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RESEARCH**

APPLICATION NUMBER:

22-505

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	22-505/N000
Priority or Standard	Standard
Submit Date(s)	May 29, 2009
Received Date(s)	May 29, 2009
PDUFA Goal Date	March 29, 2009
Division / Office	DMEP/ODEII
Reviewer Name(s)	Ali Mohamadi, M.D.
Review Completion Date	September 15, 2010
Established Name	Tesamorelin acetate
(Proposed) Trade Name	EGRIFTA
Therapeutic Class	GRF analog
Applicant	Theratechnologies Inc.
Formulation(s)	Injectable solution
Dosing Regimen	Single dose once daily
Indication(s)	To induce and maintain a reduction of excess visceral abdominal fat in HIV-infected patients with lipodystrophy
Intended Population(s)	HIV-positive patients with lipodystrophy

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1 Recommendations/Risk Benefit Assessment

Tesamorelin acetate for injection (EGRIFTA™) is a human growth hormone releasing factor (GRF) analog that has been developed by the Sponsor for the indication of reducing excess abdominal fat in HIV-infected patients with lipodystrophy. The proposed clinical dose is 2 mg once daily.

1.1 Recommendation on Regulatory Action

According to my review of the clinical data, I recommend approval of EGRIFTA for the reduction of visceral adipose tissue (VAT) in HIV-positive patients with lipodystrophy. This would be the first drug product approved for this indication, filling an unmet need in the HIV/AIDS population.

1.2 Risk Benefit Assessment

There are no available medical therapies to reduce VAT in patients with HIV lipodystrophy. Given that the Sponsor has demonstrated the drug product's efficacy, EGRIFTA can play a useful role in this population.

The Sponsor conducted two Phase 3 studies (referred to as "Pivotal Studies" in this Review), which consisted of a 6-month "Main Phase" followed by an additional 6-month "Extension Phase." These were randomized, double-blind, and placebo-controlled studies that evaluated a dose of 2 mg once daily. The Sponsor has shown good efficacy with EGRIFTA, demonstrated by reductions in percent VAT relative to placebo of 14 and 18% in the two separate Main Phase studies.

Overall, the Sponsor has also demonstrated an acceptable safety profile of EGRIFTA, although worsening glucose tolerance and elevations in serum IGF-1 – both consistent with the mechanism of GRF to raise circulating GH levels – remain concerns. In particular, patients with pre-existing glucose intolerance who were treated with EGRIFTA trended toward higher fasting blood glucose and hemoglobin A1c levels after 6 months of treatment. Furthermore, after the Main Phase, approximately one-half of patients in the treatment group had IGF-1 standard deviation scores (SDS) >2 above the mean, and one-third had SDS >3. These are parameters that must be followed closely in patients on EGRIFTA therapy.

Finally, there is the question of the validity of "percent decrease in VAT" as a primary endpoint to demonstrate clinical benefit. There have been no studies linking improvements in VAT to other, previously validated endpoints such as cardiovascular benefit. In communications with the Sponsor prior to NDA submission, the Agency did allow patient reported outcome (PRO) measures describing the degree of distress associated with an individual's belly image as evidence of clinical benefit. In particular, the PRO measure known as belly appearance distress was identified as consequential, with belly size evaluation and belly profile considered supportive. The data is mixed in terms of reaching a level of significance, both clinically and statistically. However,

testimony given by patients treated with EGRIFTA during a meeting of the Endocrinologic and Metabolic Drugs Advisory Committee (EDMAC) on May 27, 2010 indicated that whether or not the statistical data holds up, patients subjectively believe treatment with the drug had a beneficial impact in their psychological well-being. This was cited by committee members as a critical deciding factor in their votes; the panel voted 16-0 in favor of EGRIFTA's approval.

1.3 Recommendations for Postmarketing Risk Management Activities

As discussed later in this Review, cardiovascular safety was a key subject of the EDMAC meeting held on May 27, 2010. However, although the overall consensus of the committee favored implementation of a prospective, postmarketing cardiovascular outcomes trial, limitations due to the relatively small target population with HIV-related lipodystrophy would make such a study quite challenging to implement. The nature of the postmarketing requirements that may be required of the Sponsor are still under discussion, with the final recommendations to be included in the Approval letter.

1.4 Recommendations for other Post Marketing Study Commitments

EGRIFTA has been studied in subjects ≥ 18 years old. Under the Pediatric Research Equity Act (PREA), EGRIFTA must be studied in the pediatric population unless there are reasons to waive this requirement. The Sponsor requested a waiver for pediatric studies in children less than 18 years of age, and this waiver has been granted due concerns that among patients with open epiphyses, excess GH and IGF-1 may result in linear growth acceleration and excessive growth. The sponsor's pediatric plans were discussed with the Pediatric Review Committee, which agreed with the cut points for the waiver.

2 Introduction and Regulatory Background

2.1 Product Information

Product Description

EGRIFTA is a synthetic analogue of human hypothalamic Growth Hormone-Releasing Factor (hGRF), also known as Growth Hormone-Releasing Hormone (GHRH), comprised of the 44- amino acid sequence of hGRF on which a hexenoyl moiety, a C6 chain with a double bond on position 3, has been anchored on Tyr at the N-terminal part of the molecule.

Established Name

Tesamorelin acetate (also identified as TH507)

Proposed Trade Name

The proposed trade name for tesamorelin acetate is EGRIFTA™. The Division of Medication Error Prevention and Analysis found this proposed name acceptable.

Chemical Class

EGRIFTA is a New Molecular Entity (NME).

Pharmacologic Class

EGRIFTA is a synthetic analogue of hGRF, which mediates the secretion of growth hormone (GH) by binding to its receptor on pituitary somatotroph cells triggering GH synthesis and secretion.

EGRIFTA is the 3rd GHRH analogue to undergo FDA review as a New Drug Application (NDA). For details on the other two (Geref Diagnostic and Geref Pediatric), please see section 2.4.

Applicant's Proposed Indication

The Sponsor proposes EGRIFTA to induce and maintain a reduction of excess abdominal fat in HIV infected patients with lipodystrophy.

Applicant's Proposed Dosing Regimen

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

Applicant's Proposed Age Groups

Adults (≥ 18 years of age).

2.2 Tables of Currently Available Treatments for Proposed Indications

There are no currently available treatments for the indication of reduction of excess abdominal fat in HIV infected patients with lipodystrophy.

2.3 Availability of Proposed Active Ingredient in the United States

EGRIFTA is a new molecular entity and has not yet been marketed in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

Two other synthetic GHRH analogues were previously approved by the FDA.

Synthetic GHRH₁₋₂₉ (sermorelin acetate, trade name Geref Diagnostic) was previously approved by the Division as a diagnostic agent for adult GHD in the early 1990s (1 $\mu\text{g}/\text{kg}$ as a single IV injection) and as a treatment for the short stature associated with pediatric GHD in the late 1990s (30 $\mu\text{g}/\text{kg}/\text{day}$ SC; trade name Geref Pediatric). The GHRH formulation was identical in both instances.

The following adverse events (AEs) were reported, albeit rarely, after the use of Geref Diagnostic as a diagnostic agent: self-limited, transient injection site pain, redness and/or

swelling, facial flushing, pallor, headache, nausea, vomiting, dysgeusia/metallic taste, and chest tightness.

The safety profile of Geref Pediatric was similar. During clinical trials, the most common treatment-related AE was self-limited, transient injection site pain, redness and/or swelling (in ~16% of patients). Other treatment-related AEs with occurrence rates <1% included: facial flushing, headache, dizziness, somnolence, hyperactivity, dysphagia, and urticaria.

In addition, a significant percentage of Geref-exposed patients intermittently tested positive for anti-Geref antibodies. These antibodies were not associated with generalized allergic reactions, and did not appear to impact efficacy.

The NDAs for both Geref products were subsequently withdrawn for (b) (4) (Geref Pediatric in 2006 and Geref Diagnostic in 2008), and the products are no longer manufactured or marketed.

It bears noting that the patient populations, dosages, and indications for which Geref was approved are markedly different than that proposed for EGRIFTA. Since Geref Pediatric was indicated for patients under the age of 18, the safety findings do not apply to the target population for EGRIFTA. In adult patients, as noted above, Geref was only approved as a diagnostic agent for GHD at a dose of 1 µg/kg as a single IV injection. For an average-sized (e.g., 70 kg) adult, this would be approximately a dose of 0.7 mg, significantly less than the proposed dose of 2 mg for EGRIFTA. Therefore, given the lower dose, the fact that it was only given as a single IV injection; and that it was not tested in the HIV-positive population, it is difficult to extrapolate the safety findings of Geref Diagnostic to the current application.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Significant pre-submission regulatory activity under IND 61,226 included:

Type C Meeting: March 30, 2005

On March 30, 2005 the Agency and Sponsor held a Type C meeting to discuss preclinical studies and Phase 3 clinical study proposals for EGRIFTA. Based on findings from the Phase 2 studies, at this meeting both the 2mg dose for the Phase 3 studies, and the structure of the Main and Extension Phases (26 weeks each) were agreed to by the Agency. It was also agreed that patients with “diet-controlled” diabetes mellitus (i.e., FBG <150 mg/dl) would be enrolled in the study.

The Agency also agreed with the Sponsor that a study powered to support an 8% reduction in VAT would be appropriate as a measure of clinical benefit (taking into account the recommendations of the International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV held in 2004).

Finally, the Agency recommended that the Sponsor identify or develop an adequate measure of body self image in patients with HIV lipodystrophy (i.e., PRO measures) and incorporate it into its Phase 3 trials.

Type C Meeting: December 3, 2007

Since the Sponsor had already started Phase 3 trials without an End of Phase 2 Meeting having been convened, it requested a Type C Meeting to obtain further guidance from the Agency. During this meeting, the Agency accepted the PRO endpoints of Belly Appearance Distress (BAD), Body Size Evaluation (BSE) and Belly Profile (BP) as supportive secondary endpoints, and agreed with the Sponsor that BAD could be considered the most “consequential” of these when evaluating efficacy.

The final statistical analysis plan for quality of life and body image parameters after 26 weeks of treatment (Amendment SN081, October 26, 2007) had indicated that a parametric ANCOVA was to be used to analyze the belly size and belly appearance distress parameters whereas a Mann-Whitney test was to be used to analyze patient and physician-reported belly profile assessments. At this meeting, the Sponsor requested that the statistical methods proposed in the SAP to non-parametric ANCOVA for all three parameters (to provide a consistent method for all three PRO parameters). The Agency’s statistical team did not agree with this request.

At the time of this meeting, one Main Phase Study had been completed (referred later in this review as “Study 10”), whereas a second Main Phase Study (“Study 11”) was still ongoing. Neither of the Extension Phase Studies had been completed. After extended discussion, the Division agreed 1) non-parametric ANCOVAs for all 3 body image parameters (BAD, BSE and BPA) could be the primary analyses for the ongoing Phase III studies; 2) parametric ANCOVAs (BAD and BSE) and the Mann-Whitney test (BPA) must be supportive analyses for the ongoing Phase III studies; 3) parametric ANCOVAs (BAD and BSE) and the Mann-Whitney test (BPA) must be the primary analyses for the first 6 months of the completed Phase III study; and 4) nonparametric ANCOVAs for all 3 body image parameters (BAD, BSE and BPA) should be supportive analyses for the first 6 months of the completed Phase III study.

Discussion also took place with respect to controlling Type I Error by creating a rank order for the secondary endpoints. After extensive discussion, the Division agreed with the following rank order for the primary analysis of the results of the ongoing pivotal study (11): Change from baseline to Week 26 in 1) VAT; 2) triglycerides and BAD (using Hochberg); and 3) total cholesterol/HDL cholesterol ratio. The Division requested and the sponsor agreed to measure and/or calculate non-HDL cholesterol levels, and then substitute non-HDL cholesterol for triglycerides in the gatekeeper rank order noted in the previous sentence as a very important supportive analysis. With regard to the completed, unblinded pivotal study, it was agreed that the originally specified rank order (VAT, BAD, total cholesterol/HDL cholesterol ratio, triglycerides) must be used. The Division requested and the sponsor agreed to measure and/or calculate non-HDL cholesterol levels, and then substitute non-HDL cholesterol for triglycerides in the gatekeeper rank order described above.

Pre-NDA Meeting: September 19, 2008

The Sponsor's objectives for this meeting were to: (1) present results on the Phase 3 clinical studies and gain concurrence that results are consistent with proceeding with NDA preparation; (2) gain concurrence on any outstanding clinical and statistical issues; and (3) gain concurrence on the final elements of the nonclinical program. During this meeting, the Agency requested further clarification on the statistical plan for the PRO endpoints, which were provided by the Sponsor. The Agency further requested that information regarding glucose metabolism be provided both as raw data and analyzed in "shift" tables. The algorithm by which markers of immunogenicity (antibodies and neutralizing antibodies to tesamorelin and hGRF) was discussed.

