 mg/day (N=273)	Placebo (N=137)	Tesamorelin 2 mg/day (N=270)	Placebo (N=126)	Tesamorelin 2 mg/day (N=543)	Placebo (N=263)
Age (years)						
Mean (SD)	47.3 (7.30)	48.3 (7.49)	47.7 (7.48)	47.7 (7.70)	47.5 (7.40)	47.9 (7.60)
Median	46.0	48.0	47.0	47.0	47.0	48.0
Range	28; 65	31; 65	27; 65	29; 65	27; 65	28; 65
P-value[a]	0.216		0.958		0.409	
P-value[b]					0.425/0.343	
Gender n (%)						
Male	237 (86.8)	115 (83.9)	228 (84.4)	105 (83.3)	465 (85.6)	220 (83.7)
Female	36 (13.2)	22 (16.1)	42 (15.6)	21 (16.7)	78 (14.4)	43 (16.3)
P-value[c]	0.454		0.770		0.463	
P-value[d]					0.452/0.720	
Ethnic origin n (%)						
White/ Caucasian	209 (76.6)	99 (72.3)	209 (77.4)	96 (76.2)	418 (77.0)	195 (74.1)
Asian	2 (0.7)	0	1 (0.4)	2 (1.6)	3 (0.6)	2 (0.8)
Black/ African-American	37 (13.6)	22 (16.1)	34 (12.6)	12 (9.5)	71 (13.1)	34 (12.9)
Hispanic	21 (7.7)	13 (9.5)	23 (8.5)	12 (9.5)	44 (8.1)	25 (9.5)
Other	4 (1.5)	3 (2.2)	3 (1.1)	4 (3.2)	7 (1.3)	7 (2.7)
P-value[c]	0.730		0.314		0.462	
P-value[d]					0.489/0.626	

Demographic data were available for all subjects in the ITT population.

a P-value from the 1-factor (treatment group) ANOVA for the individual studies. For the combined results, the pvalue for treatment group difference is from the 2-factor (treatment group and study) ANOVA.

b P-values for treatment difference from the 2-factor (treatment group, study and treatment group-by-study) ANOVA. / Study-by-treatment group p-value.

c P-values from a Fisher's exact test, for the individual studies. For the combined results, the p-value for treatment group difference is based on the generalized linear model (binomial or multinomial as appropriate), with treatment group and study in the model.

d P-values for treatment group difference from the generalized linear model (binomial or multinomial as appropriate), with treatment group, study, and treatment group-by-study in the model. / Study-by-treatment group p-value.

HIV- and lipodystrophy syndrome-related characteristics were generally similar between groups in Study TH9507-CTR-1011. In Study TH9507/III/LIPO/010, the tesamorelin group had slightly longer mean duration of ART compared to the placebo group (56.5 vs. 48.2 months, p=0.027). Further, the distribution of type of current ART regimen was significantly different between the tesamorelin and placebo groups (p=0.038).

Table 10. HIV- and Lipodystrophy Syndrome-related Characteristics at Baseline - Main Phase ITT Population

	Study TH9507/III/LIPO/010		Study TH9507-CTR-1011		Combined Results	
	Tesamorelin 2 mg/day (N=273)	Placebo (N=137)	Tesamorelin 2 mg/day (N=270)	Placebo (N=126)	Tesamorelin 2 mg/day (N=543)	Placebo (N=263)
Duration of ART (months)	n=272	n=136	n=270	n=126	n=542	n=262
Mean (SD)	56.6 (37.25)	48.4 (31.46)	53.0 (36.63)	52.9 (36.33)	54.7 (36.84)	50.4 (33.81)
Median	49.5	43.5	43.1	45.7	45.9	43.7
Range	6; 231	5; 154	4; 180	4; 147	4; 231	4; 154
P-value[a]	0.052		0.951		0.115	
P-value[b]					0.124/0.132	
Type of ART regimen n (%)[c]						
NRTI and NNRTI (with no PI)	111 (40.7)	37 (27.0)	79 (29.3)	39 (31.0)	190 (35.0)	76 (28.9)
NRTI, NNRTI, and PI	30 (11.0)	19 (13.9)	25 (9.3)	5 (4.0)	55 (10.1)	24 (9.1)
NRTI and PI (with no NNRTI)	114 (41.8)	66 (48.2)	125 (46.3)	61 (48.4)	239 (44.0)	127 (48.3)
NRTI alone	11 (4.0)	12 (8.8)	13 (4.8)	4 (3.2)	24 (4.4)	16 (6.1)
Other	7 (2.6)	3 (2.2)	28 (10.4)	17 (13.5)	35 (6.4)	20 (7.6)
P-value[d]	0.038		0.328		0.032	
P-value[e]					0.042/0.188	
Time since lipodystrophy syndrome diagnosis (months)	n=261	n=135	n=261	n=123	n=522	n=258
Mean (SD)	50.3 (39.6)	50.6 (40.0)	65.3 (43.3)	69.7 (42.6)	57.8 (42.10)	59.7 (42.28)
Median	45.2	47.4	59.8	66.3	50.7	55.0
Range	0; 223	0; 192	-5; 211	1; 259	-5; 223	0; 259
P-value	0.957		0.346		0.471[a]	
P-value[b]					0.459/0.504	
Lipodystrophy syndrome clinical assessment n (%)						
Facial lipoatrophy	141 (51.6)	70 (51.1)	123 (45.6)	56 (44.4)	264 (48.6)	126 (47.9)
Lower limbs lipoatrophy	165 (60.4)	81 (59.1)	148 (54.8)	72 (57.1)	313 (57.6)	153 (58.2)
Upper limbs lipoatrophy	140 (51.3)	58 (42.3)	117 (43.3)	57 (45.2)	257 (47.3)	115 (43.7)
General lipoatrophy[f]	198 (72.5)	99 (72.3)	181 (67.0)	83 (65.9)	379 (69.8)	182 (69.2)
Buffalo hump	116 (42.5)	63 (46.0)	93 (34.4)	44 (34.9)	209 (38.5)	107 (40.7)
Abdominal lipohypertrophy	273 (100)	137 (100)	270 (100)	126 (100)	543 (100)	263 (100)
Breast enlargement	111 (40.7)	60 (43.8)	105 (38.9)	39 (31.0)	216 (39.8)	99 (37.6)
Subjects with ≥1 of the following signs: general lipoatrophy, buffalo hump, or breast enlargement	242 (88.6)	125 (91.2)	222 (82.2)	101 (80.2)	464 (85.5)	226 (85.9)

a P-value from the Kruskal-wallis test for the individual studies. For the combined results, the p-value for treatment group difference is from the 2-factor (treatment group and study) ANOVA.

b P-values for treatment group difference are from the 2-factor (treatment group, study and treatment group-by-study) ANOVA./ Study-by-treatment group p-value.

c For type of ART regime, results from the ISE are presented.

d P-values from a Fisher's exact test, for the individual studies. For the combined results, the p-value for treatment group difference is based on the generalized linear model (specifying the distribution of the dependent variable as multinomial) with treatment group and study in the model.

e P-values for treatment group difference is based on the generalized linear model (specifying the distribution of the dependent variable as multinomial) with treatment group, study, and treatment group-by-study in the model. / Study-by-treatment group p-value.

f Defined as presenting at least 1 sign among facial, lower limbs, or upper limbs lipoatrophy.

Compliance was assessed by counting the returned vials. Unreturned vials were counted as having been used.

Primary Efficacy Endpoint

Mean VAT values at baseline were similar between the tesamorelin and placebo groups. After 26 weeks of treatment, the mean percent change from baseline in VAT was significantly greater in the tesamorelin group, as compared with a slight increase in the placebo group.

Mean changes were numerically smaller in both groups in Study TH9507-CTR-1011 (table 15).

At week 26, 53.4% of tesamorelin-treated patients and 34.1% of the patients in the placebo group were responders in study -011, for study -010 these figures are 61.4% and 25%.

Table 11. VAT - Actual and Percent Change from Baseline to Week 26 - Main Phase ITT Population

	Study TH9507/III/LIPO/010						Study TH9507-CTR-1011					
	Tesamorelin 2 mg/day (N=273)			Placebo (N=137)			Tesamorelin 2 mg/day (N=270)			Placebo (N=126)		
VAT - Percent Change from Baseline to Week 26												
Visit	**n**	**Mean (SD)**	**LSM**	**n**	**Mean (SD)**	**LSM**	**n**	**Mean (SD)**	**LSM**	**n**	**Mean (SD)**	**LSM**
Baseline VAT (cm^2)	272	178 (76.9)	---	136	171 (76.9)	---	268	186 (86.6)	---	126	195 (95.5)	---
Week 26 - % change	272	-15.1 (20.8)	-17.8	136	5.00 (23.4)	2.23	268	-10.9 (21.2)	-13.2	126	-0.62 (18.9)	-1.86
P-value[a]	<0.001						<0.001					

LSM = least square mean

a P-values are for treatment group difference.

The cumulative distribution function of the percent change in VAT from baseline to Week 26 demonstrated that a higher proportion of subjects in the tesamorelin group than in the placebo group showed a decrease in VAT over the 26-Week treatment period.

As detailed in the pooled analysis, the effect size is related to the baseline VAT value. The higher the baseline VAT the greater the absolute, however not the percent reduction with tesamorelin (see table 12).

Table 12. VAT - Actual and Percent Change from Baseline to Week 26 by VAT at Baseline (in quartiles) - Main Phase ITT Population

	Combined Results			
	Tesamorelin 2 mg/day (N=543)		Placebo (N=263)	
Subgroup	**n**	**Mean (SD)**	**n**	**Mean (SD)**
0-25th percentile				
Baseline VAT (cm^2)	133	87.14 (23.320)	68	88.26 (20.067)
Week 26				
Actual value (cm^2)	133	76.49 (27.684)	68	96.89 (34.929)
% change	133	-11.47 (23.204)	68	8.84 (28.587)
25th-50th				
Baseline VAT (cm^2)	132	144.27 (14.418)	68	143.34 (13.698)
Week 26				
Actual value (cm^2)	132	120.92 (31.211)	68	143.27 (29.927)
% change	132	-15.91 (20.922)	68	0.01 (19.736)
50th-75th				
Baseline VAT (cm^2)	136	199.92 (18.990)	65	202.52 (18.560)
Week 26				
Actual value (cm^2)	136	173.97 (46.542)	65	202.70 (41.025)
% change	136	-12.76 (22.395)	65	0.00 (17.620)
75th-100th				
Baseline VAT (cm^2)	139	292.45 (49.767)	61	309.83 (56.312)
Week 26				
Actual value (cm^2)	139	255.85 (65.241)	61	309.65 (72.197)
% change	139	-12.38 (17.705)	61	0.00 (16.441)

	Combined Results			
	Tesamorelin 2 mg/day (N=543)		Placebo (N=263)	
Subgroup	n	Mean (SD)	n	Mean (SD)
0-25th percentile				
Baseline VAT (cm^2)	133	87.14 (23.320)	68	88.26 (20.067)
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75th-100th				
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Week 26				
Actual value (cm^2)	139	255.85 (65.241)	61	309.65 (72.197)
% change	139	-12.38 (17.705)	61	0.00 (16.441)

In study LIPO/010, daily administration of 2 mg tesamorelin to HIV patients with excess abdominal fat accumulation for 26 weeks was associated with a *decrease* from baseline in VAT of 15.1%, as compared to an *increase* of 5% in the placebo group – a difference between groups of around 20%. In study CTR 1011, the decrease from baseline in VAT was less (-10.9%) compared with little change (decrease of 0.62%) in the placebo group, so the overall difference between treatment groups was around half that seen in the LIPO/010 study.

There is no clear rationale for the differences between studies in both treatment effect and placebo response. The difference in treatment effect cannot be easily explained by differences in baseline VAT (indeed the higher baseline VAT seen in study CTR1011 might have been expected to translate into a greater treatment effect) or the small differences in other baseline characteristics. It appears to be relevant that study CTR1011 included some European patients, whilst LIPO/010 was confined to the US and Canada.

In both studies, most of the effect occurred by the 13 week timepoint.

In isolation, the clinical relevance of the change in VAT remains uncertain and the key issue is whether this is associated with improvements in the secondary endpoints.

Secondary Efficacy Endpoints

Ranked Secondary Endpoints

After discussion with the US FDA (2007) to control the Type I error for ranked secondary endpoints, efficacy endpoints including belly appearance distress, triglycerides, total cholesterol to HDL-C ratio, and non-HDL-C, were identified within Study TH9507/III/LIPO/010 and Study TH9507-CTR-1011 as key secondary efficacy endpoints to be part of a gatekeeper strategy. In the gatekeeper strategy, any key secondary endpoints were considered for statistical significance only if the primary endpoint was found to be statistically significant. A secondary endpoint was considered for statistical significance only if the secondary endpoint ordered before it was found to be statistically significant (see Table 13)

Table 13. Gatekeeper Approaches for Study TH9507/III/LIPO/010 and Study TH9507-CTR-1011

Secondary Endpoint	Ranking of Endpoint		
	Study TH9507/III/LIPO/010	Study TH9507-CTR-1011	
		Primary	Supportive
Belly appearance distress change score (change from baseline)	1	1[a]	1[a]
Change from baseline to Week 26 in triglycerides	2	1[a]	NR
Change from baseline to Week 26 in total cholesterol:HDL-C ratio	3	2	2
Change from baseline to Week 26 in non-HDL-C	NR	NR	1[a]

NR = not ranked in gatekeeper approach

a Based on Hochberg

An overview of treatment group differences for the ranked secondary endpoints in Studies TH9507/III/LIPO/010 and TH9507-CTR-1011 is provided in table 14

Table 14. Overview of Ranked Secondary Variables for Study TH9507/III/LIPO/010 and Study TH9507-CTR-1011

Secondary Endpoint	Ranking of Endpoint		
	Study TH9507/III/LIPO/010	Study TH9507-CTR-1011	
		Primary	Supportive
Belly appearance distress change score (change from baseline)	not significant (0.028†)	0.022*	0.022*
Change from baseline to Week 26 in triglycerides	<0.001†	not significant	not ranked
Change from baseline to Week 26 in total cholesterol:HDL-C ratio	<0.001†	not significant	not significant
Change from baseline to Week 26 in non-HDL-C	0.001 [not ranked]	not ranked	not significant

† Statistically significant using gatekeeper based on ranked ANCOVA for belly appearance distress.

* Statistically significant using gatekeeper based on primary ranked ANCOVA (p<0.025 as per Hochberg).

Individual results for the ranked secondary efficacy endpoints are summarized in table 15. The treatment group difference for triglyceride level in Study TH9507/III/LIPO/010 achieved p<0.001 but was considered not statistically significant per the gatekeeper approach. It was considered statistically significant per the gatekeeper approach when using ranked ANCOVA for Belly Appearance which had, however, not been defined as the primary analysis. In Study TH9507-CTR-1011, the treatment group difference was not statistically significant.

The treatment group difference for the mean total cholesterol:HDL-C ratio in Study TH9507/III/LIPO/010 achieved p<0.001 but was considered not statistically significant per the gatekeeper approach. When the gatekeeper approach was based on the supportive ranked ANCOVA for belly appearance distress, the difference was considered statistically significant. In Study TH9507-CTR-1011, the mean change from baseline to Week 26 was not significantly different between the two treatment groups.

Table 15. Belly Appearance Distress Score, Triglycerides Level, Total Cholesterol:HDL-C Ratio, and Non-HDL-C - Change from Baseline to Week 26 - Main Phase ITT Population

	Study TH9507/III/LIPO/010		Study TH9507-CTR-1011	
	Tesamorelin 2 mg/day (N=273)	Placebo (N=137)	Tesamorelin 2 mg/day (N=270)	Placebo (N=126)
Visit	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Belly Appearance Distress Score – Intent-to-Treat				
	(N=272)	(N=137)	(N=269)	(N=126)
Baseline	22.1 (22.23)	24.0 (25.68)	22.3 (24.19)	20.2 (22.07)
Change to Week 26	11.6 (26.93)	6.2 (25.82)	8.4 (28.99)	5.2 (26.61)
P-value[a]	0.076		0.022	
P-value[b]	0.028		0.083	
Triglycerides (mg/dL)				
Baseline	252 (188)	234 (145)	239 (261)	223 (144)
Change to Week 26	-50.3 (146)	9.01 (118)	-22.1 (131)	3.44 (106)
95% CI				
P-value[c]	<0.001		0.102	
P-value[d]				
Total Cholesterol:HDL-C Ratio				
n	270	134	264	126
Baseline	4.50 (1.34)	4.29 (1.24)	4.75 (1.69)	4.61 (1.61)
Change to Week 26	-0.31 (0.980)	0.21 (0.950)	-0.05 (1.01)	0.15 (0.919)
95% CI				
P-value[c]	<0.001		0.093	
P-value[d]				
Non-HDL-C[e] (mg/dL)				
n	272	134	264	126
Baseline	150.02 (41.256)	147.24 (35.878)	147 (42.6)	145 (35.9)
Change to Week 26	-10.76 (31.299)	-0.77 (25.147)	1.08 (30.5)	5.50 (26.9)
95% CI	-14.13, -3.41			
P-value[c]	0.001		0.216	
P-value[d]				

a For Study TH9507/III/LIPO/010, the ANOVA included relevant covariates (e.g., gender, age) at baseline and parametric ANCOVA for change score. For Study TH9507-CTR-1011, the ANOVA included relevant covariates (e.g., gender, age) at baseline and ranked ANCOVA including relevant covariates (e.g., gender, age) for change score.

b For Study TH9507/III/LIPO/010, the ranked ANCOVA was the supportive analysis. For Study TH9507-CTR-1011, the parametric ANCOVA was the supportive analysis.

c P-values are for treatment group difference. For the individual studies, the ANCOVA model is the variable at baseline + treatment + lipid-lowering therapy. For the combined studies, the ANCOVA model is the variable at baseline +study + treatment + lipid-lowering therapy.

d P-value is for treatment group difference. The ANCOVA model is the variable at baseline +study + treatment + lipid-lowering therapy + treatment group-by-study. / Study-by-treatment group p-value.

e For non-HDL-C, results for the TH9507/III/LIPO/010 study are taken from the ISE.

Patient Reported Outcomes Related to Belly Image

- Belly Appearance Distress

As shown in table 19, in the key secondary endpoint of patients' distress with the appearance of their abdomen, the pre-specified minimally important difference for the treatment difference was only met in 1 of the studies, this result was not statistically significant with the planned primary statistical test, and is anyway of uncertain clinical significance, corresponding to an improvement over placebo of 5.4 in a 100-point scale (i.e. 11% to 15% with tesamorelin as compared to 8% with placebo).

- Belly Size

After 26 weeks, the tesamorelin and placebo group belly size scores were improved compared to baseline in both studies. There was no difference in the change from baseline to Week 26 scores between treatment groups.

- Belly Profile

Patient reported belly profile improved more in the tesamorelin group compared to the placebo group. The mean improvement in dysmorphia was -0.6/-0.7 units in the tesamorelin group and -0.3 units in the placebo group (from baseline values of 3.3/3.2). There was no consistent difference in the change from baseline to Week 26 scores between treatment groups.

Correlations were found between the percent change from baseline to Week 26 in VAT and changes in all primary patient reported outcomes related to body image in tesamorelin-treated patients.

In summary, the results for the key secondary endpoint were not supported by clear differences in belly size and patient-reported belly profile across both studies (see table 17), nor did they translate into a clear and consistent effect in quality of life evaluations. The patient reported outcomes should also be treated with care, as the significant excess of injection site reactions in the active treatment group raise concerns about the integrity of the blinding.

Other efficacy endpoints

Triglycerides and total cholesterol: HDL-C ratio decreased among tesamorelin-treated patients and increased among placebo patients; however the changes met statistical significance in only 1 study and were otherwise clinically minimal. Generally, apart from triglycerides, mean levels of lipid parameters were within the normal range at baseline. No analysis of whether tesamorelin allowed a reduction in dose or change in lipid-lowering medication can be done, as this action was not permitted by the protocol. In the main efficacy analysis there was a small decrease in waist circumference (<2cm) and waist: hip ratio compared to placebo in both studies- these reductions are disappointingly marginal. Furthermore, the overall increase in lean body mass of around 1 kg compared to placebo may be a result of fluid retention, a common side effect of tesamorelin. A claim of improvement in cardiovascular outcomes is not sought in the proposed SmPC, not supported by the submitted data, and not capable of being assessed given the study design.

Table 16. Other efficacy endpoints – ITT-population

Study visit	**Study TH9507-CTR-1011**			**Study TH9507/III/LIPO/010**		
	Tesamorelin (n=269)	**Placebo (n=126)**	**between-group difference[1]**	**Tesamorelin (n=273)**	**Placebo (n=137)**	**between-group difference[1]**
Patient Reported Outcome measures						
Body Size (composite)*						
Baseline (mean)	42.1	45.8		41.3	41.8	
week 26 (change from BL)	-8.3	-8.3	ns (0.471)	-8.3	-6.7	ns (0.325)[+]
Body Appearance Distress (composite)[+]						
Baseline (mean)	36.1	33.0		36.0	36.1	
week 26 (change from BL)	4.2	2.8	s (0.024)	5.4	2.9	ns (0.059)
Hump Profile						
Baseline (mean)	0.9	1.0		1.0	1.1	
week 26 (change from BL)	0.0	-0.2	ns (0.347)	-0.1	-0.1	ns (0.651)

Perceived Body weight						
Baseline (mean)	47.8	42.1		44.3	44.5	
week 26 (change from BL)	3.0	-1.2	ns (0.163)	-5.7	0.73	ns (0.848)
Weight concerns						
Baseline (mean)	46.3	42.5		40.8	43.8	
week 26 (change from BL)	-8.4	-0.4	s (0.008)	-5.8	-3.9	ns (0.2)
Current Overall Appearance						
Baseline (mean)	3.4	3.3		3.5	3.4	
week 26 (change from BL)	0.8	0.4	s (0.007)	0.8	0.5	s (0.048)
IGF-1						
Baseline (mean)	146	149		161	168	
week 26 (change from BL)	+106	+2.57	s (<0.001)	+109	-16.3	s (<0.001)
Anthropometric measurements						
Waist circumference (cm)						
Baseline (mean)	105	104		104	105	
week 26 (change from BL)	-2.15	-0.81	ns (0.015)	-2.61	-1.10	s (0.006)
Hip circumference (cm)						
Baseline (mean)	101	99.8		99.7	100	
week 26 (change from BL)	0.13	-0.10	ns (0.526)	0.04	0.17	ns (0.66)
Waist-Hip Ratio						
Baseline (mean)	1.05	1.05		1.05	1.05	
week 26 (change from BL)	-0.024	-0.008	s (0.001)	-0.03	-0.02	ns (0.052)
Body composition						
Total fat (kg)						
Baseline (mean)	23.6	23.3		22.9	23.9	
week 26 (change from BL)	-0.90	0.29	s (<0.001)	-1.05	0.63	s (<0.001)
Trunk fat (kg)						
Baseline (mean)	15.3	15.2		14.9	15.3	
week 26 (change from BL)	-0.79	0.17	s (<0.001)	-1.00	0.38	s (<0.001)
Limb fat (kg)						
Baseline (mean)	7.52	7.29		7.12	7.70	
week 26 (change from BL)	0.007	0.121	ns (0.069	-0.03	0.22	s (0.012)
Lean body mass (kg)						
Baseline (mean)	62.4	60.5		62.0	61.4	
week 26 (change from BL)	1.22	-0.03	s (<0.001)	+1.32	-0.24	s (<0.001)

Visceral adipose tissue (cm^2)						
Baseline (mean)	186	195		178	171	
week 26 (change from BL)	-20.6	-0.82	s (<0.001)	-27.8	5.05	s (<0.001)
Subcutaneous adipose tissue (SAT, cm2)						
Baseline (mean)	231	226		231	239	
week 26 (change from BL)	-1.30	0.95	ns (0.552)	-3.24	2.33	ns (0.053)
VAT/SAT ratio						
Baseline (mean)	1.27	1.25		1.27	1.18	
week 26 (change from BL)	-0.22	0.03	s (0.001)	-0.25	0.07	s (<0.001)

1 Exploratory testing for statistical significance, no adjustment for multiplicity

ns=not significant; s=significant

Whilst there were numerical improvements for tesamorelin in some of the health-related quality of life subgroups, in each case these appeared very small in relation to the total possible score. The applicant has singled out results in one study (CTR1011, results in general health perceptions, symptom incidence, symptom distress scales) for statistical significance, however these were not primary or secondary endpoints, there were many additional efficacy assessments in total, and there was no control of type I error. Also, in this study there were no statistically significant differences in change from baseline scores between treatment groups for 5 out of the 8 main HRQOL scales, including the global assessment and assessment of Mental and Emotional Health, and no significant effects in the EQ-5D ratings.

Any effect of tesamorelin did not translate into an improvement in compliance with ART. Compliance was high (>95%) and comparable between tesamorelin and placebo groups in both studies, with no clinically meaningful correlations between compliance with ART therapy and the parameters related to belly size, profile or distress.

In both studies the primary efficacy endpoint results were comparable in the per-protocol analysis. Subgroup analyses showed that the primary endpoint results were consistent when accounting for gender, testosterone use, presence of IGT or diabetes, testosterone use, presence of FBG > 6 mmol/L at screening and ART regimen. There was also no clear correlation between response and presence/type of anti-tesamorelin IgG antibody.

Extension Phase (27-52 Weeks)

Study TH9507-CTR-1012 and the Extension Phase (Weeks 27 – 52) of Study TH9507/III/LIPO/010 were both studies were multicenter, randomized, parallel, double-blind, placebo-controlled studies to evaluate primarily the long-term safety and in addition the long-term efficacy of tesamorelin (2 mg/day) in HIV subjects with excess abdominal fat accumulation. Tesamorelin (or placebo) was administered once daily by subcutaneous injection.

After completing 26 weeks of treatment in the Main Phase of Study TH9507/III/LIPO/010, subjects who had a fasting blood glucose (FBG) ≤ 150 mg/dl (8.33 mmol/l) were eligible to enter the Extension Phase. After completing the 26-Week treatment period in Study TH9507-CTR-1011, subjects who had a FBG ≤ 150 mg/dl (8.33 mmol/l) were eligible to enter Study TH9507-CTR-1012.

Subjects in Study TH9507/III/LIPO/010 who received tesamorelin in the Main Phase were randomized in a 3:1 (active : placebo) ratio to receive either tesamorelin or placebo in the Extension Phase, whereas subjects who received placebo in the Main Phase were automatically switched to receive

tesamorelin in the Extension Phase. Subjects in Study TH9507-CTR-1012 who received tesamorelin in Study TH9507-CTR-1011 were randomized to either tesamorelin 2 mg/day or placebo in a 1:1 ratio. Subjects who received placebo during Study TH9507-CTR-1011 were switched to tesamorelin 2 mg/day. Comparisons undertaken between the two randomized groups, T-T and T-P, were for proof-of-concept only.

The interpretation of these long-term results is hampered by the fact that a placebo control group has not been included in any of the extension studies.

For both extension studies the patients re-randomized have been shown to tolerate and to benefit from tesamorelin in the first 26 weeks of treatment. This results in an enriched population, limiting the generalizability of the results. Moreover, not all completing the first 26 week of therapy were randomized into the extension phase: whereas only 4/211 patients did not continue study -010, only 88% of those completing study-011 and being on tesamorelin for the first 26 weeks were randomized for study -012. Bias can thus not be excluded.

Table 17. Subject Disposition - Extension Phase ITT Population

	Study TH9507/III/LIPO/010			Study TH9507-CTR-1012		
	Tesamorelin -Tesamorelin (N=154)	Tesamorelin -Placebo (N=50)	Placebo -Tesamorelin[a] (N=111)	Tesamorelin-Tesamorelin (N=92)	Tesamorelin-Placebo (N=85)	Placebo-Tesamorelin[a] (N=86)
Randomized subjects, N	155	52	115	92	86	86
ITT population[b]	154 (99.4)	50 (96.2)	111 (96.5)	92 (100.0)	85 (98.8)	86 (100.0)
Per protocol population[b]	106 (68.4)	39 (75.0)	83 (72.2)	70 (76.1)	55 (64.0)	68 (79.1)
Number of subjects who completed the Extension Phase						
Yes	129 (83.8)	40 (80.0)	87 (78.4)	80 (87.0)	63 (74.1)	72 (83.7)
No	25 (16.2)	10 (20.0)	24 (21.6)	12 (13.0)	22 (25.9)	14 (16.3)
Primary reason for discontinuation[c]						
Adverse event	5 (20.0)	3 (30.0)	12 (50.0)	1 (8.3)	4 (18.2)	5 (35.7)
Lack of compliance with protocol requirements and/or procedures	7 (28.0)	1 (10.0)	2 (8.3)	1 (8.3)	3 (13.6)	1 (7.1)
Withdrawal of consent	12 (48.0)	4 (40.0)	6 (25.0)	8 (66.7)	11 (50.0)	7 (50.0)
Lost to follow-up	1 (4.0)	2 (20.0)	3 (12.5)	2 (16.7)	2 (9.1)	1 (7.1)
Abnormal laboratory values	0	0	1 (4.2)	0	0	0
Others	0	0	0	0	3 (13.6)	0
P-value[d]						
P-value[e]						

	Study TH9507/III/LIPO/010			Study TH9507-CTR-1012		
	Tesamorelin -Tesamorelin (N=154)	Tesamorelin -Placebo (N=50)	Placebo -Tesamorelin[a] (N=111)	Tesamorelin-Tesamorelin (N=92)	Tesamorelin-Placebo (N=85)	Placebo-Tesamorelin[a] (N=86)
Randomized subjects, N	155	52	115	92	86	86
ITT population[b]	154 (99.4)	50 (96.2)	111 (96.5)	92 (100.0)	85 (98.8)	86 (100.0)
Per protocol population[b]	106 (68.4)	39 (75.0)	83 (72.2)	70 (76.1)	55 (64.0)	68 (79.1)
Number of subjects who completed the Extension Phase						
Yes	129 (83.8)	40 (80.0)	87 (78.4)	80 (87.0)	63 (74.1)	72 (83.7)
No	25 (16.2)	10 (20.0)	24 (21.6)	12 (13.0)	22 (25.9)	14 (16.3)
Primary reason for discontinuation[c]						
Adverse event	5 (20.0)	3 (30.0)	12 (50.0)	1 (8.3)	4 (18.2)	5 (35.7)
Lack of compliance with protocol requirements and/or procedures	7 (28.0)	1 (10.0)	2 (8.3)	1 (8.3)	3 (13.6)	1 (7.1)
Withdrawal of consent	12 (48.0)	4 (40.0)	6 (25.0)	8 (66.7)	11 (50.0)	7 (50.0)
Lost to follow-up	1 (4.0)	2 (20.0)	3 (12.5)	2 (16.7)	2 (9.1)	1 (7.1)
Abnormal laboratory values	0	0	1 (4.2)	0	0	0
Others	0	0	0	0	3 (13.6)	0
P-value[d]						
P-value[e]						

a Subjects who received placebo in the Main Phase were automatically switched to receive tesamorelin in the Extension Phase.

b Percentages are based on the number of randomized subjects.

c Percentages are based on the number of subjects who have discontinued prior to the end of the study

d From generalized linear model, to test the rates of primary reason for discontinuation between treatment groups (T-T versus T-P), with treatment group and study included. Subjects in the P-T group were excluded from the model.

e From generalized linear model, to test the rates of primary reason for discontinuation between treatment groups (T-T versus T-P), with treatment group, study and study-by-treatment group included. Subjects in the P-T group were excluded from the model. / Study-by-treatment group p-value.

Discontinuation during the extension phase occurred least frequently in the group staying on tesamorelin (T-T), with the most prominent difference being the lower rate of discontinuations due to adverse events.

The 3 treatment groups in the two studies displayed a similar mean age, similar proportions of males and females, and were predominantly White/Caucasian (see table 21). Noteworthy, the proportion of male/female participants continuing in the extension studies changed from baseline, i.e. less women continued in the extension studies. The three treatment groups were also similar with respect to the various body measurements, such as weight, waist circumference, and waist:hip ratio. Mean BMI and hip circumference at baseline were higher in the T-P than in the T-T group.

With respect to HIV- and lipodystrophy syndrome-related characteristics at baseline the treatment groups were overall comparable (table 18-20).

Table 18. Subject Demographics at Baseline - Extension Phase ITT Population

	Study TH9507/III/LIPO/010			Study TH9507-CTR-1012		
	Tesamorelin -Tesamorelin (N=154)	**Tesamorelin -Placebo (N=50)**	**Placebo -Tesamorelin (N=111)**	**Tesamorelin-Tesamorelin (N=92)**	**Tesamorelin-Placebo (N=85)**	**Placebo-Tesamorelin (N=86)**
Age[a] (years)						
Mean (SD)	47.7 (7.37)	46.9 (6.74)	48.3 (7.65)	47.7 (6.85)	48.8 (7.28)	48.3 (7.87)
Median	46.5	46.0	48.0	47.0	49.0	48.0
Range	28; 65	31; 60	31; 65	31; 62	32; 65	28; 65
P-value[b]	0.511			0.291		
P-value[c]	0.272			0.975		
Gender n (%)						
Male	136 (88.3)	43 (86.0)	96 (86.5)	83 (90.2)	76 (89.4)	75 (87.2)
Female	18 (11.7)	7 (14.0)	15 (13.5)	9 (9.8)	9 (10.6)	11 (12.8)
P-value[d]	0.628			1.000		
P-value[e]	0.727			0.534		
Ethnic origin n (%)						
White/Caucasian	120 (77.9)	40 (80.0)	84 (75.7)	75 (81.5)	73 (85.9)	70 (81.4)
Asian	1 (0.6)	1 (2.0)	0	0	0	2 (2.3)
Black/African-American	19 (12.3)	4 (8.0)	16 (14.4)	10 (10.9)	6 (7.1)	5 (5.8)
Hispanic	12 (7.8)	4 (8.0)	9 (8.1)	7 (7.6)	5 (5.9)	7 (8.1)
Other	2 (1.3)	1 (2.0)	2 (1.8)	0	1 (1.2)	2 (2.3)
P-value[d]	0.705			0.599		
P-value[e]	0.833			0.162		
Weight (kg)						
Mean (SD)	89.1 (13.70)	92.1 (17.35)	90.4 (13.62)	88.0 (12.56)	89.9 (13.57)	86.6 (15.39)
Median	86.8	90.5	88.5	86.4	88.6	85.6
Range	61 ; 139	56 ; 161	62 ; 128	60 ; 136	63 ; 140	60 ; 148
P-value[b]	0.211			0.339		
P-value[c]	0.913			0.202		
BMI (kg/m^2)						
Mean (SD)	28.9 (4.18)	30.2 (4.69)	29.1 (4.220	28.1 (3.81)	28.9 (3.95)	28.4 (4.25)
Median	28.0	29.5	28.4	27.5	28.2	27.3
Range	22 ; 47	22 ; 48	22 ; 46	20 ; 37	22 ; 43	22 ; 44
P-value[b]	0.082			0.140		
P-value[c]	0.465			0.935		
Waist circumference (cm)						
Mean (SD)	103.8 (8.85)	105.1 (11.98)	104.9 (9.88)	103.8 (8.25)	105.6 (9.15)	103.8 (8.93)
Median	101.1	100.8	101.7	102.2	103.4	101.3
Range	90 ; 150	94 ; 154	92 ; 138	95 ; 140	94 ; 136	94 ; 151
P-value[b]	0.400			0.168		
P-value[c]	0.694			0.429		
Hip circumference (cm)						
Mean (SD)	99.3 (8.25)	101.1 (10.69)	100.0 (8.88)	98.9 (7.02)	100.8 (8.28)	99.5 (9.81)
Median	98.7	98.7	98.5	98.0	98.8	98.3
Range	85 ; 134	88 ; 152	85 ; 130	85 ; 116	89 ; 137	87 ; 159
P-value[b]	0.201			0.104		
P-value[c]	0.869			0.774		
Waist/ Hip Ratio						
Mean (SD)	1.05 (0.0612)	1.04 (0.0569)	1.05 (0.0656)	1.05 (0.0891)	1.05 (0.0563)	1.05 (0.0593)
Median	1.05	1.02	1.04	1.04	1.04	1.04
Range	0.89 ; 1.24	0.94 ; 1.18	0.89 ; 1.23	0.87 ; 1.61	0.95 ; 1.19	0.90 ; 1.19
P-value[b]	0.469			0.764		
P-value[c]	0.357			0.577		

Waist circumference (cm) Mean (SD) Median Range	103.8 (8.85) 101.1 90 ; 150	105.1 (11.98) 100.8 94 ; 154	104.9 (9.88) 101.7 92 ; 138	103.8 (8.25) 102.2 95 ; 140	105.6 (9.15) 103.4 94 ; 136	103.8 (8.93) 101.3 94 ; 151
P-value[b]	0.400			0.168		
P-value[c]	0.694			0.429		
Hip circumference (cm) Mean (SD) Median Range	99.3 (8.25) 98.7 85 ; 134	101.1 (10.69) 98.7 88 ; 152	100.0 (8.88) 98.5 85 ; 130	98.9 (7.02) 98.0 85 ; 116	100.8 (8.28) 98.8 89 ; 137	99.5 (9.81) 98.3 87 ; 159
P-value[b]	0.201			0.104		
P-value[c]	0.869			0.774		
Waist/ Hip Ratio Mean (SD) Median Range	1.05 (0.0612) 1.05 0.89 ; 1.24	1.04 (0.0569) 1.02 0.94 ; 1.18	1.05 (0.0656) 1.04 0.89 ; 1.23	1.05 (0.0891) 1.04 0.87 ; 1.61	1.05 (0.0563) 1.04 0.95 ; 1.19	1.05 (0.0593) 1.04 0.90 ; 1.19
P-value[b]	0.469			0.764		
P-value[c]	0.357			0.577		

a Age is based on date of randomization (at Baseline).

b P-value comparing T-T versus T-P from the 1-factor (treatment group) ANOVA for the individual studies, including the T-T and T-P groups. For the combined results, the pvalue comparing T-T versus T-P is from the test of the treatment group from the 2-factor (treatment group and study) ANOVA, including the T-T and T-P groups.

c P-value from the 1-factor (treatment) ANOVA for the individual studies, comparing P-T to (T-T and T-P). For the combined results, the p-value is from the test of the treatment group from 2-factor (treatment group and study) ANOVA, comparing P-T to (T-T and T-P).

d P-value from a Fisher's exact test including T-T and T-P for the individual studies. For the combined results, the p-value comparing T-T versus T-P is from the generalized linear model (binomial or multinomial as appropriate), with treatment group and study in the model, including the T-T and T-P groups.

e P-value from a Fisher's exact test including P-T versus (T-T and T-P) for the individual studies. For the combined results, the p-value comparing P-T to (T-T and T-P) is from the generalized linear model (binomial or multinomial as appropriate), with treatment group and study in the model, including all treatment groups.