2.6 Other Relevant Background Information

HIV-Induced Lipodystrophy

HIV-associated lipodystrophy refers to a collection of symptoms and signs seen in HIV-positive patients. These include fat loss typically from the limbs or face, fat hypertrophy (including abdominal obesity and buffalo hump), dyslipidemia and insulin resistance. The reported prevalence of lipodystrophy varies enormously and really does depend on the definition used.ⁱ A larger cross-sectional study of 1348 patients from Australia reported that 53% had lipodystrophy (55% reported both peripheral lipoatrophy and central lipohypertrophy, 31% experienced peripheral lipoatrophy only and 14% had central lipohypertrophy only).ⁱⁱ Protease inhibitors are more likely to lead to body habitus changes (including lipohypertrophy), whereas nonnucleoside reverse transcriptase inhibitors (NNRTIs) more often lead to lipoatrophy.² A more recent prospective cohort study using Dual energy X-ray Absorptiometry scanning showed that 24 months treatment led to changes in limb fat only on those patients exposed to protease inhibitors, although there was considerable interindividual variability.ⁱⁱⁱ It is, however, important to note that these figures relate to the use of older protease inhibitors such as ritonavir and indinavir and not the more recently introduced drugs such as atazanavir and darunavir. An important aspect that is becoming clearer is that HIV infection per se increases the risk of body habitus changes – found in 21% of drug-naïve patients in Australia² – whereas the use of HAART increases this risk further.

Current Therapies for HIV-Induced Lipodystrophy

A number of treatment strategies have been evaluated, but unfortunately, most have met with limited success. Thus, thiazolidinediones and metformin have failed to show consistent improvements in visceral adipose tissue^{iv}. Metformin may also worsen the loss of limb fat^v. Testosterone treatment in HIV patients with low testosterone levels led to a decrease in total and subcutaneous fat, but did not have an effect on visceral fat^{vi}. Recombinant human growth hormone (rhGH), which has fat-oxidizing and lipolytic properties, leads to nonsustained loss of visceral fat, with a decrease in limb fat that may exacerbate lipoatrophy^{vii}. These disappointing results, taken together with the known adverse of rhGH, have meant that high-dose rhGH (up to 4 mg/day) cannot be recommended for treatment in such patients⁴. By contrast, physiological replacement in

patients (average dose 0.33 mg/day for 18 months) with fat accumulation and relative GH deficiency led to a reduction in visceral adipose tissue and a reduction in blood pressure and triglycerides

Combination therapies remain an option in these patients but have not been adequately tested. A very small open label study showed that although rosiglitazone improved subcutaneous fat and rhGH (2 mg/day) reduced visceral fat, the combination of rosiglitazone with rhGH was able to reduce the insulin resistance associated with rhGH. By contrast, pravastatin had little effect on body composition^{viii}.

Visceral Adipose Tissue and Cardiovascular Risk

Studies conducted over the past several decades have provided some evidence that the regional distribution of adipose tissue is the key factor explaining the relationship between adiposity and cardiometabolic risk. A number of metabolic investigations have shown that excess visceral adiposity is a key feature of a phenomenon referred to as ectopic fat deposition, which has been shown to be associated with metabolic dysfunctions. Key features associated with excess visceral fat/ectopic fat accumulation include insulin resistance, atherogenic dyslipidemia, hypertension, impaired fibrinolysis/increased risk of thrombosis, and inflammation.^{ix,x} these metabolic features, most commonly found in the viscerally obese patient, are often referred to collectively as the metabolic syndrome, which is linked to the development of cardiovascular disease (CVD).

The metabolic syndrome of visceral obesity has been described as a “multiplex” additional modifiable CVD risk factor that—when added to traditional risk factors (age, sex, smoking, blood pressure, low-density-lipoprotein (LDL) cholesterol, high-density-lipoprotein (HDL) cholesterol, diabetes, and family history of premature CVD) — determines global “cardiometabolic risk.”^{xi} The regional distribution and metabolism of adipose tissue are crucial factors that determine the existence/absence of a dysmetabolic state under the conditions of a sedentary, affluent lifestyle that promotes body fat accumulation and, ultimately, obesity. The biology of subcutaneous fat cells differs from that of visceral fat cells in many respects. Experimental studies have demonstrated that, as compared with their subcutaneous counterparts, visceral adipocytes are hyperlipolytic and have a distinct secretion profile of cytokines (often referred to as adipokines). Experimental evidence also indicates that subcutaneous fat tissue may be considered a “metabolic sink” that prevents accumulation of harmful ectopic visceral fat.^{xii}

Therefore, reducing excess adiposity, specifically visceral obesity and ectopic fat, may be a key therapeutic target to achieve a reduction in the residual burden of CVD.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Data quality and completeness were adequate to permit review.

3.2 Compliance with Good Clinical Practices

The sponsor reports that the Pivotal Studies were conducted in accordance with the principles of good clinical practice (GCP), including the ethical review board (ERB) and informed consent.

The tables below summarize the major protocol violations in the Pivotal Studies (please note that the percentages listed below are based on the total number of patients with major protocol deviations, not based on the entire study population). A similar proportion of patients in all treatment groups had each of the major protocol violations. most common major protocol violation was in both the Main and Extension Phase studies was non-compliance, which overall occurred most often in patients on tesamorelin compared with placebo (tesamorelin group in Main Phase and T-T group in Extension phase).

Table 1 Major Protocol Deviations: Studies 10 and 10-Extension

	Number of Patients (%) ¹				
	MAIN PHASE		EXTENSION PHASE		
	Tesamorelin	Placebo	Tesamorelin -Tesamorelin	Tesamorelin -Placebo	Placebo -Tesamorelin
Patients with major protocol deviations ²	65	32	48	11	28
Violation entry criteria	6 (9.2)	3 (9.4)	2 (4.2)	0	1 (3.6)
Used prohibited medication/treatment	4 (6.2)	0	6 (12.5)	1 (9.1)	1 (3.6)
New usage/dosage change in anti-hyperlipemic agent	18 (27.7)	10 (31.3)	20 (41.7)	6 (54.5)	16 (57.1)
Used anabolic steroids	1 (1.5)	1 (3.1)	1 (2.1)	0	1 (3.6)
Received wrong study treatment some time during study	3 (4.6)	0	1 (2.1)	2 (18.2)	0
Non-compliance	17 (26.2)	8 (25.0)	15 (31.3)	2 (18.2)	12 (42.9)
No post-dose VAT values	26 (40.0)	14 (43.8)	14 (29.2)	4 (36.4)	8 (28.6)

Reference: Section 14.1, Table 14.1.1.1.1 and Section 14.4, Table 14.4.1.1.1

¹Percentages are based on the total number of patients with major protocol deviations.

²Patients may be counted in more than one protocol deviation.

Source: Sponsor's Clinical Study Report, Study 10

Table 2 Major Protocol Deviations: Study 11

	Number of Patients (%) ¹		
	Tesamorelin	Placebo	Total
	N (%)	N (%)	N (%)
Violation of entry criteria	5 (6.6)	0	5 (4.5)
Change in testosterone and/or supraphysiological dose of testosterone within 6 months prior to randomization	2 (2.6)	0	2 (1.8)
New usage/dosage change in antihyperlipemic agent	11 (14.5)	11 (32.4)	22 (20.0)
Untreated hypothyroidism	2 (2.6)	0	2 (1.8)
Used prohibited medication/treatment	2 (2.6)	2 (5.9)	4 (3.6)
Use of oral hypoglycemic agents or insulin sensitizers	3 (3.9)	1 (2.9)	4 (3.6)
Non-compliance ²	30 (39.5)	7 (20.6)	37 (33.6)
No post-dose VAT values	34 (44.7)	16 (47.1)	50 (45.5)

Reference: [Table 14.1.1.1.1](#)¹Patients may be counted in more than one protocol deviation. Percentages are based on the number of patients with significant protocol violations.²Non-compliance was defined as <80% (calculated using the formula shown in Section 9.4.8).

Source: Sponsor's Clinical Study Report, Study 11

Table 3 Major Protocol Deviations: Study 12

	T-T N=92	T-P N=85	P-T N=86	Total
N ^o of patients with major protocol violations	22	30	18	70
Total number of major protocol deviations	28	37	22	87
	n ¹ (%) ²			
Violation of entry criteria	0	2 (6.7)	0	2 (2.9)
Change in testosterone and/or supraphysiological dose of testosterone within 6 months prior to randomization	0	3 (10.0)	0	3 (4.3)
Novel use or change in anti-hyperlipemic agent dosage	7 (31.8)	7 (23.3)	13 (72.2)	27 (38.6)
Untreated hypothyroidism	2 (9.1)	0	0	2 (2.9)
Use of forbidden concomitant medication(s)/treatment(s)	2 (9.1)	1 (3.3)	2 (11.1)	5 (7.1)
Use of oral hypoglycemic or insulin sensitizing agents	1 (4.5)	0	0	1 (1.4)
Non-compliant patients ³	11 (50.0)	13 (43.3)	4 (22.2)	28 (40.0)
Patients without post-dose VAT values	5 (22.7)	11 (36.7)	3 (16.7)	19 (27.1)

Source: [Table 14.1.1.1](#); [Appendix 16.2](#), [Listing 16.2.2](#)¹ Patients may be counted in more than one protocol deviation.² Percentages are based on the number of patients with significant protocol violations.³Non-compliance was defined as <80%.

Source: Sponsor's Clinical Study Report, Study 12

3.3 Financial Disclosures

All study investigators submitted financial disclosure information. The sponsor submitted financial disclosure forms (FDA Form 3455) confirming that two investigators, ^{(b) (6)} and ^{(b) (6)} had financial interests in the tesamorelin lipodystrophy program. Both acted as consultants/members of the Theratechnologies Scientific Advisory Board since 2003 and were investigators in the Phase 2 study LIPO-008, as well as each of the Pivotal Studies.

These Investigators randomized a small proportion of overall subjects in the clinical development program:

- For Main Phase Study 10, (b) (6) enrolled (b) (6) patients (b) (6) (b) (6)) and (b) (6) enrolled (b) (6) patients (b) (6) (b) (6)
- For Main Phase Study 11, (b) (6) enrolled (b) (6) patients (b) (6) (b) (6) and (b) (6) enrolled (b) (6) patients (b) (6) (b) (6)
- For Extension Phase Study 10, (b) (6) enrolled (b) (6) patients (b) (6) (b) (6)) and (b) (6) enrolled (b) (6) patients (b) (6) (b) (6)
- For Extension Phase Study 12, (b) (6) enrolled (b) (6) patients (b) (6) (b) (6)) and (b) (6) enrolled (b) (6) patients (b) (6) (b) (6)

The sponsor states that (b) (6) and (b) (6) were kept blinded to the study results until after the data had been unblinded, and that they did not have access to confidential information until it had been released by the sponsor. When evaluating the data for change in VAT (primary efficacy endpoint) among patients in both the treatment and placebo groups, there is no observable difference among patients at the above-mentioned sites compared to the mean changes for patients at all sites combined in either the Main or Extension Phases.

Based on the above, potential bias from these two Investigators would have minimal, if any, effect on Egrifta's safety and efficacy conclusions.

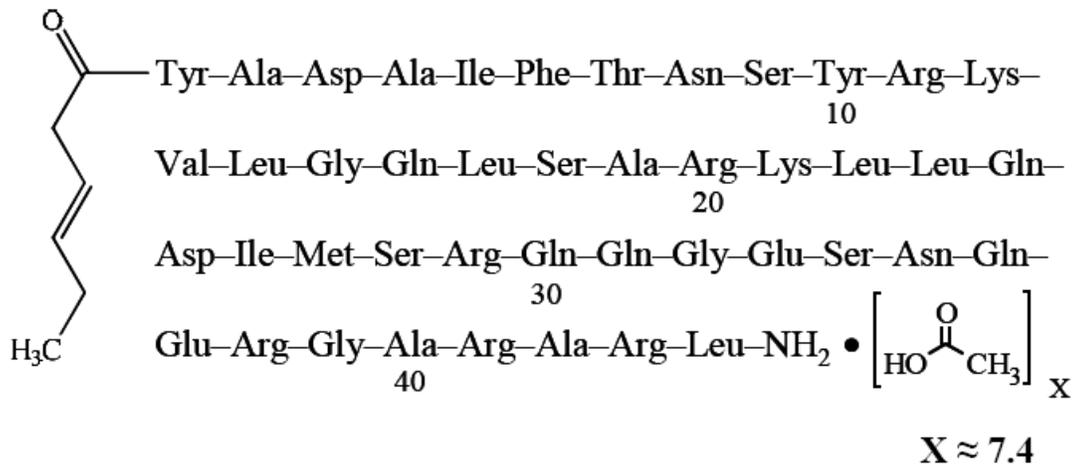
4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

See Dr. Joseph Leginus's CMC Review for full details. All issues identified in during the review have been adequately resolved.

Tesamorelin acetate is a synthetic analog of human GRF (Growth Releasing Factor) comprised of the 44 amino acid sequence of human GRF. Tesamorelin acetate is made by attaching a hexenoyl moiety, a C6 chain with a double bond at position 3, to the tyrosine residue at the N-terminal part of the molecule. The structural formula of tesamorelin acetate is presented in Figure 1 below:

Figure 1 Structural formula of tesamorelin acetate



EGRIFTA™ (tesamorelin for injection), with the dosage strength of 1 mg per vial, is a white to off-white, sterile, lyophilized powder (total content per vial including an overfill: 1.1 mg tesamorelin free base equivalent to (b) (4) per vial) with mannitol, USP as the only excipient (55 mg per vial). The drug product is packaged in a stoppered 3 mL clear glass vial, placed in an opaque carton and co-packaged in a kit that includes disposable syringes, disposable needles and reconstitution diluent. The diluent is Sterile Water for Injection, USP, an approved product of NDA 18-801. Each vial contains the overfill amount of 0.1 mg tesamorelin to ensure the drawing of 1.0 mL (for an actual dose of 1.0 mg) from each reconstituted vial. The recommended 2 mg dose requires reconstitution of 2 vials of drug product using one 2.2 mL volume of Sterile Water for Injection from a single use 10 mL vial. Immediately after reconstitution, 2 mL of the 1 mg/mL solution (pH ~ 6) is injected subcutaneously by the patient. No preservatives are added given that the reconstituted product is indicated for immediate single-use injection.