Table 19. HIV- and Lipodystrophy Syndrome-related Characteristics at Baseline - Extension Phase ITT Population

	Study TH9507/III/LIPO/010			Study TH9507-CTR-1012		
	Tesamorelin -Tesamorelin (N=154)	**Tesamorelin -Placebo (N=50)**	**Placebo -Tesamorelin (N=111)**	**Tesamorelin-Tesamorelin (N=92)**	**Tesamorelin-Placebo (N=85)**	**Placebo-Tesamorelin (N=86)**
Time since HIV diagnosis (months)	n=153	n=50	n=111	n=92	n=85	n=86
Mean (SD)	170 (63.5)	162 (59.9)	158 (65.4)	171 (59.7)	168 (71.3)	166 (67.6)
Median	179	170	158	169	182	161
Range	22; 311	43; 278	8; 288	29; 283	11; 303	27; 308
P-value[a]						
P-value[b]						
Viral load at baseline n (%)						
undetectable	109 (70.8)	29 (59.2)	75 (67.6)	77 (83.7)	68 (80.0)	75 (88.2)
50-400 copies/mL	30 (19.5)	15 (30.6)	26 (23.4)	8 (8.7)	10 (11.8)	6 (7.1)
>400 copies/mL	15 (9.7)	5 (10.2)	10 (9.0)	7 (7.6)	7 (8.2)	4 (4.7)
missing	0	1 (2.0)	0	0	0	1 (1.2)
P-value[c]		0.231			0.841	
P-value[d]			0.965			0.490
Viral load at Week 26 n (%)						
undetectable	104 (68.4)	32 (65.3)	77 (70.0)	81 (89.0)	73 (86.9)	75 (88.2)
50-400 copies/mL	30 (19.7)	14 (28.6)	22 (20.0)	4 (4.4)	8 (9.5)	6 (7.1)
>400 copies/mL	18 (11.8)	3 (6.1)	11 (10.0)	6 (6.6)	3 (3.6)	4 (4.7)
missing	2 (1.3)	1 (2.0)	1 (0.9)	1 (1.1)	1 (1.2)	1 (1.2)
P-value[c]		0.313			0.317	
P-value[d]			0.930			>0.999
CD4 cell count at baseline (cells/mm^3)	n=154	n=49	n=111	n=92	n=85	n=85
Mean (SD)	650 (311)	625 (304)	572 (261)	579 (300)	580 (272)	604 (283)
Median	598	597	528	527	553	540
Range	190; 2021	93; 1620	103; 1382	183; 1639	144; 1599	104; 1553
P-value[a]		0.626			0.983	
P-value[b]			0.040			0.518
Type of ART regimen n (%)[e]						
NRTI and NNRTI (with no PI)	60 (39.0)	27 (54.0)	31 (27.9)	32 (34.8)	23 (27.1)	28 (32.6)
NRTI and PI (with no NNRTI)	66 (42.9)	17 (34.0)	53 (47.7)	40 (43.5)	37 (43.5)	43 (50.0)
NRTI, NNRTI, and PI	18 (11.7)	4 (8.0)	15 (13.5)	5 (5.4)	13 (15.3)	2 (2.3)
NRTI alone	8 (5.2)	0	9 (8.1)	8 (8.7)	2 (2.4)	3 (3.5)
Other	2 (1.3)	2 (4.0)	3 (2.7)	7 (7.6)	10 (11.8)	10 (11.6)
P-value[f]		0.115			0.062	
P-value[g]			0.078			0.175
Time since lipodystrophy syndrome diagnosis (months)	n=148	n=49	n=109	n=89	n=81	n=84
Mean (SD)	52.3 (39.7)	48.1 (36.8)	50.2 (39.8)	66.9 (41.5)	62.1 (47.8)	71.4 (42.6)
Median	46.8	44.4	47.4	61.1	46.1	67.6
Range	0; 189	0; 140	0; 192	-5; 194	0; 211	1; 259
P-value[a]						
P-value[b]						
Lipodystrophy syndrome clinical assessment n (%)						
Facial lipoatrophy	83 (53.9)	25 (50.0)	53 (47.7)	36 (39.1)	42 (49.4)	42 (48.8)
Lower limbs lipoatrophy	103 (66.9)	29 (58.0)	66 (59.5)	48 (52.2)	46 (54.1)	51 (59.3)
Upper limbs lipoatrophy	86 (55.8)	27 (54.0)	46 (41.4)	44 (47.8)	33 (38.8)	39 (45.3)
General lipoatrophy	117 (76.0)	36 (72.0)	80 (72.1)	57 (62.0)	59 (69.4)	61 (70.9)
Buffalo hump	68 (44.2)	21 (42.0)	50 (45.0)	30 (32.6)	27 (31.8)	29 (33.7)
Abdominal lipohypertrophy	154 (100)	50 (100)	111 (100)	92 (100)	85 (100)	86 (100)

	Study TH9507/III/LIPO/010			Study TH9507-CTR-1012		
	Tesamorelin -Tesamorelin (N=154)	**Tesamorelin -Placebo (N=50)**	**Placebo -Tesamorelin (N=111)**	**Tesamorelin-Tesamorelin (N=92)**	**Tesamorelin-Placebo (N=85)**	**Placebo-Tesamorelin (N=86)**
Time since HIV diagnosis (months)	n=153	n=50	n=111	n=92	n=85	n=86
Mean (SD)	170 (63.5)	162 (59.9)	158 (65.4)	171 (59.7)	168 (71.3)	166 (67.6)
Median	179	170	158	169	182	161
Range	22; 311	43; 278	8; 288	29; 283	11; 303	27; 308
P-value[a]						
P-value[b]						
Viral load at baseline n (%)						
undetectable	109 (70.8)	29 (59.2)	75 (67.6)	77 (83.7)	68 (80.0)	75 (88.2)
50-400 copies/mL	30 (19.5)	15 (30.6)	26 (23.4)	8 (8.7)	10 (11.8)	6 (7.1)
>400 copies/mL	15 (9.7)	5 (10.2)	10 (9.0)	7 (7.6)	7 (8.2)	4 (4.7)
missing	0	1 (2.0)	0	0	0	1 (1.2)
P-value[c]		0.231			0.841	
P-value[d]			0.965			0.490
Viral load at Week 26 n (%)						
undetectable	104 (68.4)	32 (65.3)	77 (70.0)	81 (89.0)	73 (86.9)	75 (88.2)
50-400 copies/mL	30 (19.7)	14 (28.6)	22 (20.0)	4 (4.4)	8 (9.5)	6 (7.1)
>400 copies/mL	18 (11.8)	3 (6.1)	11 (10.0)	6 (6.6)	3 (3.6)	4 (4.7)
missing	2 (1.3)	1 (2.0)	1 (0.9)	1 (1.1)	1 (1.2)	1 (1.2)
P-value[c]		0.313			0.317	
P-value[d]			0.930			>0.999
CD4 cell count at baseline (cells/mm^3)	n=154	n=49	n=111	n=92	n=85	n=85
Mean (SD)	650 (311)	625 (304)	572 (261)	579 (300)	580 (272)	604 (283)
Median	598	597	528	527	553	540
Range	190; 2021	93; 1620	103; 1382	183; 1639	144; 1599	104; 1553
P-value[a]		0.626			0.983	
P-value[b]			0.040			0.518
Type of ART regimen n (%)[e]						
NRTI and NNRTI (with no PI)	60 (39.0)	27 (54.0)	31 (27.9)	32 (34.8)	23 (27.1)	28 (32.6)
NRTI and PI (with no NNRTI)	66 (42.9)	17 (34.0)	53 (47.7)	40 (43.5)	37 (43.5)	43 (50.0)
NRTI, NNRTI, and PI	18 (11.7)	4 (8.0)	15 (13.5)	5 (5.4)	13 (15.3)	2 (2.3)
NRTI alone	8 (5.2)	0	9 (8.1)	8 (8.7)	2 (2.4)	3 (3.5)
Other	2 (1.3)	2 (4.0)	3 (2.7)	7 (7.6)	10 (11.8)	10 (11.6)
P-value[f]		0.115			0.062	
P-value[g]			0.078			0.175
Time since lipodystrophy syndrome diagnosis (months)	n=148	n=49	n=109	n=89	n=81	n=84
Mean (SD)	52.3 (39.7)	48.1 (36.8)	50.2 (39.8)	66.9 (41.5)	62.1 (47.8)	71.4 (42.6)
Median	46.8	44.4	47.4	61.1	46.1	67.6
Range	0; 189	0; 140	0; 192	-5; 194	0; 211	1; 259
P-value[a]						
P-value[b]						
Lipodystrophy syndrome clinical assessment n (%)						
Facial lipoatrophy	83 (53.9)	25 (50.0)	53 (47.7)	36 (39.1)	42 (49.4)	42 (48.8)
Lower limbs lipoatrophy	103 (66.9)	29 (58.0)	66 (59.5)	48 (52.2)	46 (54.1)	51 (59.3)
Upper limbs lipoatrophy	86 (55.8)	27 (54.0)	46 (41.4)	44 (47.8)	33 (38.8)	39 (45.3)
General lipoatrophy	117 (76.0)	36 (72.0)	80 (72.1)	57 (62.0)	59 (69.4)	61 (70.9)
Buffalo hump	68 (44.2)	21 (42.0)	50 (45.0)	30 (32.6)	27 (31.8)	29 (33.7)
Abdominal lipohypertrophy	154 (100)	50 (100)	111 (100)	92 (100)	85 (100)	86 (100)

Table 20. HIV- and Lipodystrophy Syndrome-related Characteristics at Baseline - Extension Phase ITT Population (Continued)

	Study TH9507/III/LIPO/010			Study TH9507-CTR-1012		
	Tesamorelin -Tesamorelin (N=154)	Tesamorelin -Placebo (N=50)	Placebo -Tesamorelin (N=111)	Tesamorelin-Tesamorelin (N=92)	Tesamorelin-Placebo (N=85)	Placebo-Tesamorelin (N=86)
Lipodystrophy syndrome clinical assessment n (%)						
Breast enlargement	53 (34.4)	21 (42.0)	50 (45.0)	34 (37.0)	34 (40.0)	27 (31.4)
Subjects with ≥1 of the following signs: general lipoatrophy, buffalo hump, or breast enlargement	140 (90.9)	45 (90.0)	101 (91.0)	72 (78.3)	71 (83.5)	72 (83.7)

a P-value comparing T-T versus T-P from the 1-factor (treatment group) ANOVA for the individual studies, including the T-T and T-P groups. For the combined results, the p-value comparing T-T versus T-P is from the 2-factor (treatment group and study) ANOVA, including the T-T and T-P groups.

b P-value from the 1-factor (treatment) ANOVA for the individual studies, comparing P-T to (T-T and T-P). For the combined results, the p-value is from the test of the treatment group from the 2-factor (treatment group and study) ANOVA, comparing P-T to (T-T and T-P).

c P-value from a Kruskal-Wallis test, comparing T-T versus T-P.

d P-value from a Kruskal-Wallis test, comparing P-T versus (T-T and T-P).

e For type of ART regimen, individual study and combined results were taken from ISE.

f P-value from a Fisher's exact test including T-T and T-P for the individual studies. For the combined results, the p-value comparing T-T versus T-P is from the generalized linear model (specifying multinomial distribution for dependent variable), with treatment group and study in the model, including the T-T and T-P groups.

g P-value from a Fisher's exact test including P-T versus (T-T and T-P) for the individual studies. For the combined results, the p-value comparing P-T to (T-T and T-P) is from the generalized linear model (specifying multinomial distribution for dependent variable), with treatment group and study in the model, including all treatment groups

Efficacy Results

Main efficacy results for the extension studies are depicted in table 21. In Study TH9507/III/LIPO/010 patients who received tesamorelin over 52 weeks (T-T group) maintained VAT loss observed at Week 26, whereas VAT re-accumulated in those patients who discontinued treatment at Week 26 (T-P group), with most of the VAT lost regained by Week 39 of treatment. The percent change in VAT from baseline to week 52 was neither significantly different by anti-tesamorelin IgG antibodies status nor by titre category in each of the treatment groups.

At Week 52, trunk fat loss and LBM gain at Week 26 were sustained in patients in the T-T group, while patients in the T-P group lost improvements in these parameters seen at Week 26. No clinically significant changes from baseline in SAT or limb fat were observed in either group at Week 52 of treatment. As seen in the Main Phase, administration of tesamorelin for 26 weeks was associated with improvements in body composition parameters, including VAT, trunk fat, and LBM, in patients who switched from placebo to tesamorelin (P-T group). The changes reported for LBM must be viewed with caution, as DEXA does not allow differentiation of muscular tissue and water and peripheral oedema is a common adverse event of tesamorelin. Treatment with tesamorelin in this group of patients also resulted in a slight decrease in SAT. Mean changes in limb fat were small and not statistically significantly different from baseline or week 26 in each of the three treatment groups.

At Week 52 of treatment, the decreases from baseline in triglycerides and total cholesterol seen at Week 26 were sustained in both the T-T and T-P groups. Because HDL-C decreased significantly in both groups, the ratio of total cholesterol:HDL-C did not significantly decrease from baseline and LDL-C even increased in the T-T group between week 26 and week 52. Overall, the effects on blood lipids are very small, especially in comparison with available lipid-lowering therapies and do not support a respective claim for tesamorelin.

With respect to body image, patients in the T-T group maintained improvements in belly and body appearance distress, as well as in patient- and physician-reported belly profile at Week 52. On the

contrary, patients in the T-P group tended to lose improvements seen at Week 26 in belly and body appearance distress. In the ordinal regression models used for determining the clinical meaningfulness of the effects for the four primary PRO belly endpoints, inconsistent results were obtained. Also with respect to the Health related Quality of Life Score (HRQOL), no consistent results were obtained. Hence, the clinical relevance of the reported changes is questionable.

In study TH9507-CTR-1012, patients previously treated with tesamorelin for 26 weeks in study TH9507-CTR-1011, and who continued on tesamorelin for an additional 26 weeks (T-T group), maintained a 17.5% reduction in VAT.

Patients previously treated with tesamorelin for 26 weeks in study TH9507-CTR-1011, and who were randomized to placebo (T-P group), regained VAT to baseline levels within 13 weeks.

Between patients with and without anti-tesamorelin IgG antibodies there was a difference with respect to the proportion of VAT responders.

The reduction in trunk fat achieved by tesamorelin-treated patients in study TH9507-CTR-1011 was maintained in the T-T group (-0.83 kg) and lost within 13 weeks in the T-P group.

In both the T-T and P-T groups, tesamorelin decreased LDL-C, non-HDL-C, and TC but had no effect on HDL-C, and the TC:HDL-C ratio. The decrease in triglycerides observed at Week 26 in tesamorelin-treated patients was not sustained at Week 52.

Compared to Week 26, total fat decreased and LBM increased in both the T-T group and the P-T group, while the opposite occurred in the T-P group. As detailed before, the increase in LBM must be viewed with caution, as this may also be due to peripheral water retention.

Any effects in belly appearance distress and physician reported belly profile observed at Week 26, were sustained with long-term 52-week treatment with tesamorelin, and also after treatment discontinuation.

In the ordinal regression models used for determining the clinical meaningfulness of the effects for the four primary PRO belly endpoints, no significant treatment effect was detected for any of the treatment groups between baseline and week 52. Neither has a consistent or clinically relevant in HRQOL been shown. The PRO results of study -1012 must therefore be regarded as not clinically relevant.

With respect to IFG-1 levels, in both studies a slight but constant decrease was noted in the T-T group after the initial steep rise when tesamorelin therapy had commenced, raising a question over the longer-term efficacy.