The manufacturing process for the drug product involves (b) (4)

4.2 Clinical Microbiology

Not applicable—tesamorelin acetate is not an antimicrobial.

4.3 Preclinical Pharmacology/Toxicology

See Dr. Lauren Murphee Mihalcik’s Pharmacology/Toxicology review for full details.

Nonclinical safety issues relevant to clinical use included:

1. Chronic dosing with TH9507 caused slight elevations ($\uparrow 6\%$) in plasma glucose in rats given 1.6X MRHD, increasing in males to $\uparrow 12\%$ at 26X MRHD (AUC basis). A severe diabetes-like syndrome developed in dogs exposed to very high drug levels. Since hyperglycemia and insulin resistance has been associated with GH treatment in HIV patients with lipodystrophy, there is a risk for similar effects with TH9507. Clinical trials showed trends towards increased plasma glucose and HOMA-R scores for insulin resistance that were sometimes statistically significant.

2. Increases in lipids were seen in both rats and dogs and appeared to precede most of the adverse effects associated with metabolic changes; however, changes in lipid parameters were not observed in clinical subjects.

3. Evidence from the reproductive toxicity studies suggests that there is a risk of hydrocephaly or altered intracranial pressure in the offspring of animals given doses that provide exposures that are 1-2X MRHD (AUC basis). Given the known clinical risk of intracranial hypertension associated with GH treatment (see, e.g., approved labeling for Genotropin®, Humatrope®, and Norditropin®), there appears to be a risk for hydrocephaly and/or intracranial hypertension in the offspring of patients taking TH9507 during pregnancy or while breastfeeding.

The final pharmacology/toxicology recommendations are pending regarding labeling of these findings.

4.4 Clinical Pharmacology

See Dr. Ritesh Jain's Clinical Pharmacology review for full details.

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

PK/PD of Tesamorelin in Healthy Subjects

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

PK/PD of Tesamorelin in HIV Infected Patients

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

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

Absolute Bioavailability in Healthy Subject

In healthy subjects, following intravenous administration the mean elimination half-life ($t_{1/2}$ el) was observed to be 7.2 min on Day 1 and 7.8 min on Day 15 of administration, respectively. The absolute bioavailability of tesamorelin after subcutaneous injection was estimated to be less than 4%.

Drug-Drug Interaction

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

Effect of Immunogenicity on the Pharmacokinetics of Tesamorelin

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

5. Sources of Clinical Data

This review uses clinical data derived from the Sponsor's studies. Table XX summarizes tesamorelin clinical studies (excluding safety and efficacy studies), while Table XX summarizes safety and efficacy studies.

There were 10 Clinical Pharmacology studies. These include:

- Single- and multiple-dose studies
- Biopharmaceutical studies
- Pharmacokinetic and pharmacodynamic studies evaluating tesamorelin administration routes (subcutaneous vs. intravenous)
- Pharmacokinetic studies of tesamorelin delivered in various formulations
- Drug-drug interactions with antihyperglycemic agents and antiretroviral agents

The clinical program evaluating the efficacy of tesamorelin in subjects with HIV and excess abdominal fat included three multi-center, randomized, double-blind, placebo-controlled "pivotal" Phase 3 controlled clinical studies and seven supportive Phase 2 efficacy studies.

The 7 Phase 2 efficacy studies include:

- Two studies in healthy patients to evaluate the effect of tesamorelin on sleep
- One study in healthy patients to evaluate the effect of tesamorelin on the immune response
- One study in non-HIV patients with chronic obstructive pulmonary disease
- One study in non-HIV patients with hip fracture
- One study in non-HIV patients with type 2 diabetes mellitus
- One non-pivotal investigation in HIV-positive subjects to evaluate the effect of tesamorelin on VAT

The Phase 3 ("pivotal") studies include:

- Two randomized, double-blind, placebo-controlled studies evaluating the safety and efficacy of tesamorelin during the first 26 weeks of treatment
- An extension period for patients who completed the initial studies to evaluate the safety and efficacy of tesamorelin during an additional 26 weeks of treatment.

The pivotal trials are Studies TH9507/III/LIPO/010 (initial 26 weeks, plus a 26-week extension), TH9507-CTR-1011 (initial 26 weeks), and TH9507-CTR-1012 (26-week extension of TH9507-CTR-1011). For the sake of clarity, this review will simplify the nomenclature of the clinical trials and refer to these studies as follows:

- Study TH9507/III/LIPO/010 will be referred to as "**Study 10**" and its extension as "**Study 10-extension.**"
- Study TH9507-CTR-1011 will be referred to as "**Study 11.**"
- Study TH9507-CTR-1012 will be referred to as "**Study 12.**"

Study 11 and the first 6 months of Study 10 will also be referred as the **Main Phase** of these studies, while Study 10-extension and Study 12 will also be referred to, on

occasion, as the “**Extension Phase**” of the respective studies (each extension phase will have three arms, as previously defined: **T-T**, **T-P**, and the non-re-randomized arm **P-T**).

5.1 Tables of Clinical Studies

Table 4 Listing of Tesamorelin Clinical Studies, Excluding Safety and Efficacy Studies

Study Number	Objective(s) of the Study	Study Design and Type of Control	Target Population	# of Subjects	Dosage Regimen	Duration
TCHUV 10-98	BA/PK/PD	R, PC, PDB, XO	Healthy	6	Tesa 20, 40, 100, 200, 400, 1500 µg SC Tesa 200 µg IV hGRF 100, 400, 1500, 4500 µg SC Placebo SC	SD
CTR-1017	BA/PK	R, OL, P	Healthy	44	Tesa 2 mg SC Tesa 200 µg IV	SD
CTR-1013	BE/PK/PD	R, OL, XO	Healthy	88	Tesa 2.0 mL (1mg/mL) SC Tesa 0.5 mL (4 mg/mL) SC	SD
CTR-1014	PK	R, OL, XO	Healthy	12	Tesa 2 mg SC	SD
CTR-1019	PK/DDI	R, OL, XO	Healthy	58	Tesa 2 mg SC qd + simvastatin 80 mg x1 (day 6) Simvastatin 80 mg x1 (day 6)	7 days
CTR 1020	PK/DDI	R, OL, XO	Healthy	32	Tesa 2 mg SC qd + ritonavir 100 mg (day 6) Ritonavir 100 mg (day 6)	7 days
HV/002	PK/PD	R, PDB, PC, P	Healthy	39	Tesa 0.5 mg SC qd/bid Tesa 1, 2 mg SC qd Placebo SC qd	7 days
PKPD/009	PK/PD	R, OL, XO	Healthy	24	Tesa 2 mg SC qd/bid	14 days
CTR-1015	PK/PD	OL	HIV+	18	Tesa 2 mg SC qd	14 days
CTR-1016	PK/PD	R, OL, P	Healthy	24	Tesa 1, 2 mg SC qd	14 days

PK=Pharmacokinetics, PD=Pharmacodynamics, R=Randomized, DB=Double-blind, PDB= Partially double-blind; OL=Open Label, XO=Crossover, P=Parallel, PC=Placebo Controlled, SD=Single-dose, MD=Multiple dose, BE=Bioequivalence, BA=Bioavailability, DDI=Drug-Drug Interaction, SC=subcutaneous, IV=intravenous; qd =once daily, bid= twice daily

Table 5 Tesamorelin Safety and Efficacy Studies

Study Number	Study Design and Type of Control	Target Population	# of Subjects	Dosage Regimen	Duration
Phase III Studies					
LIPO/1010*	R, DB, P, PC	HIV+	410	Tesa 2 mg SC qd	52 weeks

		Excess abdominal fat		Placebo SC qd	
LIPO/1011[#]	R, DB, P, PC	HIV+ Excess abdominal fat	396	Tesa 2 mg SC qd Placebo SC qd	26 weeks
LIPO/1012[^]	R, DB, P, PC	HIV+ Excess abdominal fat	396	Tesa 2 mg SC qd Placebo SC qd	26 weeks
Phase II Studies					
LIPO/008	R, DB, P, PC	HIV+ Excess abdominal fat	61	Tesa 1, 2 mg SC qd Placebo SC qd	12 weeks
SLEEP/002	R, DB, P, PC	Healthy males HIV-	12	Tesa 0.1, 1.0 mg SC qd Placebo SC qd	7 days
SLEEP/005	R, DB, P, PC	Healthy HIV-	82	Tesa 0.1, 1.0 mg SC qd Placebo SC qd	14 days
IR/007	R, DB, P, PC	Elderly undergoing immunization HIV-	87	Tesa 1, 2 mg SC qd Placebo SC qd	8 weeks
COPD/003	R, DB, P, PC	Chronic obstructive pulmonary disease HIV-	109	Tesa 1, 2 mg SC qd Placebo SC qd	3 months
HF/004	R, DB, P, PC	Elderly recovering from hip surgery HIV-	127	Tesa 2 mg SC qd Placebo SC qd	8 weeks
DIABETIC/006	R, DB, P, PC	Type II diabetes HIV-	53	Tesa 1, 2 mg SC qd Placebo SC qd	12 weeks

*Pivotal study; Main and Extension Phases

[#]Pivotal study; Main Phase only

[^]Pivotal study; Extension Phase only

PK=Pharmacokinetics, PD=Pharmacodynamics, R=Randomized, DB=Double-blind, PC=Placebo Controlled, SC=subcutaneous, qd=once daily

5.2 Review Strategy

Sources of clinical data in this review are the original NDA submission and the Sponsor's responses to the Agency's requests for information.

The efficacy review focused on the pivotal phase 3 trials. An independent review was performed by biostatistics, Dr. Lee Ping Pian, and discussions from this review were used in this medical officer's final assessment

For the safety evaluation, all Phase 2/3 safety and efficacy studies were used. However, other than reporting deaths during the entire clinical program, emphasis has been placed on the Phase 3 "pivotal trials" (Studies 10 and 11 during the 26-week Main Phase and studies 10-extension and 12 during the subsequent 26-week Extension Phase). Safety analyses of the Main and Extension phases have been performed separately.

5.3 Discussion of Individual Studies

Table 6 summarizes the pivotal studies in detail:

Table 6 Overview of Pivotal Studies

Study ID	No. of Ctrs./ Location	Study Dates (Start– Completion)	No. of Subjects Randomized / Completed / Dropouts	Design / Control	Route and Regimen	Sex (M/F) Mean Age (Range) Race	Principal Inclusion Criteria	Primary Endpoint(s)	Other Assessments
10	43/ US, Canada	30 Jun 2005-30 Apr 2007 followed by a 26-week Extension Phase	Placebo: 137/115/22 Tesamorelin 2 mg/day 273 ³ /211/62	26-week, randomized, double-blind, placebo-controlled, parallel-group	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-infected subjects with excess abdominal fat ^b , 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	Percent change from baseline to Week 26 in VAT	Belly appearance distress score, triglycerides, total cholesterol: HDL-C ratio, non-HDL-C, IGF-1, trunk fat, total fat, LBM, SAT, limb fat, anthropometric measurements, total cholesterol, HDL-C
10-ext.	43/ US, Canada	30 Jun 2005-30 Apr 2007 preceded by a 26-week Main Phase	Tesamorelin 2 mg/day- Tesamorelin 2 mg/day: 155 ⁶ /129/25 Tesamorelin 2 mg/day- Placebo: 52 ⁵ /40/10 Placebo- Tesamorelin 2 mg/day: 115 ⁴ /87/24	26-week, randomized, double-blind, placebo-controlled, parallel-group	Tesamorelin 2 mg/day sc- Tesamorelin 2 mg/day sc Tesamorelin 2 mg/day sc- Placebo sc Placebo sc- Tesamorelin 2 mg/day sc	315 (275/40) 47.9 y (29-65) 244 (77%) Caucasian 2 (1%) Asian 39 (12%) Black 25 (8%) Hispanic 5 (2%) Other	Subjects who completed TH9507/III/ LIPO/010 (main) with a FBG ≤ 150 mg/dL	52-Week safety	VAT, belly appearance distress score, triglycerides, total cholesterol: HDL-C ratio, non-HDL-C, IGF-1, trunk fat, total fat, LBM, SAT, limb fat, anthropometric measurements, total cholesterol, HDL-C

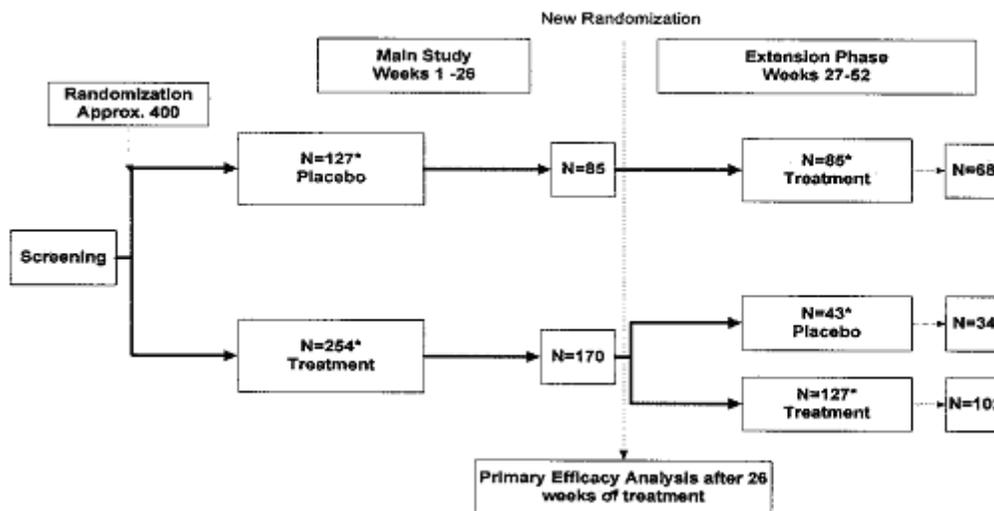
Study ID	No. of Ctrs./ Location	Study Dates (Start-Completion)	No. of Subjects Randomized / Completed / Dropouts	Design / Control	Route and Regimen	Sex (M/F) Mean Age (Range) Race	Principal Inclusion Criteria	Primary Endpoint(s)	Other Assessments
11	48 ^b / US, Canada, Europe (UK, France, Belgium, Spain)	28 Feb 2007-15 Apr 2008	Placebo: 126 ^c /92/34 Tesamorelin 2 mg/day: 270 ^c /202/68	26-week, randomized, double-blind, placebo-controlled, parallel-group	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 ^d	HIV-infected subjects with excess abdominal fat, 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	Percent change from baseline to Week 26 in VAT	Belly appearance distress score, triglycerides, total cholesterol: HDL-C ratio, non-HDL-C, trunk fat, total fat, LBM, SAT, limb fat, IGF-1, anthropometric measurements, total cholesterol, HDL-C
12	40 ^b / US, Canada, Europe (UK, France, Belgium, Spain)	30 Aug 2007-22 Oct 2008	Tesamorelin 2 mg/day- Tesamorelin 2 mg/day: 92/80/12 Tesamorelin 2 mg/day- Placebo: 86/63/22 Placebo- Tesamorelin 2 mg/day: 86/72/14	26-week, extension, randomized, double-blind, placebo-controlled, parallel-group	Tesamorelin 2 mg/day sc- Tesamorelin 2 mg/day sc Tesamorelin 2 mg/day sc- Placebo sc Placebo sc- Tesamorelin 2 mg/day sc	263 (234/29) 48.3 y (29-65) 218 (83%) White 2 (1%) Asian 21 (8%) Black 19 (7%) Hispanic 3 (1%) Other ^d	Subjects who completed TH9507-CTR-1011 with a FBG ≤ 150 mg/dL	52-Week safety	VAT, belly appearance distress score, triglycerides, total cholesterol: HDL-C ratio, non-HDL-C, trunk fat, total fat, LBM, SAT, limb fat, IGF-1, anthropometric measurements, total cholesterol, HDL-C

Source: ISE Table 1

Study Design

A schematic representation of the pivotal trials can be found in Figure 2, below, taken from the Study 10 protocol. It illustrates the general design, the points of randomization and the treatment arms. The numbers of patients indicated are not the actual numbers in the trial but those anticipated to be needed at the time when the protocol was written.

Figure 2 Schematic representation of Pivotal Trials



Main Phase: Studies 10 and 11

Main Phase Studies 10 and 11 both had similar designs and shared virtually identical inclusion criteria, as well as efficacy and safety assessments.

These were randomized, double-blind, placebo-controlled, multicenter, studies which evaluated a 2 mg dose of tesamorelin in patients with HIV-induced lipodystrophy. Studies 10 and 11 lasted 6 months each and randomized patients 2:1 drug to placebo. Patients were included in the trials if they were adult (18 to 65 years), were HIV positive with a CD4 cell count > 100 cells/mm³ and a viral load < 10,000 copies/mL, were on a stable anti-retroviral regimen for 8 weeks prior to randomization, had clinical manifestations of HIV lipodystrophy, and had evidence of abdominal fat accumulation (in males this was based on a waist circumference ≥ 95 cm and a waist-to-hip ratio ≥ 0.94; in females it was based on a waist circumference ≥ 94 cm and a waist-to-hip ratio ≥ 0.88). Exclusion criteria included malnutrition (BMI ≤ 20 kg/m²), recent opportunistic infections, type 1 diabetes, type 2 diabetes if previously treated with insulin or with oral hypoglycemic or sensitizing agents, fasting blood glucose ≥ 150 mg/dL, history of malignancy¹, hypopituitarism, change in anti-hyperlipidemic treatment within 3 months, estrogen therapy, or change in testosterone regimen and/or use of supraphysiological doses of testosterone or anabolic steroid within 6 months.

Patients were stratified according to testosterone use and glucose status in Study 10² and according to glucose status in Study 11. The number of patients randomized to the Main Phase of each trial was approximately 270 in the tesamorelin group and 130 in the placebo group. The primary efficacy endpoint for the Main Phase (Study 10 and Study 11) was the percent change from baseline to Week 26 in visceral adult fat (VAT) where VAT change was defined as cross-sectional area in cm² measured by CT scan at the L4-L5 level. Secondary endpoints were total cholesterol/HDL-cholesterol ratio, triglyceride levels, IGF-1 levels, and patient reported outcomes (PROs) related to Body Image (belly profile, belly size evaluation and belly size distress scales), all evaluated at Week 26. The studies also included a series of exploratory endpoints (“other” study assessments) which varied somewhat between the two trials. They included among others, subcutaneous adipose tissue (SAT), SAT/VAT ratio, total fat, limb fat, trunk fat, lean body mass, and anthropometric measurements (waist and hip circumference and waist-to-hip ratio).

Safety assessments included adverse events, standard chemistry and hematology analytes, urinalysis, immunogenicity, hormone measurements, and oral glucose tolerance test.

Protocol-defined analysis populations were:

¹ Except basal cell carcinoma of the skin, *in situ* carcinoma of the cervix, and stable Kaposi sarcoma not requiring treatment for the past 6 months.

² For Study 10, stratification was performed according to testosterone use and impaired glucose tolerance /diabetes condition at screening). For Study 11, patients were stratified based on glucose status (diabetes yes/no).

- Safety population (defined as all randomized patients who received at least one dose of study drug; patients were to be assigned to the actual treatment received).
- Intent-to-treat (ITT) population (defined as all randomized patients who have received at least one dose of study drug; patients were to be assigned to the randomization arm).
- Per-protocol (PP) population (defined as all patients in the Safety population with no major protocol violations who had at least one post-baseline assessment for the primary efficacy variable).

The ITT population was to be the primary analysis population. Analyses of efficacy and safety variables were to be conducted as observed case (OC) analyses and as last observation carried forward (LOCF) analyses.

The primary efficacy analysis was a drug-to-placebo comparison of the percent change in VAT from baseline to Week 26 using an analysis of covariance (ANCOVA) on the natural log ratio of VAT at Week 26 to baseline VAT. The covariate to be included in the ANCOVA model was to be the natural log baseline VAT. ANCOVA analyses were to be conducted for the secondary endpoint analyses accounting for baseline values and, if applicable, for the presence/absence of treatments that could have confounding effects (e.g. lipid lowering drugs for cholesterol and triglyceride analyses).

Extension Phase: Studies 10-extension and 12

A single daily dose of tesamorelin (2 mg) was evaluated for safety and efficacy in 2 double-blind, randomized controlled studies in the extension phase of the Phase 3 clinical program. The extension phase studies (10-extension and 12) were designed to assess long-term safety and explore duration of effects following end of treatment. To enter the extension phase patients had to have completed the first 26 weeks of the trial and to have a fasting blood glucose ≤ 150 mg at end of the Main Phase.

Subjects who received tesamorelin in the Main Phase of Study 10 were re-randomized in a 3:1 (active:placebo) ratio to receive either tesamorelin or placebo in Study 10-extension, whereas subjects who received placebo in the Main Phase were automatically switched to receive tesamorelin in the Extension Phase. Thus, the treatment groups in the Extension Phase were denoted as Tesamorelin- Tesamorelin (T-T), T-P, and Placebo- Tesamorelin (P-T). Subjects were dosed for up to 26 weeks (Week 27 – Week 52) with either tesamorelin (2 mg/day) or placebo.

Subjects who completed Study 11 were re-randomized in Study 12. Subjects who received tesamorelin in Study 11 were randomized to either tesamorelin 2 mg/day or placebo in a 1:1 ratio. Subjects who received placebo during Study 11 were switched to tesamorelin 2 mg/day. Thus, the treatment groups are denoted as T-T, T-P, and P-T. Subjects were dosed for up to 26 weeks (Week 27 – Week 52) with either tesamorelin (2 mg/day) or placebo.

6 Review of Efficacy

Efficacy Summary

See Ms. Lee Ping Pian’s Statistical Review for details.

Tesamorelin’s clinical development program included three Pivotal Phase 3 studies, which were all randomized, double-blinded, placebo-controlled studies. These include two “Main Phase” studies (010 and 011) comparing tesamorelin 2 mg/day administered subcutaneously and placebo for 26 weeks. At the end of the Main Phase, qualifying patients from Study 010 were re-randomized to receive either a 2 mg/day SC dose of tesamorelin or placebo and entered into an additional 26-week “Extension Phase” of the trial. Qualifying patients from Study 011 were re-randomized and entered into Study 012, also designated as an “Extension Phase” trial, which lasted an additional 26 weeks.

For all Pivotal Studies, the primary endpoint was percent change in visceral adipose tissue. Major secondary endpoints included: total cholesterol:HDL-C ratio and triglyceride levels; IGF-1 levels; Patient Reported Outcome scores related to body image; and various safety measures. See Tables 7 and 9 for schedules of assessments in the Main and Extension Phases, respectively.

Table 7 Schedule of Assessments – Main Phase of Pivotal Studies

Assessment/Procedure	Screening	Randomization	Treatment Period (Visit window \pm 4 days)			
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6 / ET
	Week -4	Week 0	Week 6	Week 13	Week 19	Week 26
	-28 days	Day 0	42 days	91 days	133 days	182 days
Efficacy						
CT scan (VAT, SAT)	✓ ⁸			✓		✓
DEXA scan (total fat, limb fat, trunk fat, lean body mass)	✓ ⁸			✓		✓
DEXA scan (BMC, BMD)	✓ ⁸					
Waist, hip circumferences	✓			✓		✓
Lipid profile		✓	✓ ⁹	✓		✓
IGF-1 ⁷		✓		✓		✓
Inflammatory markers		✓				✓
Bone markers		✓				✓
Patient-reported outcomes	✓	✓				✓
PK blood sampling ¹⁰		✓	✓	✓	✓	✓

⁷ IGF-1 levels were measured for the purposes of safety and efficacy assessment.

⁸ Baseline CT and DEXA scans were performed within 28 days prior to randomization providing all eligibility criteria were met.

⁹ LDL-C and Apolipoproteins A1 and B were not assessed.

¹⁰ Blood sampling for PK analyses were performed in a subgroup of patients from selected sites. A total of 11 samples (1 pre-dose and 10 post-dose) were collected at Weeks 0, 13, and 26 and 2 samples (pre-dose and t_{max} samples) were collected at Weeks 6 and 19.

Source: ISE

Table 8 Schedule of Assessments – Extension Phase of Pivotal Studies

Assessment/Procedure	Randomization	Treatment Period (Visit window \pm 4 days)					Post-treatment
	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10 / ET	30-day Follow-up	
	Week 26	Week 32	Week 39	Week 45	Week 52		
	182 days	224 days	273 days	315 days	364 days		
Efficacy							
CT scan (VAT, SAT)	✓		✓		✓		
DEXA scan (total fat, limb fat, trunk fat, lean body mass)	✓		✓		✓		
DEXA scan (BMC, BMD)					✓		
Waist, hip circumferences	✓		✓		✓		
Lipid profile	✓	✓ ⁶	✓		✓		
IGF-1 ⁵	✓		✓		✓		
Inflammatory markers	✓				✓		
Bone markers	✓				✓		
Patient-reported outcomes	✓				✓		

⁵IGF-1 levels were measured for the purposes of safety and efficacy assessment.

⁶LDL-C and Apolipoproteins A1 and B were not assessed.

Source: ISE

The data provided from the Main Phase of Studies 10 and 11 indicate that tesamorelin reduces visceral fat when measured by abdominal single slice CT at the L4-L5 level. This observation was confirmed independently in two well-designed, placebo-controlled, randomized clinical trials. The mean percent VAT change relative to placebo was -19.6% in Study 10 (95% CI:-23.7-15.3) and -11.7 in Study 11 (95% CI: -16.2, -7.1). In each study the comparison to placebo was statistically significant ($p < 0.001$). Sensitivity analyses confirmed the findings of the primary analysis described above. In patients who were continued on tesamorelin for up to one year of treatment the percent VAT reduction was maintained through Week 52 (-17.5% change from baseline for both studies combined). Interestingly, and importantly, the discontinuation of tesamorelin has resulted in reaccumulation of VAT to levels close to those recorded at baseline; this was observed within 13 weeks, the earliest timepoint of measurement after discontinuation of treatment. This indicates that, in order to maintain VAT reduction, tesamorelin treatment has to be continued long-term, likely indefinitely. This fact has important risk-benefit implications that will become apparent after the review of the safety section.

The clear effect on VAT reduction was accompanied by modest and inconsistent changes in other endpoints of interest. For instance, statistical significance was achieved at Week 26 in Study 10 for the mean change in triglycerides (-52.8 mg/dl relative to placebo; $p < 0.0001$) and non-HDL cholesterol (-10.8 mg/dl relative to placebo; $p < 0.001$). In contrast, smaller changes that did not reach statistical significance were noted in Study 11 (triglycerides: -19.9 mg/dl; $p = 0.10$; non-HDL-C +1.1 mg/dl; $p = 0.216$). In general, efficacy appeared to be greater in Study 10 over Study 11, although an explanation for this fact is not evident.