Table 21. Primary and Key Secondary Efficacy Results from Extension Phase - ITT Population

	Study TH9507/III/LIPO/010			Study TH9507-CTR-1012		
	Tesamorelin -Tesamorelin (N=154)	Tesamorelin -Placebo (N=50)	Placebo -Tesamorelin (N=111)	Tesamorelin -Tesamorelin (N=92)	Tesamorelin -Placebo (N=85)	Placebo -Tesamorelin (N=86)
Mean (SD)						
	(N=153)	**(N=50)**	**(N=110)**	**(N=91)**	**(N=85)**	**(N=86)**
Baseline VAT (cm^2)	181 (77.9)	174 (71.8)	175 (77.5)	197 (91.2)	200 (86.3)	199 (100)
Week 26 VAT (cm^2)	145 (72.1)	144 (71.8)	182 (87.1)	166 (88.9)	177 (88.1)	197 (106)
Mean (LSM)						
Week 52 - % change from Baseline	-18.1 (-21.8)	-1.63 (-4.51)	-12.5	-17.5 (-20.7)	1.28 (-2.88)	-14.0
P-value[a]		<0.001			<0.001	
Mean (SD)						
Belly Appearance Distress Score						
	(N=153)	**(N=50)**	**(N=111)**	**(N=92)**	**(N=85)**	**(N=86)**
Baseline	21.6503 (22.1671)	23.5000 (20.7696)	23.3108 (25.5333)	23.9 (24.56)	16.8 (17.63)	17.2 (19.56)
Change to Week 52	12.1732 (26.5145)	5.0000 (22.1601)	7.6577 (25.6269)	13.2 (33.83)	9.9 (24.25)	12.5 (29.52)
P-value[b]		0.020			0.005	
Mean (SD)			29			
Triglycerides (mg/dL)	**(n=154)**	**(n=50)**	**(n=111)**	**(n=92)**	**(n=85)**	**(n=86)**
Baseline	265 (207)	223 (126)	242 (152)	256 (214)	217 (170)	215 (123)
Mean (LSM)						
Change to Week 52	-51.2 (-47.8)	-31.1 (-43.8)	-25.4	-37.0 (-26.6)	3.85 (-9.67)	0.884
P-value[a]		0.828			0.414	
Mean (SD)						
Total Cholesterol:HDL-C Ratio	**(n=151)**	**(n=50)**	**(n=108)**	**(n=88)**	**(n=83)**	**(n=86)**
Baseline	4.50 (1.46)	4.32 (1.10)	4.31 (1.24)	5.01 (1.69)	4.66 (1.54)	4.57 (1.42)
Mean (LSM)						
Change to Week 52	0.04 (0.04)	0.12 (0.09)	0.32	-229 (-0.126)	0.127 (0.0010)	0.0611
P-value[a]		0.710			0.489	
Mean (SD)						
Non-HDL-C (mg/dL)[c]	**(n=154)**	**(n=50)**	**(n=111)**	**(n=88)**	**(n=83)**	**(n=86)**
Baseline	147.68 (44.146)	149.36 (35.424)	148.79 (35.560)	151 (44.5)	143 (38.0)	145 (33.5)
Mean (LSM)						
Change to Week 52	-5.31 (-5.58)	-7.37 (-6.34)	-2.80	-10.0 (-6.60)	8.29 (4.28)	0.209
P-value[d]		0.850			0.010	

a P-values are for T-T versus T-P comparisons. Only subjects in the T-T and T-P groups are included in these analyses.

b For T-T vs. T-P comparisons, ranked ANCOVA including relevant covariates (e.g., gender, age) for change from baseline to Week 52.

c For non-HDL-C, results from the ISE are presented

Clinical studies in special populations

Neither patients with relevant hepatic or renal impairment nor elderly patients (>65 y) were included in the pivotal studies.

No studies have been conducted in patients < 18 years of age.

Analysis performed across trials (pooled analyses AND meta-analysis)

Pooling the efficacy data for the primary efficacy endpoint, after 26 weeks of tesamorelin treatment, the mean percent change from baseline in VAT was 13.11%, compared with an increase of 2.30% in the placebo group. This pooled analysis should be considered purely descriptive. The two studies had the same treatment arms, the same primary endpoint, shared most secondary endpoints, and were comparatively similar at baseline. However the applicant did not plan at the outset to formally combine data from the 2 studies, and the differences between trials of treatment effect, placebo effect and baseline VAT should be noted.

Interactions (pooled analyses)

Age: No statistically significant treatment-by-age quartile interaction was observed for the percent change from baseline in VAT in the pooled main Phase studies when age was included as a categorical or a continuous covariate.

A statistically significant treatment-by-age quartile interaction was observed for the change from baseline in trunk fat in the pooled main Phase studies when age was included as a categorical covariate. Except for the third quartile of age (50th-75th percentile), the change from baseline in trunk

fat in the tesamorelin group in the other quartiles of age was statistically significant versus placebo (decrease in the tesamorelin group and increase in the placebo group). When age was included as a continuous covariate, no statistically significant treatment-by-age interaction was observed for the change from baseline in trunk fat in the pooled Main Phase studies.

Gender: The effect of tesamorelin in males was similar to that in females with no statistically significant treatment-by-gender interaction observed for the percent change from baseline in VAT or in trunk fat in the pooled main Phase studies. This is in contrast to the finding of study- 011, where a lower response was observed in the small number of female patients.

Race: No statistically significant treatment-by-race interaction was observed for the percent change from baseline in VAT or in trunk fat in the pooled Main Phase studies.

Region: No analyses of treatment-by-region were performed for the percent change from baseline in VAT in the pooled Main Phase studies. With respect to the applicability of the study results to the European target population the analysis according to region is considered of major interest. (see also 'Efficacy data and additional analyses' below)

Centre: Results of treatment-by-centre analyses of percent showed for study TH9507/III/LIPO/010 that the pooled site-by-treatment interaction was not significant ; pooled site was of borderline statistical significance (p=0.059) and for study TH9507-CTR-1011 The pooled site-by-treatment interaction and the pooled site effect were not significant, indicating no effect on centre on the overall conclusion.

Impaired glucose tolerance/diabetes condition; ART, testosterone use at baseline: A statistical significant interaction with respect to percent change from baseline in VAT or trunk fat was neither detected for treatment-by-impaired glucose tolerance/diabetes condition, baseline VAT (quartiles), treatment-by- ART at baseline, change in ART nor for testosterone use at baseline.

The greater efficacy of the tesamorelin group compared to placebo was generally consistent across these subgroups and efficacy was generally consistent with the overall results.

Supportive study(ies)

N/A

Discussion on clinical efficacy

Design and conduct of clinical studies

The applicant has submitted three pivotal studies in the indication proposed, which can indeed be considered as two studies with a main phase of 26 weeks (studies -010 and -011) and an extension period after re-randomisation of another 26 weeks (studies -010 and -012). The studies are of a very similar design.

The provided dose finding data are considered rather limited. The dose finding has primarily been orientated at the PD parameter IGF-1. However, pharmacodynamic as well as the safety data cast considerable doubt on whether the chosen dose of 2 mg tesamorelin sc per day is appropriate (see PD and Safety assessment).

Whereas study -010 was conducted exclusively in North America, European sites were included in studies -011 and -012. The studies were designed as multicentre, randomised, double-blind, placebo-controlled studies. As there is currently no licensed treatment for the sought indication in the EU, placebo control is considered appropriate for these main studies. Within the clinical programme, however, a study comparing tesamorelin with hGH would have been of interest, given that both drugs

act on the growth hormone axis and, in hindsight, the very similar results obtained with these agents (see also *Grunfeld C et al 2007*).

The applicant has provided some arguments as to why diet and exercise were not included in a comparator arm, but has not considered the consequences of having no inclusion criteria based on failure to improve with intensive diet and exercise. This is an important outstanding issue in the benefit/risk balance.

Regarding participants' selection the high rate of screening failures and a high mean BMI as well as a wide range thereof, is especially noteworthy. A clear differentiation between HIV-infected patients being overweight/obese and the claimed target population, i.e. those suffering from abdominal lipohypertrophy is not made. Some results, e.g. differential reasons for drop-out or protocol violations, question the successful blinding of these studies.

Conducting the primary analysis at 26 weeks rather than 52 weeks might have overestimated the true clinical benefit of treatment.

The relevance of the primary efficacy endpoint, "VAT reduction of at least 8%", has not been discussed by the applicant. Neither has conclusive evidence been found in the literature, indicating that the observed VAT reduction can be regarded as a surrogate for a clinically meaningful effect, e.g. a reduction in cardiovascular morbidity or mortality. Even if inter-patients as well as intra-patient variability in the longitudinal analyses were accounted for by blinding, this is in fact hampered by the obviously insufficient masking in these studies. Due to these uncertainties in the meaning of the primary endpoint, robust evidence from the secondary endpoints in terms of positive effects on blood lipids and PROs, such as patients' wellbeing and body image are considered essential in support of the claimed indication. The gatekeeper strategy including certain blood lipids and patient reported outcome measures, which was used for control of type I error and labelling purposes, as well as the other statistical methods are considered appropriate. No GCP violations have become obvious.

Efficacy data and additional analyses

The studies have consistently met their primary endpoint: VAT reduction was most pronounced in the first 13 weeks and appeared to have a kind of ceiling effect thereafter. A relevant deficiency with respect to the MAA for Europe is that the size of the effect in the European subgroup appears to be considerably smaller compared to North Americans. Tesamorelins' effects have been shown to be most pronounced in those patients with the worst baseline values (e.g. highest VAT amount, highest TC:HDL-C ratio) and at least in the general population there are considerable differences between North Americans and Europeans with respect to BMI and metabolic parameters. Also, the percentage of European patients was relatively small, adding to the uncertainty over the expected clinical benefit of tesamorelin. It is of note that European patients experienced a larger mean weight gain with tesamorelin than with placebo with a higher value of up to 14 kg after 26 weeks. With respect to the secondary and other outcome measures, no consistent or robust effects were observed for tesamorelin. The gatekeeper approach was not successful for study -011, as effects on lipids were not statistically significantly different between the groups according to the primary analysis. Moreover, for the PRO score, defined as most relevant a priori, the "Belly Appearance Distress", significant differences between tesamorelin and placebo were not seen in study -010 after the first 26 weeks. Only after 52 weeks of tesamorelin therapy a statistical significant difference between those patients switching to placebo after 26 weeks and those staying on tesamorelin for 52 weeks were seen in both studies. As a 52-week placebo group was not included in any of the long-term studies, these results must be regarded with caution. For the other parameters investigated, such as body composition, or anthropometric measures statistical significances were reported for some items. As adjustment for multiplicity was not done, this can be regarded as exploratory at best. Moreover, these changes are not regarded as substantial. Most interestingly, the patients' assessment for clinical relevance of the

observed changes in body appearance provided inconclusive results with a clear trend to indicating no benefit. Although initially claimed as a potential positive effect of reduction in VAT, an impact of tesamorelin on adherence to antiretroviral therapy has not been demonstrated. In patients discontinuing tesamorelin after 26 weeks, a quick regain in visceral adipose tissue to baseline values or even higher was recorded. Whether even a rebound phenomenon after discontinuation of tesamorelin may occur, can not be assessed, as no long-term placebo group was included in any of the studies and participants were not followed-up for longer than 52 weeks.

Conclusions on clinical efficacy

Twenty-six weeks of treatment with tesamorelin led to a consistent and statistically significant VAT reduction in HIV-infected patients with excess VAT at baseline, which was maintained over 52 weeks of continuous treatment. However, due to some methodological constraints as depicted above, the unclear clinical relevance of the arbitrarily chosen main endpoint, and the inconsistent and thus not supportive nature of the additional endpoints, the benefits of the treatment are considered questionable.

It has not been shown that tesamorelin positively influences cardiovascular risk, in fact as detailed in the safety section below, in individual patients there is a potential risk of worsening diabetic control. Neither has data been submitted to show how the specifically proposed waist circumference cut-offs correlate with cardiovascular risk in the target population,

The short duration of the main study phase might also have overestimated the treatment effect. Other major concerns surround the choice of control arms, the difference in treatment and placebo effect between the pivotal studies, the effect size in the European population and the generalisability of the results given the uncertainty about the aetiology and differential diagnosis of lipodystrophy in HIV patients.

Consequently the proposed indication is not approvable from an efficacy point of view. There are a number of other points for clarification highlighted in the assessment.

Clinical safety

The safety of tesamorelin was evaluated across 18 clinical studies, 8 Phase 1, 7 Phase 2, and 3 Phase 3 studies. In addition, safety data from 2 completed Phase 1 studies, TCHUV 10-98 and TH9507/I/HV/002, have been included. The safety population was defined as all randomized subjects who received at least 1 dose of either tesamorelin or placebo. Data were analyzed according to the treatment the subject actually received and according to Observed Case analysis, i.e. missing data were not imputed. For subjects who received multiple dose levels of tesamorelin, the analysis treatment group was defined as the maximum dose level of study treatment the subject received.

For analysis the applicant grouped the safety data into 9 study groups; Study Group 0 included pooled safety data from all 18 studies and Study Group 1 safety data from the pivotal Phase 3 trials. Fifteen studies were pooled into 5 mutually exclusive groups (1, 3, 5, 6, and 7) based on the study population and study phase. Results from Study TH9507/II/Diabetic/006 (Study Group 4) of individuals with diabetes were presented separately. The study designs and populations of the 2 remaining studies, TH9507/II/LIPO/008 (Study Group 2) and TH9507-CTR-1015 (Study Group 8), were inconsistent with the pooling strategy and consequently, were not pooled with other studies.

Safety parameters evaluated in the tesamorelin clinical program included adverse events (AEs), routine safety laboratory tests (i.e. blood chemistry, haematology, and urinalysis), IGF-1 levels, IGFBP-3 levels, glucose parameters (i.e. fasting blood glucose [FBG], 2-hour glucose on the Oral Glucose Tolerance Test [OGTT], insulin levels, calculated homeostasis model assessment-insulin

resistance [HOMA-IR], glycosolated haemoglobin [HbA1c]), anti-tesamorelin IgG antibodies, anti-tesamorelin IgE antibodies, neutralizing antibodies (NAbs), HIV viral load and CD4 cell count, vital signs, electrocardiograms (ECG), echocardiography (ECHO), physical examination, and concomitant medications. Other relevant clinical and non-clinical data included investigation of suspected cases of hypersensitivity reaction, observations from animal studies and PK, PD, and DDI data.

Patient exposure

In Study Group 0, weeks 0-26, 1222 subjects received tesamorelin and 459 subjects received placebo. Among tesamorelin-treated subjects, 953 received 2 mg/day sc, 179 ≤ 1 mg/day sc, 68 received 4 mg/day sc, and 22 received 0.2 mg/day iv (see table 22).

Table 22. Subject Accounting and Final Study Disposition by Treatment Assignment for 0-26 Weeks All Study Groups Combined (Study Group 0)

	Tesamorelin Dose Groups				
	sc			iv	
	4 mg/day	2 mg/day	≤1 mg/day	0.2 mg/day	Placebo
No. subjects in safety population	**68**	**953**	**179**	**22**	**459**
No. (%) subjects who completed study	65 (95.6)	779 (81.7)	165 (92.2)	21 (95.5)	372 (81.0)
Primary reason for discontinuation (as per CRF): n (%)					
Adverse event	1 (1.5)	72 (7.6)	4 (2.2)	0	23 (5.0)
Lack of compliance with protocol requirements and/or procedures	0	14 (1.5)	0	0	2 (0.4)
Withdrawal of consent	0	61 (6.4)	6 (3.4)	1 (4.5)	34 (7.4)
Lost to follow-up	0	14 (1.5)	0	0	9 (2.0)
Other	2 (2.9)	13 (1.4)	4 (2.2)	0	19 (4.1)

In Study Group 1, 543 subjects received tesamorelin 2 mg/day and 263 placebo during the main phases of the HIV pivotal studies. In both the main and extension phases (T-T) 246 subjects received tesamorelin, while 135 subjects received tesamorelin in the Main Phase and placebo in the Extension (T-P), and 197 subjects placebo in the Main Phase and tesamorelin in the Extension (P-T) (see table 23).

Table 23. Subject Accounting and Final Study Disposition by Study and Treatment Assignment HIV Pivotal – MAIN PHASE (Study Group 1)

	TH9507/III/LIPO/010		TH9507-CTR-1011		Combined	
	Tesamorelin 2 mg/day	Placebo	Tesamorelin 2 mg/day	Placebo	Tesamorelin 2 mg/day	Placebo
No. subjects in safety population	**273**	**137**	**270**	**126**	**543**	**263**
No. (%) subjects who completed study	211 (77.3)	115 (83.9)	202 (74.8)	92 (73.0)	413 (76.1)	207 (78.7)
Primary reason for discontinuation (as per CRF): n (%)						
Adverse event	26 (9.5)	6 (4.4)	26 (9.6)	12 (9.5)	52 (9.6)	18 (6.8)
Lack of compliance with protocol requirements and/or procedures	8 (2.9)	0	5 (1.9)	1 (0.8)	13 (2.4)	1 (0.4)
Withdrawal of consent	19 (7.0)	12 (8.8)	24 (8.9)	7 (5.6)	43 (7.9)	19 (7.2)
Lost to follow-up	7 (2.6)	2 (1.5)	5 (1.9)	7 (5.6)	12 (2.2)	9 (3.4)
Other	2 (0.7)	2 (1.5)	8 (3.0)	7 (5.6)	10 (1.8)	9 (3.4)

Table 24. Subject Accounting and Final Study Disposition by Study and Treatment Assignment HIV Pivotal – EXTENSION PHASE (Study Group 1)

	TH9507/III/LIPO/010			TH9507-CTR-1012			Combined		
	Tesamorelin-Tesamorelin	Tesamorelin-Placebo	Placebo-Tesamorelin	Tesamorelin-Tesamorelin	Tesamorelin-Placebo	Placebo-Tesamorelin	Tesamorelin-Tesamorelin	Tesamorelin-Placebo	Placebo-Tesamorelin
No. subjects in safety population	**154**	**50**	**111**	**92**	**85**	**86**	**246**	**135**	**197**
No. (%) subjects who completed study	129 (83.8)	40 (80.0)	87 (78.4)	80 (87.0)	63 (74.1)	72 (83.7)	209 (85.0)	103 (76.3)	159 (80.7)
Primary reason for discontinuation (as per CRF): n (%)									
Adverse event	5 (3.2)	3 (6.0)	13 (11.7)	1 (1.1)	4 (4.7)	5 (5.8)	6 (2.4)	7 (5.2)	18 (9.1)
Lack of compliance with protocol requirements and/or procedures	7 (4.5)	1 (2.0)	2 (1.8)	1 (1.1)	3 (3.5)	1 (1.2)	8 (3.3)	4 (3.0)	3 (1.5)
Withdrawal of consent	12 (7.8)	4 (8.0)	6 (5.4)	8 (8.7)	11 (12.9)	7 (8.1)	20 (8.1)	15 (11.1)	13 (6.6)
Lost to follow-up	1 (0.6)	2 (4.0)	3 (2.7)	2 (2.2)	2 (2.4)	1 (1.2)	3 (1.2)	4 (3.0)	4 (2.0)
Other	1 (0.6)	0	0	0	2 (2.4)	0	1 (0.4)	2 (1.5)	0

Reference: ISS Table 1.1e
Note: Tesamorelin refers to tesamorelin 2 mg/day.