Patient reported outcomes related to body image showed either negative statistical results (BSE) or only modest and inconsistent changes (BAD, BP). This should not be surprising given the fact that the drug resulted in only a small reduction in waist circumference (1.5 cm relative to placebo) along with no significant effect on SAT and a relatively small increase in total body muscle mass.

The 2 mg regimen of Egrifta also produced favorable effects on total fat (1.4 kg reduction relative to placebo), trunk fat (1.2 kg reduction relative to placebo), and lean body mass (increase of 1.4 kg relative to placebo) that were both statistically significant and consistent with previously reported data for rhGH.

Finally, observations made at Week 52 were, in general, consistent with those at Week 26.

6.1 Indication

The Sponsor proposes tesamorelin as a primary therapy to induce and maintain a reduction of excess abdominal fat in HIV-infected patients with lipodystrophy.

6.1.1 Methods

The results of the Pivotal Phase 3 studies (Main and Extension Phases) were the primary data used in the efficacy analysis. These randomized, double-blind, placebo-controlled studies were of sufficient duration to allow for adequate assessment of the primary efficacy endpoint.

6.1.2 Demographics

6.1.2.1 Main Phase of Pivotal Trials

The patient baseline characteristics for the individual studies and for both studies combined are shown in Table 9. For the pooled studies, the tesamorelin and placebo groups showed similar demographic and anthropometric measurements at baseline. Specifically, the mean age was 47.5 and 47.9 years for the tesamorelin and placebo groups, respectively, and ranged from 27 to 65 years. The majority of individuals were male (85.0%) and White/Caucasian (76.1%). The tesamorelin and placebo groups were also similar with respect to the various body measurements, such as weight, BMI, waist and hip circumference, and waist: hip ratio. Mean values for the tesamorelin and placebo groups, respectively were: weight, 89.3 and 88.6 kg; BMI, 29.0 and 29.0 kg/m²; waist circumference, 104.6 and 104.5 cm; hip circumference, 100.1 and 99.9 cm; and waist: hip ratio, 1.0 and 1.0.

The profile for the baseline demographic and anthropometric measurements of Studies 10 and 11 was also similar and balanced.

Table 9 Baseline Demographics and Anthropometric Measurements – Main Phase ITT Population

		Study 010		Study 011		Combined Results	
		Tesamorelin N=273	Placebo N=137	Tesamorelin N=270	Placebo N=126	Tesamorelin N=543	Placebo N=263
Age (years)	Mean (SD)	47.3 (7.32)	48.3 (7.51)	47.6 (7.49)	47.6 (7.72)	47.5 (7.40)	47.9 (7.60)
	Range	28; 65	31; 65	27; 65	28; 65	27; 65	28; 65
Gender	Male	237	115	228	105	465	220

n (%)		(86.8)	(83.9)	(84.4)	(83.3)	(85.6)	(83.7)
	Female	36 (13.2)	22 (16.1)	42 (15.6)	21 (16.7)	78 (14.4)	43 (16.3)
Ethnic origin n (%)	White	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	37 (13.6)	22 (16.1)	34 (12.6)	12 (9.5)	34 (12.9)	71 (13.1)
	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)
Weight (kg)	Mean (SD)	89.6 (14.06)	90.0 (13.65)	89.0 (13.59)	87.1 (15.55)	89.3 (13.82)	88.6 (14.64)
	Range	56; 161	62; 128	54; 140	52; 148	54; 161	52; 148
BMI (kg/m²)	Mean (SD)	29.2 (4.17)	29.2 (4.24)	28.8 (4.26)	28.7 (4.22)	29.0 (4.21)	29.0 (4.23)
	Range	22; 48	22; 46	20; 46	22; 44	20; 48	22; 46
Waist circumf. (cm)	Mean (SD)	104.2 (9.54)	104.6 (9.49)	105.0 (9.03)	104.4 (9.08)	104.6 (9.29)	104.5 (9.28)
	Range	90; 154	92; 138	94; 149	94; 151	90; 154	92; 151
Hip circumf. (cm)	Mean (SD)	99.7 (8.53)	100.0 (9.31)	100.6 (8.37)	99.8 (9.26)	100.1 (8.46)	99.9 (9.27)
	Range	85; 152	83; 130	83; 137	87; 159	83; 152	83; 159
Waist: Hip Ratio	Mean (SD)	1.0 (0.06)	1.0 (0.07)	1.0 (0.07)	1.0 (0.07)	1.0 (0.07)	1.0 (0.07)
	Range	1; 1	1; 1	1; 2	1; 1	1; 2	1; 1

Source: ISE Table 3

The baseline characteristics related to HIV diagnosis and immune status as well as lipodystrophy features were in general well balanced (summarized in Table 10). For the pooled studies, the tesamorelin and placebo groups had similar duration since time of initial diagnosis of HIV infection, CD4 and CD8 cell counts, and the majority of subjects in both groups (75.0% and 78.3%, respectively) had undetectable viral load. The mean duration of anti retroviral therapy (ART) was slightly longer in the tesamorelin group (54.7±36.84 months) than in the placebo group (50.4±33.81 months), but this difference was not statistically significant. There were differences with respect to treatment subgroups of the ART regimen³.

Abdominal lipohypertrophy was present in all subjects in both groups. General lipodystrophy was reported in 69.8% of tesamorelin subjects and in 69.2% of placebo subjects.

Table 10 Baseline HIV- and Lipodystrophy Syndrome-Related Characteristics – Main Phase ITT Population

		Study 010		Study 011		Combined Results	
		Tesamorelin N=273	Placebo N=137	Tesamorelin N=270	Placebo N=126	Tesamorelin N=543	Placebo N=263
Time since HIV dx (months)	Mean (SD)	161.6 (62.98)	155.9 (63.79)	169.9 (66.60)	163.9 (67.95)	165.8 (64.88)	159.7 (65.81)
	Range	13; 311	8; 288	10; 326	26; 308	10; 326	8; 308
Viral load n (%)	Undect.	186 (68.1)	97 (70.8)	221 (81.9)	109 (86.5)	407 (75.0)	206 (78.3)
	50-400 copy /mL	62 (22.7)	28 (20.4)	30 (11.1)	12 (9.5)	92 (16.9)	40 (15.2)
	>400 copy /mL	25 (9.2)	12 (8.8)	19 (7.0)	5 (4.0)	44 (8.1)	17 (6.5)
CD4 cell count	Mean (SD)	617.1 (299.03)	585.3 (283.96)	588.3 (290.40)	599.8 (277.65)	602.7 (294.84)	592.2 (280.52)
	Range	93; 2021	103; 1623	110; 1749	104; 1553	93; 2021	103; 1623
CD8 cell count	Mean (SD)	940.4 (422.81)	1024 (470.25)	971.5 (440.98)	929.7 (375.02)	956.0 (431.88)	978.9 (429.11)

³ About half the subjects in both the tesamorelin and placebo groups (44.0% and 48.3%, respectively) reported taking a nucleoside reverse transcriptase inhibitor (NRTI) and a PI, and very few subjects (4.4% and 6.1%, respectively) reported taking an NRTI alone. More tesamorelin-treated subjects reported taking an NRTI and a non-nucleoside reverse transcriptase inhibitor (NNRTI) with no PI than placebo-treated subjects (35% and 29%, respectively). Not surprisingly, there were some differences between Studies 10 and 11. For instance, in Study 10, the tesamorelin group had slightly longer mean duration of ART compared to the placebo group (56.5 vs. 48.2 months), and there were some imbalances in the types of current ART regimen.

	Range	238; 4247	10; 3680	187; 3848	277; 2020	187; 4247	10; 3680
Duration of ART (months)	Mean (SD)	56.5 (37.14)	48.2 (31.36)	52.9 (36.52)	52.8 (36.24)	54.7 (36.84)	50.4 (33.81)
	Range	6; 231	5; 154	4; 179	4; 146	4; 231	4; 154
Type of ART regimen (%)	NRTI and NNRTI	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	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)
Time since lipodys. dx (months)	Mean (SD)	50.3 (39.59)	50.6 (40.02)	65.3 (43.27)	69.7 (42.59)	57.8 (42.10)	59.7 (42.28)
	Range	0; 223	0; 192	-5; 211	1; 259	-5; 223	0; 259
Lipodys. clinical findings (%)	Facial	141 (51.6)	70 (51.1)	123 (45.6)	56 (44.4)	264 (48.6)	126 (47.9)
	Lower limb	165 (60.4)	81 (59.1)	148 (54.8)	72 (57.1)	313 (57.6)	153 (58.2)
	Upper limb	140 (51.3)	58 (42.3)	117 (43.3)	57 (45.2)	257 (47.3)	115 (43.7)
	Gen. lipo-atrophy	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)
	Abdom.	273 (100)	137 (100)	270 (100)	126 (100)	543 (100)	263 (100)
	Breast size increas.	111 (40.7)	60 (43.8)	105 (38.9)	39 (31.0)	216 (39.8)	99 (37.6)
	≥1 finding	242 (88.6)	125 (91.2)	222 (82.2)	101 (80.2)	464 (85.5)	226 (85.9)

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Source: ISE Table 4

6.1.2.2 Extension Phase of Pivotal Trials

As shown in Table 11, in the pooled Extension Phase studies, the three treatment groups (T-T, T-P, and P-T) displayed similar mean ages (approximately 48 years; range: 28-65 years), similar proportions of males and females (approximately 88% and 12%, respectively), and were predominantly White/Caucasian (approximately 80%). The three treatment groups were also similar with respect to the various body measurements, such as weight, waist circumference, and waist:hip ratio. Statistically significant differences were observed between the T-T and T-P groups for mean BMI and hip circumference at baseline, with a higher mean BMI and hip circumference in the T-P group (29.4 kg/m² and 100.9 cm, respectively) compared to the T-T group (28.6 kg/m² and 99.1 cm, respectively).

Table 11 Baseline Demographics/Anthropometric Measurements – Extension Phase ITT Population (Both Pivotal Studies Combined)

		Combined Results		
		T-T N=246	T-P N=135	P-T N=197
Age (years)	Mean (SD)	47.7 (7.16)	48.1 (7.12)	48.3 (7.73)
	Range	28; 65	31; 65	28; 65
Gender n (%)	Male	219 (89.0)	119 (88.1)	171 (86.8)
	Female	27 (11.0)	16 (11.9)	26 (13.2)
Ethnic origin n (%)	White	195 (79.3)	113 (83.7)	154 (78.2)
	Asian	1 (0.4)	1 (0.7)	2 (1.0)
	Black	29 (11.8)	10 (7.4)	21 (10.7)
	Hispanic	19 (7.7)	9 (6.7)	16 (8.1)
	Other	2 (0.8)	2 (1.5)	4 (2.0)
Weight (kg)	Mean (SD)	88.7 (13.27)	90.7 (15.06)	88.7 (14.50)
	Range	60; 139	56; 161	57; 148
BMI (kg/m ²)	Mean (SD)	28.6 (4.06)	29.4 (4.26)	28.8 (4.23)
	Range	20; 47	22; 48	22; 46
Waist circumf. (cm)	Mean (SD)	103.8 (8.61)	105.4 (10.25)	104.4 (9.47)
	Range	90; 150	94; 154	92; 151
Hip circumf. (cm)	Mean (SD)	99.1 (7.80)	100.9 (9.21)	99.8 (9.28)
	Range	85; 134	88; 152	85; 159
Waist: hip ratio	Mean (SD)	1.05 (0.0728)	1.05 (0.0565)	1.05 (0.0629)
	Range	0.87;1.61	0.94; 1.19	0.89; 1.23

Source: ISE Table 15

As shown in Table 12, similar profile for demographic and anthropometric measurements at baseline was observed in Studies 10-extension and 12; however, no statistically significant differences were observed between the T-T and T-P groups for mean BMI and mean hip circumference at baseline in each individual study.

Table 12 Baseline Demographics/Anthropometric Measurements – Extension Phase ITT Population (Individual Pivotal Studies)

		Study 10-extension			Study 12		
		T-T N=154	T-P N=50	P-T N=111	T-T N=92	T-P N=85	P-T N=86
Age (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)
	Range	28; 65	31; 60	31; 65	31; 62	32; 65	28; 65
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)
Ethnic origin n (%)	White	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	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 (1.2)	1 (2.0)	2 (1.8)	0	1 (1.2)	2 (2.3)
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)
	Range	61; 139	56; 161	62; 128	60; 136	63; 140	57; 148
BMI (kg/m²)	Mean (SD)	28.9 (4.18)	30.2 (4.69)	29.1 (4.22)	28.1 (3.81)	28.9 (3.95)	28.4 (4.25)
	Range	22; 47	22; 48	22; 46	20; 37	22; 43	22; 44
Waist circumf. (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)
	Range	90; 150	94; 154	92; 138	95; 140	94; 136	94; 151
Hip circumf. (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)
	Range	85; 134	88; 152	85; 130	85; 116	89; 137	87; 159
Waist: hip ratio	Mean (SD)	1.05 (0.061)	1.04 (0.056)	1.05 (0.66)	1.05 (0.089)	1.05 (0.056)	1.05 (0.059)
	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

Source: ISE Table 15

For other baseline characteristics in the ITT population of the pooled Extension Phase studies, the three treatment groups had similar mean times since HIV diagnosis, mean times since diagnosis of lipodystrophy syndrome, durations of ART regimen, proportions of patients with undetectable viral load at baseline, mean CD4 cell counts at baseline and Week 26, and mean CD8 cell counts at baseline and Week 26. The distribution of viral

load at Week 26 was statistically significant between the T-T and T-P groups. A statistically significant difference was also observed between the combined T-T and T-P groups versus P-T group for type of ART regimen. Comparable percentages of patients in each treatment group displayed general lipoatrophy: 70.7% in the T-T, 70.4% in the T-P, and 71.6% in the P-T groups. Abdominal lipohypertrophy was present in all patients in the 3 treatment groups.