Demographic characteristics were similar among treatment groups. Mean age across groups ranged from 44.6 to 46.5 years. The majority of subjects were male and Caucasian. Baseline HIV-related characteristics were generally similar between groups. The mean duration of HIV condition ranged from 10.6 to 12.1 years and the majority of subjects had undetectable viral loads. The mean duration of ART therapy ranged from 71.8 to 77.3 months. A summary of the cumulative exposure to tesamorelin, stratified by study and time on study for Study Group 1 is given in table 25.

Table 25. Summary of Cumulative Exposure to Tesamorelin, Stratified by Study and Time on Study (0-13 weeks, 14-26 weeks, 27-39 weeks, 40-52 weeks, and ≥ 52 weeks) (Study Group 1)

Parameter	Statistic	TH9507/III/LIPO/010 (Main & Extension Phase) TH9507 2 mg/day (N=384)	TH9507-CTR-1011 & TH9507-CTR-1012 (Main & Extension Phase) TH9507 2 mg/day (N=356)	Combined Results TH9507 2 mg/day (N=740)
Cumulative Duration of Exposure to Tesamorelin (Days)	N	381	354	735
	Mean	225.5	200.4	213.4
	SD	108.8	103.0	106.7
	Median	183.0	182.0	182.0
	Min., Max.	2; 423	1; 394	1; 423
Subjects with exposure of:				
0 - 13 Weeks		384 (100.0)	356 (100.0)	740 (100.0)
14 - 26 Weeks		339 (88.3)	308 (86.5)	647 (87.4)
27 - 39 Weeks		217 (56.5)	183 (51.4)	400 (54.1)
40 - 52 Weeks		139 (36.2)	86 (24.2)	225 (30.4)
≥ 52 Weeks		27 (7.0)	16 (4.5)	43 (5.8)

* Total exposure (cumulative) to Tesamorelin 2 mg will be calculated for each subject across the Main (TH9507/III/LIPO/010 Main and TH9507-CTR-1011) and Extension (TH9507/III/LIPO/010 Extension and TH9507-CTR-1012) phases as the sum of the exposure to Tesamorelin 2 mg in each phase. ISS Table 1.3.2

This safety database is in accordance with current guidelines. However, there are no controlled data beyond 26 weeks of continuous exposure, only 209 subjects completed 52 weeks, and there are no relevant data ≥ 52 weeks; percentages of women as well as ethnicities other than white are low.

Adverse events

In both groups, tesamorelin and placebo, a higher proportion of subjects reported AEs for the time on study period 0-13 weeks (71.8% and 64.7%, respectively) compared to 14-26 weeks (51.5% and 49.0%, respectively). For the Main Phase of Study Group 1 (HIV Pivotal Studies) the applicant tabulated AEs comparing tesamorelin to placebo, while for the Extension Phase the T-T, T-P, and P-T groups were tabulated. AEs occurring in ≥ 5% of tesamorelin-treated subjects and more frequently in the tesamorelin group than placebo are presented in the table 26.

Table 26. Number (%) of Subjects with AEs ≥ 5% and in More Than One and More Frequently on Tesamorelin than Placebo by Treatment Assignment HIV Pivotal – MAIN and EXTENSION PHASE (Study Group 1)

	TH9507/III/LIPO/010 TH9507-CTR-1011		TH9507/III/LIPO/010 TH9507-CTR-1012		
	0-26 Weeks		27-52 Weeks		
	Tesamorelin 2 mg/day	Placebo	Tesamorelin-Tesamorelin	Tesamorelin-Placebo	Placebo-Tesamorelin
No. subjects in safety population	**543**	**263**	**246**	**135**	**197**
No. subjects with AEs	425 (78.3)	187 (71.1)	154 (62.6)	81 (60.0)	146 (74.1)
SOC Preferred Term					
General disorders and administration site conditions	**189 (34.8)**	**65 (24.7)**	**32 (13.0)**	**21 (15.6)**	**53 (26.9)**
Injection site erythema	46 (8.5)	7 (2.7)	3 (1.2)	0	13 (6.6)
Injection site pruritus	41 (7.6)	2 (0.8)	5 (2.0)	0	16 (8.1)
Oedema peripheral	33 (6.1)	6 (2.3)	5 (2.0)	0	8 (4.1)
Infections and infestations	**144 (26.5)**	**78 (29.7)**	**69 (28.0)**	**30 (22.2)**	**50 (25.4)**
Upper respiratory tract infection	23 (4.2)	17 (6.5)	18 (7.3)	5 (3.7)	8 (4.1)
Musculoskeletal and connective tissue disorders	**158 (29.1)**	**63 (24.0)**	**33 (13.4)**	**19 (14.1)**	**66 (33.5)**
Arthralgia	72 (13.3)	29 (11.0)	14 (5.7)	8 (5.9)	29 (14.7)
Pain in extremity	33 (6.1)	12 (4.6)	8 (3.3)	1 (0.7)	15 (7.6)
Myalgia	30 (5.5)	5 (1.9)	3 (1.2)	0	7 (3.6)

Reference: ISS, Tables 1.4.1.1, 1.4.1.1e, 1.4.1.2 and 1.4.1.2e, Appendix D

Notes: Tesamorelin refers to tesamorelin 2 mg/day. AEs occurring in ≥5% of tesamorelin-treated subjects and more frequently in tesamorelin than placebo subjects in the Main Phase are also shown for the Extension Phase. Similarly, AEs occurring in ≥5% of T-T subjects and more frequently in T-T than T-P subjects in the Extension Phase are also shown for the Main Phase.

Injection related AEs as well as peripheral oedema and myalgia were considerably more frequent in the tesamorelin group compared to placebo; thus it is questionable whether blinding could have been maintained during the trial.

AEs considered by the applicant to be treatment related and with a higher frequency with tesamorelin compared to placebo were especially palpitations, vomiting, injection related AEs, peripheral oedema, pain in extremity, myalgia, paraesthesia, hypoaesthesia, depression, hypertension, increased creatine phosphokinase, and hypertriglyceridaemia. The comparison of main vs. extension phase shows that while these AEs occurred more frequently with tesamorelin in the main phase, incidences were far lower in the extension phase T-T and T-P groups, and in the P-T group incidences were comparable to those in the tesamorelin main phase group. Correspondingly, the incidence of AEs was lower in patients continuously on tesamorelin for 52 weeks compared tesamorelin in the main phase only. These observations, together with the considerable difference in the incidence of dropouts, indicate a relevant selection bias for the extension phase. The analysis of injection site related AEs by study time period again emphasises the high incidence of such events and a time profile suggestive of differential dropout.

Table 27. Clinical Trial Adverse Drug Reactions

Common and Very Common Adverse Drug Reactions (Frequency ≥ 1%)				
	26-Week Main Phase		26-Week Extension Phase	
Body System Preferred Term	**Tesamorelin 2 mg/d (N=543) %**	**Placebo (N=263) %**	**T - T (N=246) %**	**T - Pl (N=135) %**
Cardiac disorders				
Palpitations	1.1	0.4		
Gastrointestinal disorders				
Nausea	4.4	3.8		
Vomiting	2.6	0.0	2.0	0.7
Dyspepsia	1.7	0.8		
Abdominal pain upper	1.1	0.8		
General disorders and administration site conditions				
Injection site erythema	8.5	2.7	1.2	0.0
Injection site pruritus	7.6	0.8	2.0	0.0
Oedema peripheral	6.1	2.3	2.0	0.0
Injection site pain	4.1	3.0		
Injection site irritation	2.9	1.1		
Pain	1.7	1.1		
Injection site haemorrhage	1.7	0.4		
Injection site urticaria	1.7	0.4		
Injection site swelling	1.5	0.4		
Injection site reaction	1.3	0.8		
Chest pain	1.1	0.8		
Injection site rash	1.1	0.0		
Injury, poisoning and procedural complications				
Muscle strain	1.1	0.0		
Investigations				
Blood creatine phosphokinase increased	1.5	0.4		
Metabolism and nutrition disorders				
Hypertriglyceridaemia	1.1	0.4		
Musculoskeletal and connective tissue disorders				
Arthralgia	13.3	11.0		
Pain in extremity	6.1	4.6	3.3	0.7
Myalgia	5.5	1.9	1.2	0.0
Musculoskeletal pain	1.8	0.8		
Musculoskeletal stiffness	1.7	0.4		
Joint stiffness	1.5	0.8		
Muscle spasms	1.1	0.8		
Joint swelling	1.1	0.0		
Nervous system disorders				
Paraesthesia	4.8	2.3	1.6	1.5
Hypoaesthesia	4.2	1.5	1.6	0.7
Carpal tunnel syndrome	1.5	0.0		
Neuropathy peripheral			1.6	1.5
Dizziness			1.6	1.5
Psychiatric disorders				
Depression	2.0	1.5	1.6	0.7
Insomnia			1.2	0.0
Skin and subcutaneous tissue disorders				
Rash	3.7	1.5		
Pruritus	2.4	1.1	1.2	0.7
Urticaria			1.2	0.0
Night sweats	1.1	0.4	1.2	0.0
Vascular disorders				
Hypertension	1.3	0.8	1.6	1.5
Hot flush			1.2	0.7

Table 28. Clinical Trial Adverse Drug Reactions

Less Common Adverse Drug Reactions (Frequency < 1%; occurred in greater than 1 study subject)		
	26-Week Main Phase	**26-Week Extension Phase**
Blood and lymphatic system disorders	Anaemia, Polycythaemia	Lymphadenopathy
Cardiac disorders	Tachycardia	
Ear and labyrinth disorders	Vertigo	
Endocrine disorders	Hypogonadism	Hypogonadism
Eye disorders	Conjunctivitis, Eye swelling	
Gastrointestinal disorders	Abdominal distension, Dry mouth, Flatulence, Paraesthesia oral, Stomach discomfort	Gastritis, Abdominal distension, Stomach discomfort
General disorders and administration site conditions	Injection site mass, Asthenia, Cyst, Energy increased, Injection site nodule, Local swelling	Injection site irritation, Chest pain, Injection site nodule, Injection site reaction, Injection site haemorrhage
Immune system disorders		Hypersensitivity
Injury, poisoning and procedural complications	Limb injury, Epicondylitis	Muscle strain
Investigations	Weight increased, Blood glucose increased, Blood insulin increased, Weight decreased	Cardiac murmur
Metabolism and nutrition disorders	Hyperlipidaemia, Decreased appetite, Glucose tolerance impaired, Hyperglycaemia, Gout	
Musculoskeletal and connective tissue disorders	Muscular weakness, Plantar fasciitis, Tenosynovitis stenosans, Arthritis, Axillary mass,Trigger finger	Musculoskeletal stiffness, Joint stiffness, Musculoskeletal pain, Musculoskeletal chest pain
Nervous system disorders	Dysgeusia, Sciatica, Migraine, Sinus headache, Facial palsy, Tension headache	Carpal tunnel syndrome, Memory impairment
Psychiatric disorders	Stress	
Renal and urinary disorders	Dysuria	
Reproductive system and breast disorders	Breast enlargement, Benign prostatic hyperplasia, Breast tenderness	
Respiratory, thoracic and mediastinal disorders	Bronchial hyperreactivity	
Skin and subcutaneous tissue disorders	Dry skin, Skin disorder, Rash papular	Hyperhidrosis

Notes: Tesamorelin refers to tesamorelin 2 mg/day.

During the pivotal HIV trials the incidence of AEs known to be related to GH was 25.6% in patients on tesamorelin and 13.7% on placebo. AEs known to be related to GH and occurring in ≥ 1% of patients on tesamorelin and more frequently than on placebo in both phases were peripheral oedema, pain in extremity, myalgia, paraesthesia, and hypoaesthesia. With the therapeutic use of GH or IGF-1 AEs lymphoid tissue hyperplasia and intracranial hypertension have been described.

Tesamorelin also consistently increased IGF-1 levels; IGF-1 levels at baseline were comparable between groups. After 26 weeks of treatment, about 35% of HIV patients on tesamorelin in the pivotal trials had IGF-1 standard deviation scores above +3, compared to 2.2% to 2.7% on placebo. About 45% to 50% on tesamorelin had IGF-1 standard deviation scores above +2. An analysis of changes in IGF-1 levels by age showed a greater percentage of T-T treated subjects in the Extension Phase above the median age (> 48 years) shifted from IGF-1 SDS ≤ +2 to SDS > +2 (34.0%) as compared to below the median age (20.4%), indicating a possible trend for larger shifts among older subjects with longer exposure to tesamorelin. In study TH9507/I/PKPD/009 the molar ratio of IGF-1 to IGFBP-3 increased from Day 1 to Day 15 indicating an increase in free IGF-1.

Table 29. Mean IGF-1 SDS (0-26 Weeks) by Treatment Assignment HIV Pivotal – Main Phase (Study Group 1)

		TH9507/III/LIPO/010		TH9507-CTR-1011		Combined	
		Tesamorelin 2 mg/day (N=273)	Placebo (N=137)	Tesamorelin 2 mg/day (N=270)	Placebo (N=126)	Tesamorelin 2 mg/day (N=543)	Placebo (N=263)
Baseline	N	269	136	265	125	534	261
	Mean (SD)	-0.16 (1.22)	-0.00 (1.68)	-0.46 (1.41)	-0.43 (1.34)	-0.31 (1.32)	-0.21 (1.54)
	SDS ≤ +2 n (%)	251 (93.3)	125 (91.9)	250 (94.3)	120 (96.0)	501 (93.8)	245 (93.9)
	SDS ≤ +3 n (%)	266 (98.9)	128 (94.1)	260 (98.1)	123 (98.4)	526 (98.5)	251 (96.2)
Week 26	N	207	111	198	91	405	202
	Mean (SD)	2.51 (2.78)	-0.42 (1.29)	2.28 (2.91)	-0.48 (1.23)	2.39 (2.85)	-0.45 (1.26)
	SDS > +2 n (%)	103 (49.8)	6 (5.4)	89 (44.9)	4 (4.4)	192 (47.4)	10 (5.0)
	SDS > +3 n (%)	73 (35.3)	3 (2.7)	71 (35.9)	2 (2.2)	144 (35.6)	5 (2.5)

The applicant has suggested that the current age and gender matched reference ranges for IGF-1 might not be relevant to the target population; this is argument is not acceptable. However even when IGF-1 is re-analysed based on the observed means and standard deviations at baseline, 30-40% of patients treated with tesamorelin for 26 weeks shifted to having an IGF-1 more than 2 standard deviations outside the amended range.

The incidence of GH AEs is related to the administered dose (e.g. SmPC Omnitrope) and recently an increase in the risk of mortality in patients treated with GH during childhood has been discussed (long-term epidemiological study 'Santé Adulte GH Enfant' (SAGhE).). Increased IGF-1 levels as well as HIV infection are associated with an increased risk of cancer (e.g. Achenbach et al., 2011; SmPC Omnitrope).

In conclusion, although according to the applicant the rational for tesamorelin application in contrast to GH in the envisaged patient population is the avoidance of GH related AEs, there is clearly a considerably and clinically relevant higher incidence of AEs known to be related to GH and an alarming degree of increases in IGF-1 SDS > +3. Data from a clinical trial comparing tesamorelin AEs in relation to GH have not been provided. The significant and clinically relevant increase in IGF-1 levels is still considered a Major Concern; IGF-1 levels should remain within the physiological range adjusted for age and gender, i.e. within ± 2SDS. Efficacy data for an individualised dosing to keep IGF-1 within this range are not available.

Cardiomegaly and subsequent heart failure are known consequences of long-term growth hormone excess in adults. Overall safety data on cardiac AEs including ECG and ECHO do not show an increased risk with tesamorelin compared to placebo. However, in the HIV Pivotal Study Main Phases for tesamorelin compared to placebo there were increased frequencies of hypertension (1.3 vs. 0.8, respectively), palpitations (1.1 vs. 0.4, respectively), and tachycardia (no frequency given). There was an excess of peripheral oedema, occurring in 6.1% of tesamorelin-treated patients. No appropriate response has been provided regarding this issue. Considering that the database is too small for a definite conclusion on these AEs the applicant is requested to discuss how these issues will be further investigated including the RMP.

ECGs done in studies CTR 1011-2 and read centrally by a cardiologist blinded to treatment allocation did not reveal a concern. Taking into account the relevant preclinical work and in vitro data, the cumulative safety data support the applicant's decision to omit a thorough QT study.

Serious adverse events and deaths

Relatively more people on tesamorelin compared to placebo died during the clinical trials. However, the analysis of these cases does not indicate a specific causal relation to tesamorelin treatment; the absolute numbers are low and patients generally had a medical history relevant to the AE leading to death. Narratives of all cases have been provided. There was one patient on placebo during the Main Phase and tesamorelin 2 mg/day during the Extension Phase who died after tonsillectomy and surgical removal of polyps; the death was deemed unrelated to study treatment by the investigators.

Overall, from the provided data no increase in the incidence of SAEs in patients treated with tesamorelin compared to placebo is seen. While the reporting rate of SAE was comparable between groups the proportion of subjects with SAEs considered to be related to study treatment was higher with tesamorelin compared to placebo. The applicant specifically provided an analysis of cancer AEs. However, since controlled exposure is limited to 26 weeks, this analysis is of no value.