HIV- and lipodystrophy syndrome-related characteristics were generally similar in Studies 10-extension and 12. However, in Study 10-extension, a statistically significant difference was observed between the combined T-T and T-P groups versus P-T group for the duration of ART regimen; the T-T and T-P groups had longer mean duration than the P-T group.

6.1.3 Subject Disposition

6.1.3.1 Main Phase of Pivotal Trials

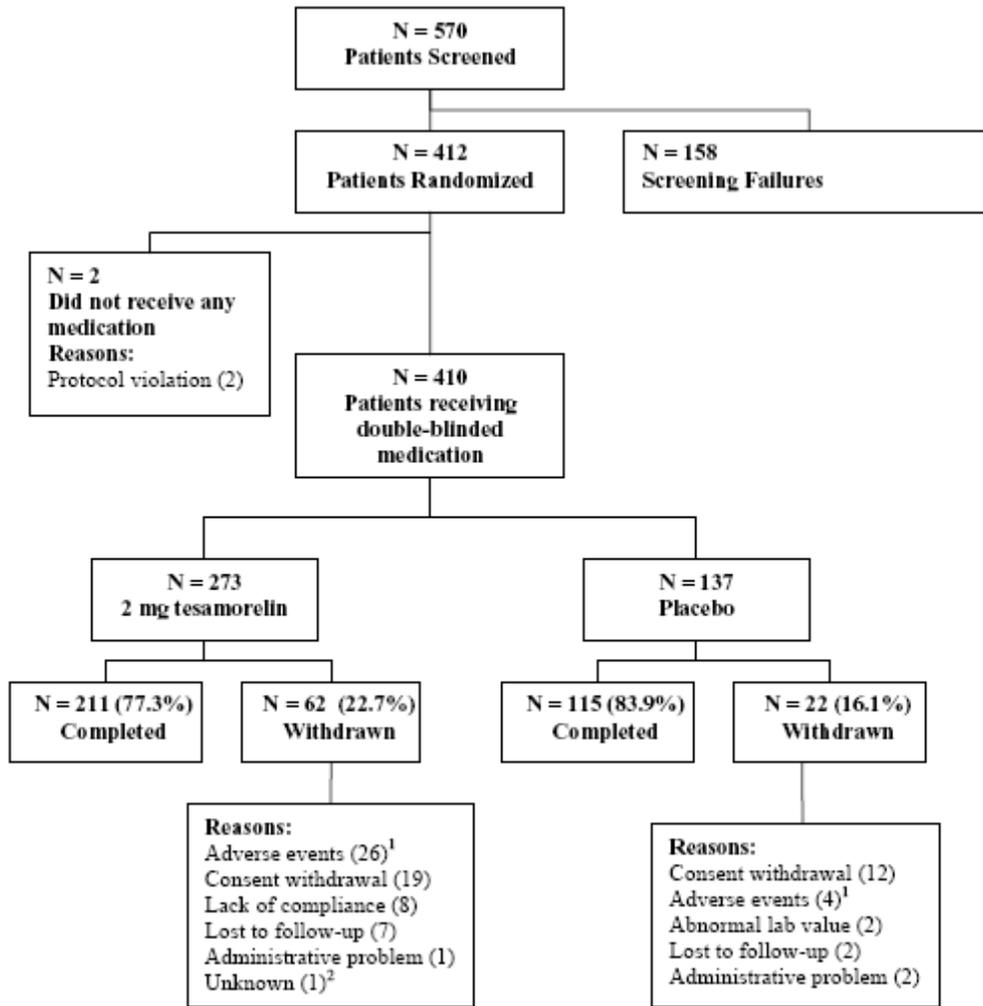
Study 10

In total, 570 individuals were screened and 412 were randomized to receive tesamorelin or placebo. Two patients who were randomized to the tesamorelin arm did not receive any study drug when it was revealed that their testosterone regimen had changed in violation of an exclusion criterion. Thus, in total, the tesamorelin group included 273 patients and the placebo group included 137 patients.

Of the 412 randomized patients, a similar proportion in each treatment arm completed the Main Phase: 211 (77.3 %) patients in the tesamorelin group and 115 (83.9%) patients in the placebo group. At each post-baseline study visit (i.e., Week 6 onwards), the proportion of patients who continued in the study was high ($\geq 78\%$) and similar between treatment groups.

In both treatment groups, the main reasons for early study discontinuation were AEs and consent withdrawal. More tesamorelin than placebo patients reported AEs as the primary reason for early study discontinuation: 26 of 273 (9.5%) tesamorelin patients vs. four of 137 (2.9%) placebo patients. Lack of compliance also was cited in more tesamorelin patients (eight tesamorelin and no placebo patients). Similar proportions of patients in each treatment group withdrew their consent and discontinued the study prematurely: 19 of 273 tesamorelin patients (7.0%) vs. 12 of 137 placebo patients (8.8%). Figure 3 depicts patient disposition during the Main Phase of Study 10.

Figure 3 Patient Disposition – Study 10



Source: TH9507/III/LIPO/010 CSR – Figure 2

Study 11

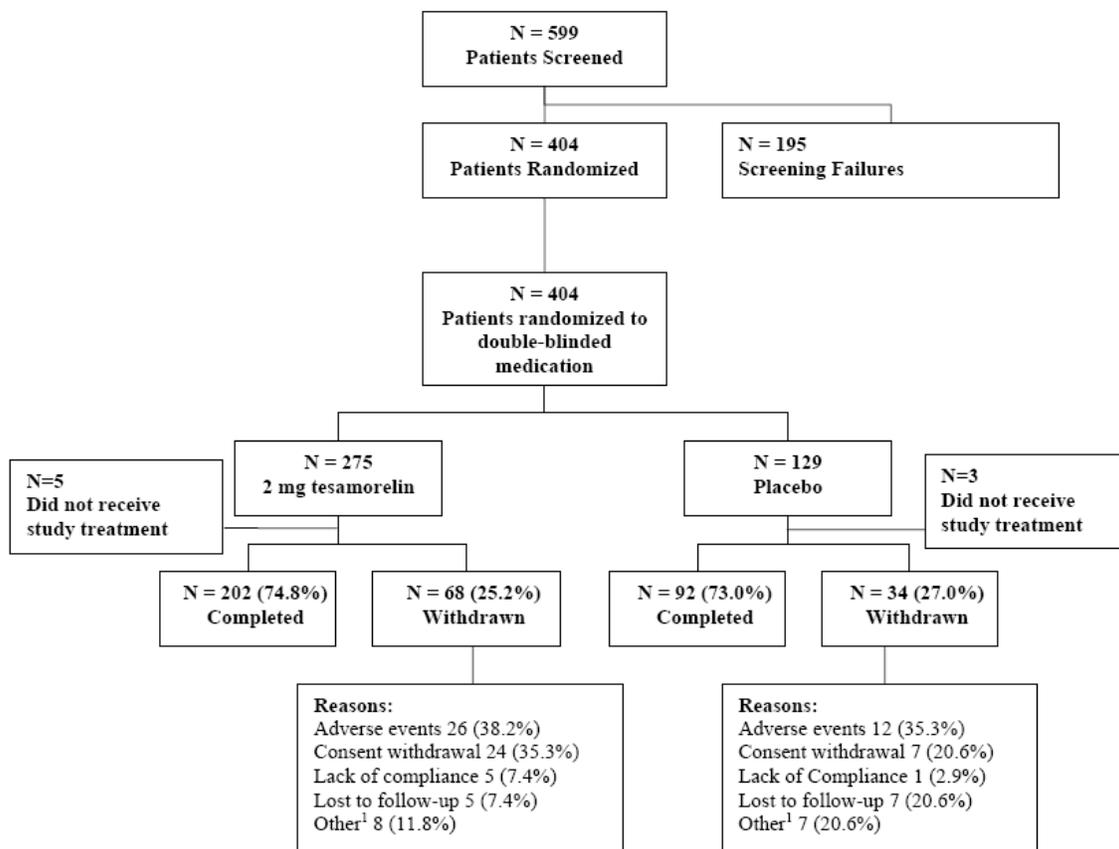
In total, 599 individuals were screened; 195 failed screening procedures and thus, 404 were randomized into the study. Reasons for screen failure were: failure to meet inclusion criteria (137 patients, 70.3%), withdrawal of consent (25 patients, 12.8%), and other (32 patients, 16.4%). The reason for screen failure was not specified for one patient. Eight patients were randomized to treatment but did not receive study treatment, and were thus excluded from the PP, safety and ITT populations.

In total, the tesamorelin group included 275 patients and the placebo group included 129 patients. Of the randomized patients who received at least one dose of study treatment, similar proportions of patients in each treatment group completed the study (74.8% tesamorelin and 73.0% placebo).

For those patients discontinuing from treatment, AEs were the most common reason (38.2% tesamorelin and 35.3% placebo) followed by withdrawal of consent (35.3% tesamorelin and 20.6% placebo). Lack of compliance was relatively low in frequency (7.4% tesamorelin and 2.9% placebo).

Figure 4 depicts patient disposition during the Main Phase of Study 11.

Figure 4 Patient Disposition – Study 11



Source: TH9507-CTR-1011 CSR – Figure 2

Both Pivotal Studies Combined

Across both pivotal studies 816 patients were randomized to tesamorelin (N=550) or placebo (N=266). The ITT population (defined in study protocol as all randomized subjects who received at least one dose of study treatment) consisted of 543 patients who received tesamorelin and 263 patients who received placebo (Table 13, below). When data from both studies were pooled, there were similar proportions of completers by treatment group (76.1% tesamorelin and 78.7% of placebo). However, among patients who discontinued, more patients discontinued due to adverse events in the tesamorelin group (40.0%) than placebo (32.1%) and more tesamorelin patients were non-compliant (10% vs. 1.8% placebo). Conversely, more patients in the placebo arms were lost for follow-up and or discontinued for “other reasons” including administrative problems,

concomitant medical conditions, violation of inclusion or exclusion criteria, drug abuse, inability to administer study medication, and randomization error (16.1% vs. 6.9% tesamorelin group). Withdrawal of consent was the same between groups (33.1% tesamorelin and 33.9% placebo).

Largely similar percentages of patients discontinued tesamorelin during the individual studies (77.3% in Study 10 and 74.8 in Study 11), but there were larger between-study differences for placebo completers (higher in Study 10).

Table 13 Subject Disposition – Main Phase ITT Population

	Study 010		Study 011		Combined Results	
	Tesamorelin N=273	Placebo N=137	Tesamorelin N=270	Placebo N=126	Tesamorelin N=543	Placebo N=263
Randomized n (%)	275 (100)	137 (100)	275 (100)	129 (100)	550 (100)	266 (100)
ITT population^a n (%)	273 (99.3)	137 (100.00)	270 (98.2)	126 (97.7)	543 (98.7)	263 (98.9)
Completed^b n (%)	211 (77.3)	115 (83.9)	202 (74.8)	92 (73.0)	413 (76.1)	207 (78.7)
Discontinued n (%)	62 (22.7)	22 (16.1)	68 (25.2)	34 (27.0)	130 (23.9)	56 (21.3)
Primary reason^c						
Adverse event n (%)	26 (41.9)	6 (27.3)	26 (38.2)	12 (35.3)	52 (40.0)	18 (32.1)
Protocol non- compliance 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)
Other n (%)	1 (1.6)	2 (9.1)	8 (11.8)	7 (20.6)	9 (6.9)	9 (16.1)

Source: ISE Table 2

^aPercentages based on the number of randomized subjects.

^bPercentages based on the number of subjects in ITT population.

^cPercentages based on number of subjects who discontinued prior to end of study.

6.1.3.2 Extension Phase of Pivotal Trials

Table 14 describes patient disposition and reasons for patient withdrawal in the Extension Phase studies.

Table 14 Patient Disposition – Extension Phase (Individual Pivotal Studies)

	Study 10-extension			Study 12		
	Tesamorelin N=211	Placebo N=115		Tesamorelin N=202	Placebo N=92	
Completed Main study						
Excluded from Extension	7	4		---	---	
Included in Extension	204	111		177	86	
Treatment sequence	T-T	T-P	P-T	T-T	T-P	P-T
n	154	50	111	92	85	86
Completed Extension	129 (84%)	40 (80%)	87 (78%)	80 (87%)	63 (74%)	72 (84%)
Withdrawal Of Consent	12 (8%)	4 (8%)	6 (5%)	8 (9%)	11 (13%)	7 (8%)
Adverse Event	5 (3%)	3 (6%)	12 (11%)	1 (1%)	4 (5%)	5 (6%)
Lack Of Compliance	7 (5%)	1 (2%)	2 (2%)	1 (1%)	3 (4%)	1 (1%)
Lost To Follow-Up	1 (.7%)	2 (4%)	3 (3%)	2 (2%)	2 (2%)	1 (1%)
Other	---	---	---	0	2 (2%)	0
Abnormal Laboratory Value	0	0	1 (0.9%)	---	---	---

Source: ISE Table 14

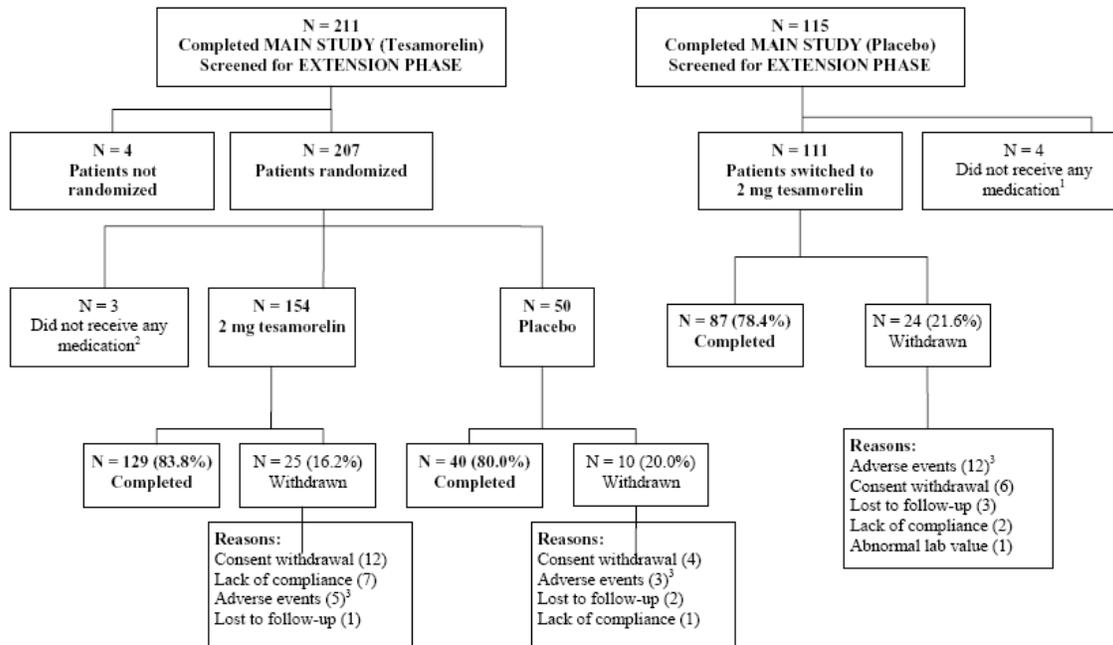
Study 10-extension

The 26-week Main Phase Study 10 was completed by 211 patients in the tesamorelin group and by 115 patients in the placebo group. Of 211 patients who received tesamorelin in the Main Phase, 207 patients were randomized into the Study 10-extension. However, the randomization procedure was initiated prematurely for three patients who had not yet decided to participate and who later declined; these three patients did not receive any study treatment. Thus, 204 patients entered Study 10-extension: 154 patients were randomized to receive tesamorelin (T-T group) and 50 patients were randomized to receive placebo (T-P group). Of 115 patients who received placebo in the Main Phase of Study 10, four declined to participate in Study 10-extension and did not receive any study treatment. Thus, study treatment was switched from placebo to tesamorelin (P-T group) in 111 patients.

The proportion of patients who completed Study 10-extension was similar between the two randomized treatment groups: 129 (83.8%) patients in the T-T group and 40 (80.0%) patients in the T-P group completed the Extension Phase. The main reasons for study discontinuation were consent withdrawal and lack of compliance in the T-T group, and AE and consent withdrawal in the T-P group. Among the 111 patients in the P-T group, 87 (78.4%) completed Study 10-extension. Early study discontinuation was mainly due to AEs. At each study visit (i.e, Week 32 onwards), the proportion of patients who continued in the study was high ($\geq 78\%$) and similar among the three treatment groups.

Figure 5 outlines patient disposition during the Extension Phase of Study 10.

Figure 5 Patient Disposition – Study 10-extension



Source: TH9507/III/LIPO/010 CSR – Figure 3

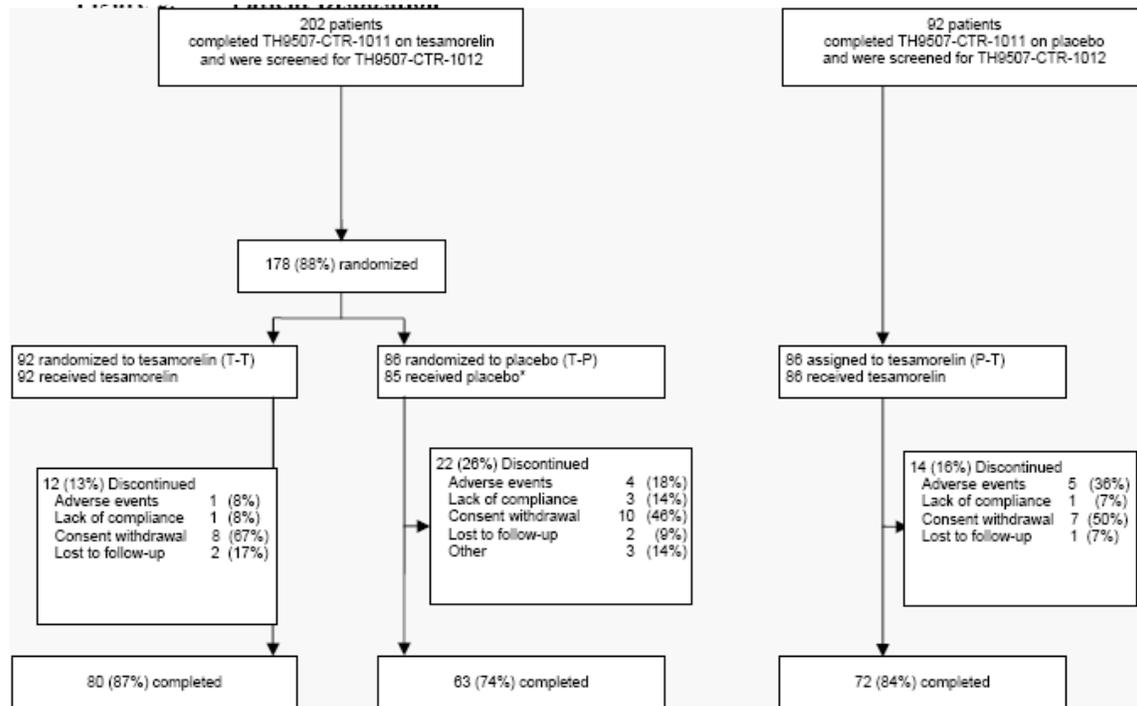
Study 12

Two-hundred and ninety-four patients completed Study 11: 202 in the tesamorelin group and 92 in the placebo group. Two hundred and sixty-three of them (89%) subsequently enrolled in study 12.

Of 202 patients who received tesamorelin in Main Phase Study 11, 178 patients (88%) were randomized: 92 patients were randomized to receive tesamorelin (T-T group) and 86 patients were randomized to receive placebo (T-P group). One patient (#5260) did not sign the informed consent form but was randomized. The patient did not receive study treatment and was not included in the safety or ITT populations. Of 92 patients who received placebo in Study 11, 86 patients (93%) were switched from placebo to tesamorelin (P-T group). A greater proportion of tesamorelin-treated patients (T-T, 87% and P-T, 84%) completed the study compared to placebo-treated patients (74%). The main reason for study discontinuation in all groups was withdrawal of consent.

Figure 6 outlines patient disposition during Study 12.

Figure 6 Patient Disposition – Study 12



Source: TH9507-CTR-1012 CSR – Figure 2

Both Pivotal Studies Combined

As shown in Table 15, in the pooled Extension Phase studies, of 413 tesamorelin patients who completed the Main Phase studies, a total of 381 patients entered the Extension Phase: 246 patients were randomized to receive tesamorelin (T-T group) and 135 patients were randomized to receive placebo (T-P group). Study treatment was switched from placebo to tesamorelin (P-T group) in 197 patients.

The proportion of patients who completed the Extension Phase was 85.0% (209 patients) in the T-T group and 76.3% (103 patients) in the T-P group. In the P-T group, 80.7% (159 patients) completed the Extension Phase. A greater proportion of patients who discontinued in the P-T group reported adverse event as the primary reason for early study discontinuation (44.7%) compared to the T-T and T-P groups (16.2% and 21.9%, respectively).

Table 15 Patient Disposition – Extension Phase (Both Pivotal Studies Combined)

	Combined Results		
	T-T N=246	T-P N=135	P-T N=197
# of subjects completed Ext. Phase n (%)	209 (85.0)	103 (76.3)	159 (80.7)
Discontinuation: Reason n (%)			
Adverse event	6 (16.2)	7 (21.9)	17 (44.7)
Non-compliance	8 (21.6)	4 (12.5)	3 (7.9)
Withdrawal of consent	20 (54.1)	15 (46.9)	13 (34.2)
Lost to follow-up	3 (8.1)	4 (12.5)	4 (10.5)
Abnormal lab values	0	0	1 (2.6)
Other	0	2 (6.3)	0

Source: ISE Table 14

6.1.4 Analysis of Primary Endpoint(s)

There are currently no approved drug products in the US for the proposed indication i.e. treatment of increased abdominal fat in patients with HIV. The sponsor has selected as its primary efficacy endpoint the percent change in VAT from baseline to Week 26 in the ITT population, using last observation carried forward analysis. VAT was assessed by CT scan from a single 5 mm slice obtained at the level of L4-L5 inter-vertebral disc space. CT scans were performed at local facilities and obtained within 28 days prior to randomization and at Weeks 13 and 26. The treatment effect was tested using ANCOVA on the natural logarithm of the ratio of VAT at Week 26 to VAT at baseline.

The sponsor argues VAT is an appropriate endpoint in the HIV-positive population for the following reasons:

- Data from the Fat Redistribution and Metabolic Changes in HIV Infection (FRAM) showed that increased VAT was associated with higher prevalence of dyslipidemia, diabetes and elevated 10-year CVD Framingham Risk Score (Wohl et al., 2008).
- Data from longitudinal, prospective studies indicate that self-reported lipodystrophy symptoms are independently associated with nonadherence to ART. The results from a study involving 277 HIV-infected patients showed that 30% of these patients failed to maintain adherence to ART after 20 months of follow-up and that non-adherent patients were more likely to have a bigger belly and a wider waist (Duran et al., 2001).

- In agreement with these findings are data showing that self-perception of fat accumulation and longer duration on ART were both related to subsequent non adherence (Ammassari et al., 2002; Vergel, 2008). Taken together, the results from these studies suggest that reduction of VAT may help improve patient-outcomes related to body image and, thereby, adherence to otherwise effective ART
- Formal recommendations from the 2004 Forum for Collaborative HIV Research (Snyder, 2006) have established an “expected decline” of 8% in VAT for patients with HIV lipodystrophy receiving rhGH products in trials of up to 26 weeks’ duration. This minimum difference provides an objective measure to use when evaluating the efficacy of treatment.

As per the recommendations described above, the Sponsor recommended a cutoff of 8% to estimate a clinically relevant response to drug treatment. This proposal was discussed with and confirmed by the Agency at a post-phase 2 meeting on March 30, 2005. By the Sponsor’s definitions, a “VAT responder” is considered a subject with a change from baseline in VAT of $\geq 8\%$, whereas a “VAT non-responder is a subject with a change from baseline in VAT $< 8\%$.

6.1.4.1 Main Phase of Pivotal Trials

As previously mentioned, the primary efficacy analysis was a drug-to-placebo comparison of the percent change in VAT from baseline to Week 26 using an analysis of covariance (ANCOVA). The results, as analyzed by the FDA statistical reviewer, are presented in Table 16 for the intent-to-treat (ITT) population. The mean absolute change from baseline in VAT for tesamorelin relative to placebo was -31.9 cm^2 in Study 10 and -20.6 cm^2 in Study 11. The prespecified primary efficacy analysis, the mean % change in VAT in the tesamorelin group relative to placebo, was statistically significant ($p < 0.001$) in each of the studies. Specifically, the mean % change in VAT was -19.6% (95% CI: $-23.7, -15.3$) in Study 10 and -11.7% (95% CI: $-16.2, -7$) in Study 11.

Table 16 ANCOVA* Results for VAT % change and change from baseline to Week 26 – Main Phase of Pivotal Trials (ITT, LOCF)

Study		Tesamorelin		Placebo		Treatment difference from placebo
		n	Mean	n	Mean	LSM, (SE), [95% CI], p-value
10	Baseline (SD)	272	178.3 (76.9)	136	171.0 (76.9)	
	% change (SE)		-17.8% (1.6)		+2.2% (2.2)	-19.6% (2.7) [-23.7, -15.3] $p < 0.001$
	Change (SE)		-27.4 (2.2)		+4.4 (3.2)	-31.9 (3.9) [-39.5, -24.3] $p < 0.001$
11	Baseline (SD)	268	186.5 (86.6)	126	194.9 (95.5)	
	% change (SE)		-13.8% (1.5)		-2.4% (2.2)	-11.7% (2.7) [-16.2, -7.1] $p < 0.001$
	Change (SE)		-21.0 (2.4)		-0.4 (3.5)	-20.6 (4.2) [-28.8, -12.3] $p < 0.001$

Source: FDA Statistical Reviewer

*Analysis of covariance model with treatment as fixed effect and baseline VAT as covariate.

An analysis of VAT % change conducted in completers indicated similar results (Table 17). It is not entirely clear why the two trials yielded quite different VAT reductions given the similarity in design, inclusion criteria, and baseline patient characteristics. Compliance does not seem to have played a part because the percentage of patients who were <80% compliant in the tesamorelin arm was actually lower in Study 10 (26.2%) versus Study 11 (39.5%), while they were similar in the placebo arms (25% in Study 10 and 20.6% in Study 11).