Laboratory findings

Increases from baseline in creatine kinase were observed in each treatment group, but with a greater incidence in the tesamorelin-treated group. This still needs to be further discussed by the applicant. Otherwise no clinically relevant changes regarding clinical chemistries or urinalysis have been seen. Regarding haematology, in the Main Phase more patients on tesamorelin had shifts from low or normal at baseline to high in eosinophils (4.3%) compared to placebo (2.0%); similarly in the Extension Phase shifts from low or normal at baseline to high in eosinophils occurred (T-T 6.2% vs. T-P 3.3%).

In the main phase, 1.7% on tesamorelin compared to 0.4% on placebo experienced a glucose-related AE. Tesamorelin had no statistically significant effect on fasting blood glucose, insulin, or insulin resistance, but the mean change from baseline in HbA_{1c} was statistically significantly higher with tesamorelin compared to placebo. The proportion of subjects classified as diabetic based on HbA_{1c} levels increased from baseline in both groups, but to a considerably higher extent on tesamorelin (6.6%) compared to placebo (2.5%); 28 (5.34%) patients on tesamorelin compared to 6 (2.35%) on placebo had at least 1 post-baseline HbA_{1c} value ≥ 6.5% and 7 (1.34%) vs. none had at least 1 post-baseline value ≥ 7%. Two subjects in Phase 3 on tesamorelin were discontinued due to increases in FBG levels. For the combined Main and Extension Phase analysis, 7.0% on tesamorelin compared to 5.9% on placebo had FBG shifts to ≥ 7 mmol/L (126 mg/dL) at least once; 33.2% and 19.6%, respectively, had a FBG shift to 5.6-7 mmol/L (100-126 mg/dL). Of the patients classified as diet-controlled diabetic at baseline (≥ 7-8.4 mmol/L (126-150 mg/dL)), five (50%) on tesamorelin compared to one (11%) on placebo shifted to > 8.4 mmol/L (150 mg/dL).

No clinically relevant differences between treatments have been reported for shifts to higher viral load or changes in CD4 cell counts from the provided analysis.

Safety in special populations

In general, the AE profile of tesamorelin appears not to be influenced by age. However, in the Extension Phase a greater percentage of T-T treated subjects above the median age (> 48 years) shifted from IGF-1 SDS ≤ +2 to SDS > +2 (34.0%) as compared to below the median age (20.4%), indicating a possible trend for larger shifts among older subjects with longer exposure to tesamorelin.

The small number of females relative to males and of ethnicities other than White do not allow for a meaningful analysis of AEs by gender or ethnicity. The applicant should provide further discussion on the appropriateness of data in females and on ethnic factors.

No clinically significant differences in AEs were observed among BMI subpopulations.

Regarding liver function AEs the applicant has now provided and discussed available data. At study entry, hepatic function was only assessed in terms of ALT and AST being ≥ 3 times the upper limit of normal. Screening assessments were inadequate to define post-hoc hepatic function in terms of Child-Pugh classification. The AST/ALT exclusion criteria cannot completely rule out hepatic impairment, although the general exclusion criteria included any co-morbid condition that would not allow the patient to complete the study. There are no safety data in any patients with renal impairment. The applicant should propose appropriate amendments to the SmPC.

Immunological events

About 50% of all patients treated with tesamorelin developed anti-tesamorelin IgG antibodies. This high prevalence was maintained with continuous treatment for 52 weeks; about 10% of these patients showed high titres. The prevalence of anti-tesamorelin IgG antibodies decreased with treatment discontinuation. About 60% of tesamorelin IgG antibody positive subjects showed cross-reactivity with hGRF. Twelve of 122 subjects exposed to tesamorelin for 52 weeks (T-T group) were hGRF NAb-positive. In subjects on tesamorelin for 26 weeks, 171 subjects tested anti-tesamorelin IgG antibody-positive and of those 12 subjects were hGRF NAb-positive. In a sub-group of randomly selected anti-tesamorelin IgG antibody positive and negative subjects in Study TH9507/III/LIPO/010 none of the subjects tested positive for anti-tesamorelin IgE antibodies. Two subjects with hypersensitivity reactions tested positive for anti-tesamorelin IgE antibodies. Both showed increased eosinophil counts. Hypersensitivity reactions occurred in 2.9% and 4.1% of subjects in the tesamorelin and the P-T groups, respectively during 26 weeks of treatment; there were no cases of anaphylactic reactions or other SAE of hypersensitivity. However, cases did include several skin reactions graded as severe, 1 patient with symptoms including tongue swelling, and 1 report which included dyspnoea. Given the high incidence of antibody development and hypersensitivity reactions, the possibility of anaphylactic reactions is considered very likely.

Safety related to drug-drug interactions and other interactions

No clinically relevant safety issues related to DDIs and other interactions have been identified. In general, subpopulations were too small for any meaningful interpretation of the results.

Discontinuation due to AES

Overall, AEs leading to discontinuation, occurring at an incidence of ≥ 1.0%, and more frequent than on placebo were nausea, arthralgia, and headache. SAEs leading to discontinuation occurred in 2.5% on tesamorelin and 2.2% on placebo; AEs leading to discontinuation and considered related to study drug by investigators occurred in 4.9% on tesamorelin and 3.1% on placebo.

In the pivotal HIV trials during the Main Phase fewer patients on tesamorelin completed the Main Phase compared to placebo (76.1% vs. 78.7%, respectively). AEs were the reason for discontinuation in 9.6% on tesamorelin and 6.8% on placebo; corresponding figures for withdrawal of consent were 7.9% and 7.2%, respectively. Discontinuation due to GH related AEs occurred in 4.2% on tesamorelin and 1.5% on placebo; incidences for discontinuation due to injection site related AEs were 4.6% and 1.5%, respectively. Twelve (2.2%) patients on tesamorelin had a hypersensitivity reaction resulting in discontinuation. During the Extension Phase the incidence of AEs leading to discontinuation was highest in the P-T group with 9.1% compared to 2.4% in the T-T and 5.2% in the T-P group. Hypersensitivity reaction resulting in discontinuation occurred in 3 patients in the T-T group (1.2%), no patient in the T-P, and 6 patients in the P-T group (3.0%). AEs leading to discontinuation in > 2.0% on tesamorelin during the Main Phase were arthralgia (2.4%) and headache (2.2%). Overall, in the Main

Phase AEs associated with injection were the most common leading to premature discontinuation; during the Extension Phase, no AE led to premature discontinuation in ≥ 1.0% of T-T subjects.

Table 30. Number (%) of Subjects with AEs Leading to Discontinuation (0-26 Weeks or 27-52 Weeks) Occurring in ≥ 1.0% of Subjects on Tesamorelin and More Frequently than in Placebo by Treatment Assignment HIV Pivotal - MAIN and EXTENSION PHASE (Study Group 1)

	TH9507/III/LIPO/010 TH9507-CTR-1011		**TH9507/III/LIPO/010 TH9507-CTR-1012**		
	0-26 Weeks		**27-52 Weeks**		
	Tesamorelin 2 mg/day	**Placebo**	**Tesamorelin-Tesamorelin**	**Tesamorelin-Placebo**	**Placebo-Tesamorelin**
No. subjects in safety population	**543**	**263**	**246**	**135**	**197**
No. subjects with AEs leading to premature discontinuation	52 (9.6)	16 (6.1)	5 (2.0)	6 (4.4)	16 (8.1)
System Organ Class Preferred Term					
Gastrointestinal disorders	**15 (2.8)**	**6 (2.3)**	**2 (0.8)**	**1 (0.7)**	**4 (2.0)**
Nausea	7 (1.3)	1 (0.4)	1 (0.4)	1 (0.7)	1 (0.5)
General disorders and administration site conditions	**32 (5.9)**	**7 (2.7)**	**1 (0.4)**	**3 (2.2)**	**10 (5.1)**
Injection site erythema	10 (1.8)	0	0	0	1 (0.5)
Injection site pruritus	10 (1.8)	0	0	0	6 (3.0)
Injection site pain	7 (1.3)	2 (0.8)	0	0	0
Oedema peripheral	7 (1.3)	0	0	0	0
Injection site urticaria	6 (1.1)	0	0	0	1 (0.5)
Musculoskeletal and connective tissue disorders	**22 (4.1)**	**5 (1.9)**	**1 (0.4)**	**0**	**5 (2.5)**
Arthralgia	13 (2.4)	2 (0.8)	1 (0.4)	0	1 (0.5)
Pain in extremity	6 (1.1)	2 (0.8)	0	0	1 (0.5)
Nervous system disorders	22 (4.1)	3 (1.1)	**1 (0.4)**	**1 (0.7)**	**5 (2.5)**
Headache	12 (2.2)	1 (0.4)	0	0	1 (0.5)

Notes: Tesamorelin refers to tesamorelin 2 mg/day. No AEs leading to premature discontinuation occurred in ≥1.0% of T-T subjects in the Extension Phase.

Post marketing experience

According to the applicant tesamorelin is marketed in the USA since December 2010. The limited data available do not indicate previously unknown safety issues.

Discussion on clinical safety

The safety database provided for this application is in accordance with current guidelines, but there are no controlled data beyond 26 weeks of continuous exposure, only 209 subjects completed 52 weeks, and there are no relevant data ≥ 52 weeks. The mean age of subjects was comparable between groups for the Phase 3 pivotal trials in HIV patients, but in the overall safety population the proportion of subjects ≥ 65 years in the tesamorelin group was considerably lower than in the placebo group (16.0% vs. 26.6%, respectively). Percentages of women as well as ethnicities other than white are low.

Injection related AEs as well as peripheral oedema and myalgia were considerably more frequent in the tesamorelin group compared to placebo; thus it is questionable whether blinding has been maintained during the trial. AEs considered by the applicant to be treatment related and with a higher frequency with tesamorelin compared to placebo where especially palpitations, vomiting, injection related AEs, peripheral oedema, pain in extremity, myalgia, paraesthesia, hypoaesthesia, depression, hypertension,

increased creatine phosphokinase, and hypertriglyceridaemia.. The comparison of main vs. extension phase shows that while these AEs occurred more frequently with tesamorelin in the main phase, incidences were far lower in the extension phase T-T and T-P groups, and in the P-T group incidences were comparable to those in the tesamorelin main phase group. Correspondingly, the incidence of AEs was lower in patients continuously on tesamorelin for 52 weeks compared tesamorelin in the main phase only. These observations, together with the considerable difference in the incidence of dropouts, indicate a relevant selection bias for the extension phase. The analysis of injection site related AEs by study time period again emphasises the high incidence of such events and a time profile suggestive of differential dropout.

During the pivotal HIV trials the incidence of AEs known to be related to GH was 25.6% in patients on tesamorelin and 13.7% on placebo. AEs known to be related to GH and occurring in ≥ 1% of patients on tesamorelin and more frequently than on placebo in both phases were peripheral oedema, pain in extremity, myalgia, paraesthesia, and hypoaesthesia. With the therapeutic use of GH or IGF-1 AEs lymphoid tissue hyperplasia and intracranial hypertension have been described.

Tesamorelin also consistently increased IGF-1 levels; IGF-1 levels at baseline were comparable between groups. After 26 weeks of treatment, about 35% of HIV patients on tesamorelin in the pivotal trials had IGF-1 standard deviation scores above +3, compared to 2.2% to 2.7% on placebo. About 45% to 50% on tesamorelin had IGF-1 standard deviation scores above +2. An analysis of changes in IGF-1 levels by age showed a greater percentage of T-T treated subjects in the Extension Phase above the median age (> 48 years) shifted from IGF-1 SDS ≤ +2 to SDS > +2 (34.0%) as compared to below the median age (20.4%), indicating a possible trend for larger shifts among older subjects with longer exposure to tesamorelin. In study TH9507/I/PKPD/009 the molar ratio of IGF-1 to IGFBP-3 increased from Day 1 to Day 15 indicating an increase in free IGF-1.

The incidence of GH AEs is related to the administered dose (e.g. SmPC Omnitrope) and recently an increase in the risk of mortality in patients treated with GH during childhood has been discussed (long-term epidemiological study 'Santé Adulte GH Enfant' (SAGhE). Increased IGF-1 levels as well as HIV infection are associated with an increased risk of cancer (e.g. Achenbach et al., 2011; SmPC Omnitrope).

In conclusion, although according to the applicant the rational for tesamorelin application in contrast to GH in the envisaged patient population is the avoidance of GH related AEs, there is clearly a considerably and clinically relevant higher incidence of AEs known to be related to GH and an alarming degree of increases in IGF-1 SDS > +3. The significant and clinically relevant increase in IGF-1 levels is considered a Major Concern; IGF-1 levels should remain within the physiological range adjusted for age and gender, i.e. within ± 2SDS.

Overall safety data on cardiac AEs including ECG and ECHO do not show an increased risk with tesamorelin compared to placebo. However, in the HIV Pivotal Study Main Phases for tesamorelin compared to placebo there were increased frequencies of hypertension (1.3 vs. 0.8, respectively), palpitations (1.1 vs. 0.4, respectively), and tachycardia (no frequency given). This issue has not been adequately addressed by the applicant.

Relatively more people on tesamorelin compared to placebo died during the clinical trials. However, the analysis of these cases does not indicate a specific causal relation to tesamorelin treatment; the absolute numbers are low and patients generally had a medical history relevant to the AE leading to death. Narratives of all cases have been provided.

Overall, from the provided data no increase in the incidence of SAEs in patients treated with tesamorelin compared to placebo is seen. While the reporting rate of SAE was comparable between groups the proportion of subjects with SAEs considered to be related to study treatment was higher

with tesamorelin compared to placebo. The applicant specifically provided an analysis of cancer AEs. However, since controlled exposure is limited to 26 weeks, this analysis is of no value.

Increases from baseline in creatine kinase were observed in each treatment group, but with a greater incidence in the tesamorelin-treated group. This still needs to be further discussed by the applicant. Otherwise, no clinically relevant changes regarding clinical chemistries or urinalysis have been seen. Regarding haematology, in the Main Phase more patients on tesamorelin had shifts from low or normal at baseline to high in eosinophils (4.3%) compared to placebo (2.0%); similarly in the Extension Phase shifts from low or normal at baseline to high in eosinophils occurred (T-T 6.2% vs. T-P 3.3%).

In the main phase, 1.7% on tesamorelin compared to 0.4% on placebo experienced a glucose-related AE. Tesamorelin had no statistically significant effect on fasting blood glucose, insulin, or insulin resistance, but the mean change from baseline in HbA_{1c} was statistically significantly higher with tesamorelin compared to placebo.

The proportion of subjects classified as diabetic based on HbA_{1c} levels increased from baseline in both groups, but to a considerably higher extent on tesamorelin (6.6%) compared to placebo (2.5%); 28 (5.34%) patients on tesamorelin compared to 6 (2.35%) on placebo had at least 1 post-baseline HbA_{1c} value ≥ 6.5% and 7 (1.34%) vs. none had at least 1 post-baseline value ≥ 7%. Two subjects in Phase 3 on tesamorelin were discontinued due to increases in FBG levels. For the combined Main and Extension Phase analysis, 7.0% on tesamorelin compared to 5.9% on placebo had FBG shifts to ≥ 7 mmol/L (126 mg/dL) at least once; 33.2% and 19.6%, respectively, had a FBG shift to 5.6-7 mmol/L (100-126 mg/dL). Of the patients classified as diet-controlled diabetic at baseline (≥ 7-8.4 mmol/L (126-150 mg/dL)), five (50%) on tesamorelin compared to one (11%) on placebo shifted to > 8.4 mmol/L (150 mg/dL). In individual patients there is a potential risk of worsening diabetic control.

No clinically relevant differences between treatments have been reported for shifts to higher viral load or changes in CD4 cell counts from the provided analysis.

In general, the AE profile of tesamorelin appears not to be influenced by age. However, analysis of shifts of IGF-1 the Extension Phase indicated a possible trend for larger shifts among older subjects with longer exposure to tesamorelin.

The small number of females relative to males and of ethnicities other than White does not allow for a meaningful analysis of AEs by gender or ethnicity. The applicant should provide further discussion on the appropriateness of data in females and on ethnic factors.

No clinically significant differences in AEs were observed among BMI subpopulations.

Regarding liver function AEs the applicant has now provided and discussed available data. At study entry, hepatic function was only assessed in terms of ALT and AST being ≥ 3 times the upper limit of normal. Screening assessments were inadequate to define post-hoc hepatic function in terms of Child-Pugh classification. The AST/ALT exclusion criteria cannot completely rule out hepatic impairment, although the general exclusion criteria included any co-morbid condition that would not allow the patient to complete the study. There are no safety data in any patients with renal impairment. The applicant should propose appropriate amendments to the SmPC.

About 50% of all patients treated with tesamorelin developed anti-tesamorelin IgG antibodies. This high prevalence was maintained with continuous treatment for 52 weeks; about 10% of these patients showed high titres. The prevalence of anti-tesamorelin IgG antibodies decreased with treatment discontinuation. About 60% of tesamorelin IgG antibody positive subjects showed cross-reactivity with hGRF; this is of considerable concern. Twelve of 122 subjects exposed to tesamorelin for 52 weeks (T-T group) were hGRF NAb-positive. In subjects on tesamorelin for 26 weeks, 171 subjects tested anti-

tesamorelin IgG antibody-positive and of those 12 subjects were hGRF NAb-positive. In a sub-group of randomly selected anti-tesamorelin IgG antibody positive and negative subjects in Study TH9507/III/LIPO/010 none subjects tested positive for anti-tesamorelin IgE antibodies. Two subjects with hypersensitivity reactions tested positive for anti-tesamorelin IgE antibodies. Both showed increased eosinophil counts. No information is available on the nature of the immune response following re-exposure after a treatment-free interval. Hypersensitivity reactions occurred in 2.9% and 4.1% of subjects in the tesamorelin and the P-T groups, respectively during 26 weeks of treatment; there were no cases of anaphylactic reactions or other SAE of hypersensitivity. However, given the high incidence of antibody development and hypersensitivity reactions, the possibility of anaphylactic reactions is considered very likely.

No clinically relevant safety issues related to DDIs and other interactions have been identified. In general, subpopulations were too small for any meaningful interpretation of the results.

Overall, AEs leading to discontinuation, occurring at an incidence of ≥ 1.0%, and more frequent than on placebo were nausea, arthralgia, and headache. SAEs leading to discontinuation occurred in 2.5% on tesamorelin and 2.2% on placebo; AEs leading to discontinuation and considered related to study drug by investigators occurred in 4.9% on tesamorelin and 3.1% on placebo. In the pivotal HIV trials during the Main Phase fewer patients on tesamorelin completed the Main Phase compared to placebo (76.1% vs. 78.7%, respectively). AEs were the reason for discontinuation in 9.6% on tesamorelin and 6.8% on placebo; corresponding figures for withdrawal of consent were 7.9% and 7.2%, respectively. Discontinuation due to GH related AEs occurred in 4.2% on tesamorelin and 1.5% on placebo; incidences for discontinuation due to injection site related AEs were 4.6% and 1.5%, respectively. Twelve (2.2%) patients on tesamorelin had a hypersensitivity reaction resulting in discontinuation. During the Extension Phase the incidence of AEs leading to discontinuation was highest in the P-T group with 9.1% compared to 2.4% in the T-T and 5.2% in the T-P group. Hypersensitivity reaction resulting in discontinuation occurred in 3 patients in the T-T group (1.2%), no patient in the T-P, and 6 patients in the P-T group (3.0%). AEs leading to discontinuation in > 2.0% on tesamorelin during the Main Phase were arthralgia (2.4%) and headache (2.2%). Overall, in the Main Phase AEs associated with injection were the most common leading to premature discontinuation; during the Extension Phase, no AE led to premature discontinuation in ≥ 1.0% of T-T subjects.

According to the applicant tesamorelin is marketed in the USA since December 2010. The limited data available do not indicate previously unknown safety issues.

Conclusions on clinical safety

The safety database provided for this application is in accordance with current guidelines, but missing controlled data beyond 26 weeks of continuous exposure limits the interpretation of the safety results. In addition only 209 subjects completed 52 weeks and there are no relevant data ≥ 52 weeks. Percentages of women as well as ethnicities other than white are low.

There was a relevant difference in the incidence of injection related AEs as well as for peripheral oedema and myalgia. The comparison of main vs. extension phase shows that while treatment emergent AEs occurred more frequently with tesamorelin in the main phase, incidences were far lower in the extension phase T-T and T-P groups, and in the P-T group incidences were comparable to those in the tesamorelin main phase group. Correspondingly, the incidence of AEs was lower in patients on tesamorelin for 52 weeks compared tesamorelin in the main phase only. The differences in the incidences of injection site related AEs by study time period again emphasises the high incidence of such events and a time profile suggestive of differential dropout. Overall these results question the blinding of treatments.

There is a clear and clinically relevant increase in the incidence of AEs known to be related to GH, including increased IGF-1 levels; IGF-1 levels at baseline were comparable between groups. After 26 weeks of treatment, about 35% of HIV patients on tesamorelin had IGF-1 > SDS +3, compared to 2.2% to 2.7% on placebo and about 45% to 50% on tesamorelin had IGF-1 standard deviation scores above +2. An analysis of changes in IGF-1 levels by age indicated a possible trend for larger shifts among older subjects with longer exposure. In addition in study TH9507/I/PKPD/009 the molar ratio of IGF-1 to IGFBP-3 increased from Day 1 to Day 15 indicating an increase in free IGF-1. Considering that increased IGF-1 levels as well as HIV infection are associated with an increased risk of cancer this finding is considered a Major Concern; IGF-1 levels should remain within the physiological range adjusted for age and gender, i.e. within ± 2SDS. The incidence of relevant AEs of therapeutic GH is related to the administered dose and recently an increase in the risk of mortality in patients treated with GH, especially with higher doses, during childhood has been discussed (SAGhE study). Also linked with the increase in IGF-1 levels is the potential to worsen the development of diabetic retinopathy. This is relevant to a significant proportion of the target population.

About 50% of all patients treated with tesamorelin developed anti-tesamorelin IgG antibodies, which was maintained with continuous treatment; about 10% of these patients showed high titres. About 60% of tesamorelin IgG antibody positive subjects showed cross-reactivity with hGRF; this is of considerable concern. About 10% tested positive of hGRF neutralising antibodies. Whilst the available observations suggest that neutralizing antibodies to endogenous GHRH are reversible, there is limited data and more information is needed.

Hypersensitivity reactions occurred in 2.9% and 4.1% of subjects in the tesamorelin and the P-T groups, respectively during 26 weeks of treatment and two subjects with hypersensitivity reactions tested positive for anti-tesamorelin IgE antibodies. There were no cases of anaphylactic reactions or other SAE of hypersensitivity. However, given the high incidence of antibody development and hypersensitivity reactions, the possibility of anaphylactic reactions is considered very likely. There is no information on the immune response following re-exposure after a treatment-free interval

Overall, AEs leading to discontinuation, occurring at an incidence of ≥ 1.0%, and more frequent than on placebo were nausea, arthralgia, and headache. AEs leading to discontinuation and considered related to study drug by investigators occurred in 4.9% on tesamorelin and 3.1% on placebo. In the pivotal trials fewer patients on tesamorelin completed the Main Phase compared to placebo (76.1% vs. 78.7%, respectively). Twelve (2.2%) patients on tesamorelin had a hypersensitivity reaction resulting in discontinuation.

Relatively more people on tesamorelin compared to placebo died during the clinical trials, but no specific causal relation to tesamorelin has been identified.

Regarding haematology, in the Main Phase more patients on tesamorelin had shifts from low or normal at baseline to high in eosinophils (4.3%) compared to placebo (2.0%); similarly in the Extension Phase shifts from low or normal at baseline to high in eosinophils occurred (T-T 6.2% vs. T-P 3.3%).

In the main phase, 1.7% on tesamorelin compared to 0.4% on placebo experienced a glucose-related AE. Tesamorelin had no statistically significant effect on FBG, insulin, or insulin resistance, but the mean change from baseline in HbA_{1c} was statistically significantly higher with tesamorelin compared to placebo. In individual patients there is a potential risk of worsening diabetic control with tesamorelin treatment.

No clinically relevant differences between treatments have been reported for shifts to higher viral load or changes in CD4 cell counts from the provided analysis.

In general, the AE profile of tesamorelin appears not to be influenced by age. However, analysis of shifts of IGF-1 the Extension Phase indicated a possible trend for larger shifts among older subjects with longer exposure to tesamorelin.

The small numbers of females relative to males as well as of ethnicities other than White do not allow for a meaningful analysis of AEs by gender or ethnicities. The applicant should provide further discussion on the appropriateness of data in females and on ethnic factors. Regarding liver function AEs the applicant has now provided and discussed available data. At study entry, hepatic function was only assessed in terms of ALT and AST being ≥ 3 times the upper limit of normal; screening assessments were inadequate to define post-hoc hepatic function in terms of Child-Pugh classification. There are no safety data in any patients with renal impairment. The applicant should propose appropriate amendments to the SmPC.

In conclusion there are major concerns regarding the safety of tesamorelin administration. Tesamorelin consistently increased IGF-1 levels > SDS +3 and increased IGF-1 levels as well as HIV infection are associated with an increased risk of cancer; IGF-1 levels should remain within the physiological range adjusted for age and gender, i.e. within ± 2SDS. Regarding the treatment of patients with renal or hepatic impairment appropriate amendments to the SmPC are required,

Pharmacovigilance system

The applicant has provided documents that set out a detailed description of the Ferrer International S.A. and Theratechnologies Inc. system of pharmacovigilance (Version 2 dated 22/23 December 2011). A statement signed by the qualified person for pharmacovigilance, indicating that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country has been provided.

The Rapporteurs consider that the Pharmacovigilance system as described by the applicant fulfils the requirements as described in Volume 9A of the Rules Governing Medicinal Products in the European Union and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

However, the applicant is urged to update the SOP list according to the information provided in the Response Document with the next update to the DDPS.

Risk management plan

Safety Specification

Pharmacovigilance plan

The applicant has provided the following pharmacovigilance plan.

Safety concern	Planned Action(s)
Important identified risks:	
Glucose intolerance	Routine pharmacovigilance activities only
Hypersensitivity reactions	Routine pharmacovigilance activities only
Injection site reactions	Routine pharmacovigilance activities only
For the identified risks, each is clinically manageable and routine pharmacovigilance activities are sufficiently sensitive to determine if risk is changing in nature over time with respect to nature of events and frequency of occurrence.	
Important potential risks	
Malignancy	Routine pharmacovigilance activities Malignancy register Targeted follow-up enquiry US Long term observational study (EMR200147-501Observational LTOS Protocol Ver 2)
Diabetic retinopathy	Routine pharmacovigilance activities US Clinical trial - Prospective randomized and placebo controlled study of rate of progression of diabetic retinopathy (EMR200147_500 EMDS DiabeticRetinop Prot V2). US Long term observational study (EMR200147-501Observational LTOS Protocol Ver 2)
Cardiovascular events	Routine pharmacovigilance activities US Clinical trial - Prospective randomized and placebo controlled study of rate of progression of diabetic retinopathy (EMR200147_500 EMDS DiabeticRetinop Prot V2). US Long term observational study (EMR200147-501Observational LTOS Protocol Ver 2)
Musculoskeletal events	Routine pharmacovigilance activities
Fluid retention	Routine pharmacovigilance activities
Off-label use	Routine pharmacovigilance activities
Mortality in acute critical illness	Routine pharmacovigilance activities
Routine pharmacovigilance activities are sufficient to detect and monitor musculoskeletal events, fluid retention, off label use and mortality in acute critical illness. It is not considered necessary to plan or implement a tesamorelin utilization study to address off-label use at the present time. This will be monitored and reassessed if off-label use becomes identified as a real risk through routine pharmacovigilance activities..	

retention, off label use and mortality in acute critical illness.

It is not considered necessary to plan or implement a tesamorelin utilization study to address off-label use at the present time. This will be monitored and reassessed if off-label use becomes identified as a real risk through routine pharmacovigilance activities..

Important missing information	
Long term usage	Routine pharmacovigilance activities US Long term observational study (EMR200147-501Observational LTOS Protocol Ver 2)
Safety in pregnancy	Routine Pharmacovigilance activities
Elderly patients (limited information)	Routine Pharmacovigilance activities
Ethnic groups other than white Caucasian (limited information)	Routine Pharmacovigilance activities
Female patients (limited information)	Routine Pharmacovigilance activities
HIV patients with concurrent co-morbidity including opportunistic infection	Routine Pharmacovigilance activities
HIV patients with concomitant methadone treatment	Routine Pharmacovigilance activities
Patients with renal and/or hepatic impairment	Routine Pharmacovigilance activities
Safety in pregnancy: Tesamorelin will be contraindicated in pregnancy. Routine monitoring of spontaneously reported pregnancy with FU until pregnancy outcome is known is part of routine PV activities and is appropriately sensitive to determine risk over time. Additionally spontaneous reporting of adverse pregnancy outcome is part of routine PV activities. For missing information in elderly patients, non-white, non-caucasian population, female patients, HIV with co-morbidity and concurrent methadone and patients with renal and/or hepatic insufficiency, monitoring through routine pharmacovigilance activities with appropriate periodic aggregate review is sufficiently sensitive to determine if differences in the safety profile of tesamorelin exist in these populations.	

Although the applicant has included at least some of the requested items the updated RMP still fails to address important safety concerns adequately.

Most of the points raised by the CHMP remain unresolved or still require major amendments from the applicant. The RMP gives the impression that the applicant may have included the requested terms but worked very superficially.

Some aspects like description of pre-clinical findings, interaction with cortisone, formation of neutralising antibodies, estimated numbers of treated patients, benign intracranial hypertension and injection side reactions have either not be addressed at all or not adequately explained.

Major concerns like elevated IGF-1 levels have not been included in the RMP. Off-label use has not been discussed. The target population for the product remains diffuse so that a considerable off-label use has to be expected.

The design of the proposed observational study is not acceptable due to biases. The applicant should consider a cohort study instead.

For the randomised controlled study the applicant is requested to provide the calculations for the power of the study to detect differences for the MACE secondary endpoint and should discuss interim reports in case of the occurrence of imbalanced MACE cases.

The malignancy registry needs an update. To evaluate missing information and potential risks as well as monitor identified risks the malignancy registry should not only include patients with cancer in their

medical history but should be mandatory for all patients treated with tesamorelin. Including all patients the registry would also be a tool to monitor and control off-label use.

Evaluation of the need for a risk minimisation plan

The applicant considered for the potential risk "malignancy", "diabetic retinopathy" as well as for "cardiovascular events" , "off-label use" and "mortality in acute critical illness" and for the missing long time usage routine risk minimisation activities as not sufficient and plans for all risks and missing information the provision of educational material.

However, the planed educational material has a promotional character rather than an educational one. It should be updated. The new version should strictly focus on the organisation and handling of the malignancy registry. It should inform HCPs on the safety concerns they should monitor and how to avoid risks for the patients.

Risk minimisation plan

See above.

4. ORPHAN MEDICINAL PRODUCTS

N/A

5. BENEFIT RISK ASSESSMENT

The proposed indication for Egrifta is the treatment of excess visceral abdominal fat in treatment experienced HIV-infected adult patients and patients should now be identified by waist circumference of at least 95cm in men, and of 94 cm in women; the intended dose is 2 mg sc daily.

Efficacy and safety are based on a clinical program including 3 multicentre, randomized, double-blind, placebo-controlled Phase 3 studies (TH9507/III/LIPO/010, TH9507-CTR-1011, and TH9507-CTR-1012). The 26-week main treatment phase (TH9507/III/LIPO/010 Main Phase and TH9507-CTR-1011) was followed by a 26-week extension phase (TH9507/III/LIPO/010 Extension Phase and TH9507-CTR-1012). After a Phase 2 study (TH9507/II/LIPO/008) had evaluated the efficacy of two subcutaneous doses of tesamorelin (1 mg and 2 mg per day) as well as placebo over a 12-Week treatment period, these studies were aimed at further investigating the effects of 2 mg TH9507 following 26 weeks of treatment in larger populations of HIV infected male and female patients on ART experiencing excess abdominal fat accumulation.

Benefits

Beneficial effects

The development of tesamorelin for HIV-infected patients with excess abdominal fat may potentially address an unmet medical need.

The primary goal (and study endpoint) is the reduction of VAT. The reduction in VAT is supposed to result in two clinically meaningful benefits for the patient. On the one hand the therapy aims at reducing the cardiovascular risks in a population known to be at increased risk of cardiovascular

morbidity/mortality due to further adverse effects of the antiretroviral therapy, such as increased insulin resistance or diabetes. On the other hand the patients' self-perception and by this, patients' quality of life as well as their adherence to the antiretroviral therapy should be improved.

In the two pivotal studies the arbitrarily defined primary efficacy endpoint, reduction in VAT, was fully met. With a difference to placebo of -20.1 cm^2 (study -010) and -10.28 cm^2 (study -011) the effect size was clearly greater than the predefined minimum difference of 8% reduction in visceral adipose tissue between tesamorelin and placebo. This was maintained over a further 6 months of treatment, and extension phase data also showed that in patients switching from tesamorelin to placebo, the effect was reversed within the first weeks after discontinuation of tesamorelin. The effect size was generally maintained in subgroup analyses including gender, testosterone use, presence of impaired glucose control at baseline, ART regimen and presence of anti-tesamorelin antibody status.

Regarding the ranked key secondary endpoints, as pre-defined per gatekeeper approach, i.e. PRO "belly appearance distress score" as first level, triglycerides and total cholesterol:HDL-cholesterol ratio as following levels, the testing strategy did not prove successful for study -010 for the primary analysis (first level not significant), but only when supportive analyses were also considered, whereas for study -011 there were no significant results observed below the significant first level.

Administration of tesamorelin 2 mg was associated with a statistically significant improvement in the patient-reported outcome related to distress with the "belly appearance" after 26 weeks, as well as small numerical improvements in total cholesterol, non-HDL cholesterol and triglycerides.

Uncertainty in the knowledge about the beneficial effects

Uncertainty in the beneficial effects of tesamorelin is considerable.

Claimed therapeutic indication/case definition

First of all, the targeted condition/patient population "HIV-infected patients with lipohypertrophy" can not be regarded as established. There is no universally recognised clinical definition and assessment may be difficult in practice as central fat accumulation is common in the general population, increasing with age. There are difficulties to distinguish visceral adiposity secondary to ART from "middle-aged spread", i.e. the common increase in weight, abdominal girth, and VAT as a normal component of aging in the general population. This is all the more important given the fact that 35% of the participants in the pivotal studies had a BMI > 30 kg/m^2 and can thus be considered not to be different from non HIV-infected patients with respect to their VAT amount (*Joy T et al. J Acquir Immune Defic Syndr 2008)*. Early descriptions of visceral fat accumulation were confounded by subcutaneous fat loss in limbs, which accentuates the appearance of the abdomen. Moreover, commencement of effective antiretroviral therapy is associated with a restoration to health in the depleted compartments, including a rise in lean body mass and trunk and limb fat (*Moyle G et al. AIDS Rev 2010; 12: 3-14*). With a revised wording proposal for the therapeutic indication the applicant wishes to account for the inclusion criteria of the pivotal studies and intends to prevent off-label use of tesamorelin as weight-lowering agent: "EGRIFTA is indicated for the treatment of excess visceral abdominal fat in treatment-experienced HIV-infected adult patients. Patients should be identified by waist circumference at least 95 cm in men, and 94 cm in women. It is not intended for weight loss management (weight neutral effect)."

First, this implies the definition of "excess VAT": a threshold of > 130 cm^2 has been set, extrapolated from a study in diabetic, non HIV-infected subjects, where an increase in CVR has been shown above this value. It is not clear if these data are applicable to HIV-infected patients. Given that data from HIV-infected patients indicate that decreased SAT may play a more important role in CVR than

increase in VAT, this extrapolation remains questionable. Moreover, the cut-offs for waist circumference as used in the pivotal studies have been shown to overestimate the VAT in more than 20% of the overall study population and in more than 25% of the EU subpopulation.

In conclusion, the use of tesamorelin in the proposed therapeutic indication is considered to be based on a chain of assumption with a lack of clear evidence. Therefore, it is difficult to quantify how the product might really be used in clinical practice, and whether such use would have a positive risk: benefit.

Clinical significance of VAT reduction

The proposed indications give no clarification as to why the prescriber should be treating excess visceral abdominal fat.

The use of change in VAT as a primary endpoint and the methodology used to measure this followed recommendations from an expert group (HIV Forum). In both studies, the primary endpoint met the pre-specified clinically relevant difference between tesamorelin and placebo of an 8% reduction in VAT, but this threshold was arbitrarily chosen. In isolation, the clinical relevance of the observed change in VAT remains uncertain, and it has not been clinically validated. In particular, there are no data available to show that reducing VAT in HIV patients improves hard endpoints related to cardiovascular morbidity and mortality, either specifically with tesamorelin or more generally. The difference in the effect size between the two studies with respect to VAT reduction (reduction of VAT by -10.9% and -15.1% in studies -011 and -010) does not increase the confidence in tesamorelin's overall efficacy.

The observed changes in VAT need to be associated with meaningful improvements in the secondary endpoints, in particular patient self- image and quality of life, lipid parameters or other parameters known to influence cardiovascular risk, or compliance with ART treatment. This has not been shown. There is good evidence that increased visceral fat, waist measurement and waist-hip ratio have a positive association with diabetes, cardiac and vascular disease, however it is less certain whether these markers relate to cause or effect. Apart from achieving a reduction in visceral fat, it is therefore necessary to know whether this translates to a reduced risk of these disorders. In fact, in individual patients there is a potential risk of worsening diabetic control.

In the key secondary endpoint of patients' distress with the appearance of their abdomen, the pre-specified minimally important difference for the treatment difference was only met in 1 of the studies, was not statistically significant with the primary statistical test, and is of uncertain clinical significance, corresponding to an improvement over placebo of 5.4 in a 100-point scale. The results for this endpoint were not supported by clear differences in belly size and patient-reported belly profile across both studies, nor did they translate into a clear and consistent effect in the other quality of life evaluations. Also, tesamorelin treatment was not associated with greater compliance with ART compared to placebo.

Triglycerides and total cholesterol:HDL-C ratio decreased among tesamorelin-treated patients and increased among placebo patients; however the changes met statistical significance in only 1 study and were otherwise clinically minimal. Generally, apart from triglycerides, mean levels of lipid parameters were within the normal range at baseline, and as made clear in the relevant CHMP guideline, an isolated effect on triglycerides is not expected to be the sole basis for demonstration of efficacy of a new lipid-modifying agent. For illustration, triglyceride levels were reduced modestly by 9 to 13%, whereas approved lipid-lowering therapies, such as statins have shown decreases of up to 30%. For the more important LDL-cholesterol, a surrogate for CV risk, after 52 weeks of tesamorelin treatment a very modest decrease of less than 10 mg/dl was observed in study -011/12, and even a

slight increase of about 2 mg/dl was reported in study -010. There are no data to show that tesamorelin reduces the need for treatment with lipid-lowering drugs.

Furthermore, the validity of all results is questionable due to methodological problems.

Potential over-estimation of treatment effect

Whilst there was a 6 month extension period in both pivotal studies, there is no arm for comparison involving patients staying on placebo for 1 year. As highlighted in previous CHMP advice, this design would have better defined the spontaneous course of lipodystrophy and the placebo-subtracted effect. In particular, the placebo response at 6 months turned out to be non negligible and different between the 2 pivotal studies, and the continuing need for once-daily subcutaneous injections might have adversely affected the quality of life results over a longer treatment period. Also, as follow-up in the extension studies is limited to 52 weeks a rebound effect after discontinuation of tesamorelin cannot be excluded.

Insufficient blinding

There are several indications for an insufficient blinding (e.g. differential drop-out, characteristic and frequently occurring adverse reactions of tesamorelin). Indeed, this puts into question all efficacy measures, as bias could have been introduced easily. Most of all, however, the patient reported outcomes are affected by this; they could no longer be regarded to provide any reliable information.

Methodology of primary efficacy evaluation

VAT reduction was assessed by a single slice CT scan, which has been shown to be prone to considerable variabililty.

Differences between the 2 pivotal studies

The effect size in pivotal study CTR1011 was around half that seen in the LIPO/010 study, accounted for by differences in both treatment effect and placebo response. It may be relevant that study CTR1011 included some European patients, whilst LIPO/010 was confined to the US and Canada. Indeed, literature data indicate that characteristics of HIV infected patients with HARS are appreciably different between the USA and Europe (*Lo J et al. AIDS 2010, 24: 2127-35 and Guaraldi G et al. AIDS 2011; 25: 1199-1205*). With altogether 73 patients the European subgroup is quite small and also the smaller effect size reported for this subgroup is of concern; additional analyses provided by the applicant do not give reassurance in this regard. So far there is considerable uncertainty whether results from studies performed at non-European sites can be extrapolated to the European population.

Comparative benefit of switching ART

Whilst there is no approved therapy in the proposed indication, the benefits of tesamorelin need to be considered in light of other possible therapeutic actions. The applicant states that switching ART has been shown to improve lipoatrophy and some metabolic parameters, but not to specifically reverse fat accumulation.

The applicant took this position during prior CHMP scientific advice, but were advised that a third treatment arm with patients switching to a HAART regimen with less propensity to lipodystrophy could still be included and would provide supportive evidence of efficacy. This has not been done.

In fact, more recent studies do suggest the potential for improvement in VAT with switching therapies. *(e.g. Stanley TL, Joy T, Hadigan CM et al.*: Effects of switching from lopinavir/ritonavir to atazanavir/ritonavir on muscle glucose uptake and visceral fat in HIV-infected patients. AIDS 23(11), 1349-1357 (2009) and *Tebas P, Zhang J, Hafner R et al.*: J. Antimicrob. Chemother. 63 (5), 998-1005 (2009)).

However, in the absence of strong evidence that a switch could be beneficial in managing a side effect (lipohypertrophy) of an efficient HAART treatment, it could have been difficult to justify taking the risk of potentially affecting the virological status of the tesamorelin study subjects.

Whilst more studies are needed, changing ART regime would seem a more rational step than adding tesamorelin in some patients.

Comparative benefit of exercise and diet

Whilst the applicant maintains that studies of diet and exercise have shown "limited success" in reducing VAT, more accurately there are no large scale data, and it remains clinically rational, particularly for subjects without significant lipoatrophy, to attempt to optimise diet and exercise before considering any specific therapy to reduce VAT. The applicant has not provided data on the effectiveness of intensive diet and exercise in reducing VAT, and not adequately justified why this was not considered as a comparator arm of the study, or an inclusion criteria used based on failure to improve with intensive diet and exercise.

Other issues

Evaluation of treatment compliance could be regarded as unreliable due to the method used, i.e. imputation of unreturned vials as being used. The applicant provided an analysis considering unreturned vials as patients being non compliant and further details on number/proportion of unused vials per category. It is agreed that estimates of compliance are not significantly altered by these additional analyses.

Further bias may have been introduced by use of concomitant medications, especially testosterone. However, further analyses indicate that the effect of tesamorelin on VAT reduction was not impacted by the use of testosterone.

Also, the high rate of screening failures for either abnormal laboratory values, abnormal result to one of the test procedures or not meeting established anthropometric criteria in both studies is noteworthy, questioning the extrapolation of the study results for real life conditions.

There is also no data on the effectiveness of tesamorelin in the proposed indication for the elderly, or patients with hepatic or renal impairment, which could be addressed by a respective wording in the SmPC.

Risks

Unfavourable effects

There is a clear and clinically relevant increase in the incidence of AEs known to be related to GH, including increased IGF-1 levels; IGF-1 levels at baseline were comparable between groups. After 26 weeks of treatment, about 35% of HIV patients on tesamorelin had IGF-1 > SDS +3, compared to 2.2% to 2.7% on placebo and about 45% to 50% on tesamorelin had IGF-1 standard deviation scores above +2. An analysis of changes in IGF-1 levels by age indicated a possible trend for larger shifts among older subjects with longer exposure. In addition in study TH9507/I/PKPD/009 the molar ratio of

IGF-1 to IGFBP-3 increased from Day 1 to Day 15 indicating an increase in free IGF-1. Considering that increased IGF-1 levels as well as HIV infection are associated with an increased risk of cancer this finding is considered a Major Concern; IGF-1 levels should remain within the physiological range adjusted for age and gender, i.e. within ± 2SDS.

About 50% of all patients treated with tesamorelin developed anti-tesamorelin IgG antibodies, which was maintained with continuous treatment; about 10% of these patients showed high titres. About 60% of tesamorelin IgG antibody positive subjects showed cross-reactivity with hGRF; this is of considerable concern. About 10% tested positive of hGRF neutralising antibodies. Hypersensitivity reactions occurred in 2.9% and 4.1% of subjects in the tesamorelin and the P-T groups, respectively during 26 weeks of treatment and two subjects with hypersensitivity reactions tested positive for anti-tesamorelin IgE antibodies. In the Main Phases of the pivotal trials more patients on tesamorelin had shifts from low or normal at baseline to high in eosinophils (4.3%) compared to placebo (2.0%); similarly in the Extension Phases shifts from low or normal at baseline to high in eosinophils occurred (T-T 6.2% vs. T-P 3.3%). There were no cases of anaphylactic reactions or other SAE of hypersensitivity.

In the main phase, 1.7% on tesamorelin compared to 0.4% on placebo experienced a glucose-related AE. Tesamorelin had no statistically significant effect on FBG, insulin, or insulin resistance, but the mean change from baseline in HbA_{1c} was statistically significantly higher with tesamorelin compared to placebo.

Relatively more people on tesamorelin compared to placebo died during the clinical trials, but no specific causal relation to tesamorelin has been identified.

Compared to placebo there was a relevant increase in the incidence of injection related AEs as well as for peripheral oedema and myalgia In HIV-infected patients treated with tesamorelin. The comparison of main vs. extension phase shows that there was also a difference in the incidences of injection site related AEs by study time period; the time profile is suggestive of differential dropout. Overall, AEs leading to discontinuation, occurring at an incidence of ≥ 1.0% and more frequent than on placebo were nausea, arthralgia, and headache. AEs leading to discontinuation and considered related to study drug by investigators occurred in 4.9% on tesamorelin and 3.1% on placebo. In the pivotal trials fewer patients on tesamorelin completed the Main Phase compared to placebo (76.1% vs. 78.7%, respectively). Twelve (2.2%) patients on tesamorelin had a hypersensitivity reaction resulting in discontinuation.

Uncertainty in the knowledge about the unfavourable effects

In study TH9507/I/PKPD/009 the molar ratio of IGF-1 to IGFBP-3 increased from Day 1 to Day 15 indicating an increase in free IGF-1; information on the molar ratios of IGF-1 to IGFBP-3 in the pivotal trials in HIV-infected patients is missing.

Regarding AEs known to be related to GH no direct comparison to therapeutic GH is available; it is currently not clear how these increased incidences correlate to the known AE profile for GH. The incidence of relevant AEs of therapeutic GH is related to the administered dose and recently an increase in the risk of mortality in patients treated with GH, especially with higher doses, during childhood has been discussed (SAGhE study).

There were no cases of anaphylactic reactions or other SAE of hypersensitivity. However, given the high incidence of antibody development and hypersensitivity reactions, the possibility of anaphylactic reactions is considered very likely.

There is also no information on the immune response following re-exposure after a treatment-free interval, and whilst the available observations suggest that neutralizing antibodies to endogenous GHRH are reversible, there is limited data and more information is needed.

The analysis by age group above or below median age is considered insufficient for the assessment of age related AEs. The small numbers of females relative to males as well as of ethnicities other than White do not allow for a meaningful analysis of AEs by gender or ethnicities. Regarding liver function AEs an analysis of AEs by liver function using accepted criteria for different liver function status is missing.

The applicant proposes tesamorelin for long-term use. However, there are no controlled data beyond 26 weeks of continuous exposure and only 209 subjects completed 52 weeks. Thus no assessment of long-term safety can be performed. The CHMP in its previous scientific advice recommended an increase in the overall study duration to 2 years. The clear differences in the incidence of injection related AEs and the time profile of these AEs are suggestive of differential dropout and thus questions the blinding of treatments.

Balance

Importance of favourable and unfavourable effects

As HIV patients live longer, it is recognised that the effect of morbidity not related to infection or malignancy becomes more important, as does minimising the side effects from ART.

The development of tesamorelin may address a potential unmet medical need. For reduction of the abdominal fat accumulation in HIV-infected patients, so far no treatment has been approved. However it first needs to be established that treatment of excess VAT is in itself a valid therapeutic target, and the potential benefits of other therapeutic actions (diet/exercise, switching to alternative ART) need to be considered. The condition has not consistently been shown to be reversible upon discontinuation of certain antiretroviral agents, which are attributed to be causative.

The observed beneficial effects are considered to be an influence on a biomarker (VAT) with an arbitrary threshold (8% reduction), which has not been clinically validated. The reduction in VAT is supposed to result in two clinically meaningful benefits for the patients: it may result in or be associated with a reduction in CV risk and may, by counteracting the VAT increase, which is attributed to antiretroviral therapy, improve the patients' self-perception and by this increase patients' compliance to the antiretroviral regimen.

There is no doubt that vascular risk is becoming a dominant issue in HIV disease as survival is more secure. The mechanisms are still very unclear, but are strongest for the notion that the disease is associated with a generalised abnormality of endothelial function. Lipids may or may not be important, but there is no strong evidence that they are, and so manipulation of conventional risk factors is not well founded as a target for treatment.

Although involvement of the face (lipoatrophy) is a more common component of lipodystrophy and potentially more stigmatizing in the way it can mark out HIV patients, increased abdominal size could adversely affect body image perception and well-being. If patients are genuinely distressed by the appearance of abdominal fat distribution then this could be a reasonable therapeutic target – however this is not reflected in the proposed indications, nor has an improvement been conclusively shown in the submitted data.

Tesamorelin does not result in consistent, robust and meaningful effects on the surrogate parameters used as secondary endpoints, e.g. lipid profiles. Neither has improved compliance to antiretroviral

therapy been shown. Methodological uncertainties further diminish the benefit that can reasonably be expected.

Regarding the unfavourable effects the high incidence of IGF-1 increases > SDS +3 compared to placebo is of major concern, representing a potential increased risk in the development or progression of malignancies, as well as risk of development or progression of diabetic retinopathy. IGF-1 levels should generally remain within the physiological range adjusted for age and gender, i.e. within ± 2SDS.

The high amount of patients developing IgG antibodies is worrisome, especially since neutralising antibodies and cross-reactivity with hGRF have been identified. The limited safety database does currently not allow assessing the possible consequences of long-term exposure with tesamorelin as regards human GRF including reversibility of possible effects.

More patients on tesamorelin than on placebo experienced a glucose-related AE and the mean change from baseline in HbA_{1c} was statistically significantly higher with tesamorelin compared to placebo. These effects on glucose metabolism might counteract the possible beneficial effect on cardiovascular morbidity and mortality.

Relatively more people on tesamorelin compared to placebo died during the clinical trials, but no specific causal relation to tesamorelin has been identified. Overall, the incidence of GH related AEs is clearly increased. There were no cases of anaphylactic reactions or other SAE of hypersensitivity, but given the incidence of antibody development and hypersensitivity reactions, occurrence of anaphylactic reactions is considered very likely.

Benefit-risk balance

Beneficial effects are restricted to a biomarker, for which it is unknown whether it translates into a clinical effect and which effect size is modest at best. There are no data available to show that reducing VAT in HIV patients with excess abdominal fat improves cardiovascular morbidity and mortality, either specifically with tesamorelin or more generally. It is also not considered that the observed change in VAT was associated with consistent and clinically meaningful improvements in patient self-image, quality of life, lipid parameters, other parameters known to influence cardiovascular risk, or compliance with ART treatment. The study duration may overestimate the treatment effect. Significant methodological uncertainties in the studies further diminish the magnitude of the expected benefit.

The high percentage of increases in IGF-1 > SDS +3 as well as the high amount of patients developing anti-tesamorelin antibodies including neutralising antibodies and cross-reactivity to hGRF are considered the major risks involved with tesamorelin treatment. Also the effects on glucose metabolism indicate that hypothetical beneficial effects on cardiovascular morbidity and mortality might be counteracted by these adverse effects. Also, the occurrence of anaphylactic reactions is considered very likely.

Discussion on the benefit-risk assessment

Whereas tesamorelin might by reduction of VAT in HIV infected patients with excess abdominal fat contribute to a reduction in CV risk and lead to an improvement in patients' quality of life as well as their antiretroviral treatment adherence, the clinical trials performed do not provide evidence of these potential benefits exceeding the effect on VAT.

The compound on the other hand leads to several adverse effects, which are potentially serious and severe in nature. The high percentage of increases in IGF-1 > SDS +3 is considered to outweigh the beneficial effects seen with tesamorelin. This finding together with the increase in AEs known to be

related to GH indicates that from the safety perspective the tesamorelin dose might be too high. The incidence of relevant AEs of therapeutic GH is related to the administered dose and recently an increase in the risk of mortality in patients treated with GH, especially with higher doses, during childhood has been discussed (SAGhE study).

In addition it is currently not clear whether patients on tesamorelin will develop neutralising antibodies and cross-reactivity to hGRF with long-term exposure. Adverse effects on the physiological process can not be excluded. Also, it is currently not clear whether tesamorelin might induce other AEs related to GH therapy and the occurrence of anaphylactic reactions is considered very likely.

That there are no controlled data beyond 26 weeks of continuous exposure and only 209 subjects were exposed for 52 weeks adds to the uncertainty regarding the risks involved with tesamorelin treatment. No assessment of long-term safety can be performed. The clear differences in the incidence of injection related AEs and the time profile of these AEs are suggestive of differential dropout and thus questions the blinding of treatments.

Overall, the effects of tesamorelin on IGF-1 levels, antibody formation, and glucose metabolism are considered to clearly outweigh the beneficial effects seen with tesamorelin.

Conclusions

The overall B/R of Egrifta is negative.

6. RECOMMENDED CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION IN CASE OF A POSITIVE BENEFIT RISK ASSESSMENT

Proposed list of recommendations:

N/A

Other conditions

None

Summary of product characteristics (SmPC)

At present, the SmPC is still not considered approvable and will currently not be assessed due to the remaining major objections and other concerns on quality, safety and efficacy. However, the applicant should amend its proposed SmPC in line with the points raised in the LoQ and in the PIQ technical review.

Labelling

See section 7.3.

Package leaflet (PL)

See section 7.3.

User consultation

In general, although the user testing of the leaflet is acceptable, issue raised in the SmPC will need to be reflected in the leaflet.

Conclusion from the checklist for the review of user consultation

The user testing of the provided leaflet is acceptable. However, the final leaflet will have to reflect required changes to the SmPC.