Table 17 ANCOVA* results for VAT % change from Baseline– Main Phase of Pivotal Trials (Individual Studies, Completers Only)

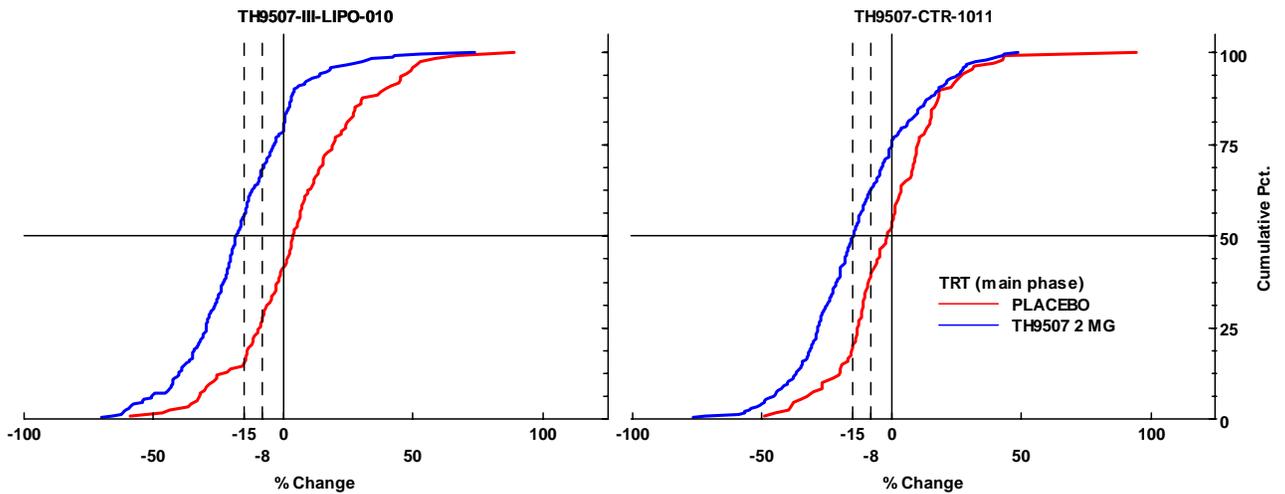
Study		TH9507 (2 mg)		Placebo		Treatment difference at Week 26
		n	Mean	n	Mean	LSM, (SE), [95% CI], p-value
10	Baseline (SD)	210	180.0 (77.0)	114	173.0 (78.2)	
	% change (SE)	210	-21.3% (1.9)	114	+2.3% (2.5)	-23.1 (3.2) [-27.7, -18.3] p<0.01
11	Baseline (SD)	201	186.5 (86.6)	92	194.9 (95.5)	
	% change (SE)	201	-16.6% (1.9)	92	-3.8% (2.8)	-13.4 (3.3) [-18.8, -7.6] p<0.01

Source: FDA Statistical Review

* Analysis of covariance included treatment as fixed effect and baseline as covariate.

Consistent with the results described above, cumulative distribution graphs of the percent of VAT change show a clear separation between drug and placebo, more so in Study 10, which showed the largest treatment effect (graph generated by the FDA statistical reviewer). In the statistical graphs tesamorelin is identified as TH9507, which is a premarketing name.

Figure 7 Cumulative Distribution Function of the Percent Change in VAT by Treatment Group at Week 26 –Main Phase of Pivotal Trials (Individual Studies)



Source: FDA Statistical Review

Efficacy data pooled from both studies is presented by time on trial in Table 18. The mean VAT at baseline was 182.36 cm² for the tesamorelin group and 182.49 cm² for the placebo group. After 13 weeks of treatment, the mean percent change from baseline in VAT was statistically significantly greater in the tesamorelin group (decrease of 10.32%) compared with the placebo group (increase of 1.36%). By week 26, the mean percent change in the tesamorelin group showed a decrease of 13.11% compared to an increase of 2.30% in placebo (p<0.001).

Table 18 Change in VAT (cm²) from Baseline – Main Phase of Pivotal Trials

		Study 10		Study 11		Combined Results	
		Tesamorelin N=273	Placebo N=137	Tesamorelin N=270	Placebo N=126	Tesamorelin N=543	Placebo N=263
Baseline	n	272 ¹	136 ¹	268	126	540	262
	Mean	178.29	170.96	186.49	194.94	182.36	182.49
	SD	76.94	76.92	85.56	95.45	81.88	86.99
	Range	25.3; 461.5	45.1; 425.6	28.1; 427.3	29.9; 447.4	25.3; 461.5	29.9; 447.4
Week 13	n	272	136	268	126	540	262
	Mean	156.73	172.68	169.86	191.54	163.25	181.75
	SD	76.91	78.32	83.47	95.25	80.43	87.22
	Range	24.1; 534.8	33.9; 473.4	27.4; 411.8	33.0; 505.8	24.1; 534.8	33.0; 505.8
	Change from Baseline	-21.56 (33.61)	1.73 (30.05)	-16.62 (32.76)	-3.40 (35.44)	-19.11 (33.25)	-0.74 (32.79)
	Percent change (SD)	-12.06 (17.48)	2.96 (21.86)	-8.57 (15.89)	-0.36 (19.72)	-10.32 (16.79)	1.36 (20.89)
	LSM	-13.83	0.67	-10.11	-2.09	-12.00	-0.62
	p-value	<.001		<.001		<.001	
Week 26	n	272	136	268	126	540	262
	Mean	150.54	176.00	165.71	194.12	158.07	184.71
	SD	74.07	81.70	87.01	100.17	81.03	91.32
	Range	15.4; 461.9	30.3; 428.2	20.6; 446.5	33.5; 461.1	15.4; 461.9	30.3; 461.1
	Change from Baseline	-27.75 (38.66)	5.05 (36.40)	-20.77 (42.11)	-0.82 (32.39)	-24.29 (40.52)	2.23 (34.59)
	Percent change (SD)	-15.13 (20.84)	5.0 (23.43)	-11.06 (21.28)	-0.62 (18.90)	-13.11 (21.14)	2.30 (21.52)
	LSM	-17.82	2.23	-13.84	-2.39	-15.89	0.08
	p-value	<.001		<.001		<.001	

Source: ISE Table 5.1

¹One tesamorelin patient and one placebo patient were excluded from the analysis because their baseline VAT was missing.

Subgroup analyses by gender

Tables 19 and 20 summarize the treatment effect by gender at Weeks 13 and 26 in the Main Phase of each pivotal study using ANCOVA for analysis. Results from the subgroup analyses by gender showed that the percent change from baseline in VAT at

Weeks 13 and 26 was similar for females across studies for identical timepoints but different for males (larger reductions from baseline in Study 10). Comparisons between changes in males and females were more discordant at Week 13 but more similar at Week 26. Of note, baseline VAT was significantly less in females compared with males in both pivotal trials.

Table 19 Gender Analysis of % Change in VAT at Weeks 13 and 26* – Study 10 (Main Phase)

Visit		Tesamorelin (N=273)			Placebo (N=137)			P- value
		n	Mean (SD)	LSM	n	Mean (SD)	LSM	
Baseline VAT (cm²)		272	178 (76.9)	---	136	171 (76.9)	---	---
Week 13	Actual value (cm²)	272	157 (76.9)	---	137	175 (82.2)	---	---
	% change (all patients)	272	-12.1 (17.5)	-12.6	136	3.0 (21.9)	2.1	<0.001
	% change in males	237	-12.7 (17.6)	-14.5	114	2.6 (22.8)	0.2	<0.001
	% change in females	35	-7.8 (15.9)	-8.9	22	4.7 (16.5)	3.1	0.009
Week 26								
Week 26	Actual value (cm²)	273	150 (74.1)	---	137	178 (85.0)	---	---
	% change (all patients)	272	-15.1 (20.8)	-17.8	136	5.0 (23.4)	2.3	<0.001
	% change in males	237	-15.3 (20.7)	-18.0	114	4.8 (24.2)	1.9	<0.001
	% change in females	35	-13.9 (21.9)	-16.7	22	6.1 (19.4)	4.3	0.001

Source: TH9507/III/LIPO/010 CSR – Table 25

*ITT Analysis, LOCF

Table 20 Gender Analysis of % Change in VAT at Weeks 13 and 26* – Study 11 (Main Phase)

Visit		Tesamorelin (N=270)			Placebo (N=126)			P- value
		n	Mean (SD)	LSM	n	Mean (SD)	LSM	
Baseline VAT (cm²)		268	186 (86.6)	---	126	195 (95.5)	---	---
Week 13	Actual value (cm²)	269	170 (83.3)	---	126	192 (95.3)	---	---
	% change	268	-8.57 (15.9)	-12.6	126	-0.36 (19.7)	-2.1	<0.001
	% change in males	226	-8.85 (16.5)	-10.5	105	-0.42 (20.9)	-2.34	<0.001
	% change in females	42	-7.05 (12.4)	-7.77	21	-0.06 (12.6)	-1.13	0.06
Week 26								
Week 26	Actual value (cm²)	269	166 (86.8)	---	126	194 (100)	---	---
	% change	268	-10.9 (21.2)	-13.8	126	-0.62 (18.9)	-2.6	<0.001
	% change in males	226	-10.9 (21.8)	-13.8	105	-0.05 (19.0)	-1.8	<0.001
	% change in females	42	-11.2 (18.4)	-13.3	21	-3.46 (18.6)	-5.1	0.127

Source: TH9507-CTR-1011 CSR – Table 14.2.1.6.1.1, Table 14.2.1.6.1.2, Table 14.2.1.6.1.3

*ITT Analysis, LOCF

Several sensitivity analyses were conducted in order to evaluate the effect of covariates other than gender on the percent change from baseline in VAT during the Main Phase; such covariates included testosterone use, impaired glucose tolerance/Type 2 Diabetes, antiretroviral regimen, number of days on protease inhibitor, race, age, and country. The percent change from baseline in VAT remained significant between patients in the tesamorelin and placebo groups regardless of the status of any of the above covariates.

6.1.4.4 Extension Phase of Pivotal Trials

The T-T group can be compared with the T-P group to assess durability of tesamorelin effect over a 52-week period. In the pooled Extension Phase studies (shown in Table 21), mean baseline (Week 0) VAT was 186.59 for the T-T group and 185.78 for the T-P group. At the start of the Extension Phase (after 26 Weeks of treatment with tesamorelin), mean VAT had decreased by 17.11% in the T-T group and by 14.50% in the T-P group. However, after 13 weeks of the Extension Phase (Week 39 of the trials), the mean VAT percent change from baseline held steady in the T-T group (-16.35%), whereas patients in the T-P group had experienced a reversal of the VAT reduction they experienced in the Main Phase (mean VAT percent change from baseline of -0.93%) This pattern held through week 52, with a mean percent VAT decrease of 17.50% and an increase of 0.28% for T-T and T-P groups respectively (p<0.001 using LSM analysis).

The P-T group can be compared with the T-P group to assess for a reversion to baseline characteristics following tesamorelin withdrawal. In the pooled Extension Phase studies, mean baseline (Week 0) VAT for P-T was 187.25, similar to the T-P group. At the start of the Extension Phase, mean VAT had increased by 1.94% in the P-T group; after 13 weeks of the Extension Phase (Week 39), the mean VAT had decreased by 10.06%, whereas those in the T-P group (as mentioned above) had begun to experience a reaccumulation of VAT. At week 52, patients in the P-T group had a mean VAT decrease of 13.26% from baseline, comparable to those in the T-T group (p<0.001 using LSM analysis).

Table 21 Change in VAT from Baseline – Extension Phase of Pivotal Trials (Both Trials Combined)

		Combined Results		
		T-T N=246	T-P N=135	P-T N=197
Baseline	n	244	135	196
	Mean	186.59	190.24	185.78
	SD	83.32	81.87	88.70
	Range	25.3; 461.5	28.1; 427.2	29.9; 447.4
Week 26	n	244	135	196
	Mean	153.30	164.63	187.25
	SD	79.36	83.78	94.08
	Range	15.4; 461.9	20.6; 414.0	30.3; 461.1
	Change from Baseline (cm²)/ (SD)	-33.9 (44.16)	-25.61 (43.32)	1.46 (37.98)

	Percent change (SD)	-17.11 (22.50)	-14.50 (22.57)	1.94 (22.95)
Week 39	n	244	135	196
	Mean	154.68	185.99	168.11
	SD	78.38	85.19	93.78
	Range	10.7; 483.3	26.0; 445.6	20.5; 502.3
	Change from Baseline (cm²)/ (SD)	-31.92 (44.21)	-4.24 (44.25)	-17.67 (39.52)
	Percent change (SD)	-16.35 (21.66)	-0.93 (-4.90)	-10.06 (20.69)
	LSM	-18.84	-4.90	---
	p-value	<0.01		
Week 52	n	244	135	196
	Mean	151.45	188.27	160.64
	SD	79.06	89.57	89.72
	Range	14.1; 498.9	26.0; 493.2	18.8; 457.6
	Change from Baseline (cm²)/ (SD)	-35.14 (50.35)	-1.96 (48.23)	-25.14 (44.14)
	Percent change (SD)	-17.50 (23.29)	0.28 (26.29)	-13.26 (-12.68)
	LSM	-20.98	-3.79	---
	p-value	<0.01		

Source: ISE Table 5.2

As shown in Table 22, the results of Studies 10-extension and 12 were generally similar by Week 52, with patterns for the T-T, T-P, and P-T groups comparable to those seen in the pooled data above. The differences in mean change in VAT from baseline (Week 0) between the T-T and P-T groups compared with T-P were statistically significant using LSM analysis in both pivotal studies.

Table 22 Change in VAT from Baseline – Extension Phase of Pivotal Trials (Individual Trials)

		Study 10-extension			Study 12		
		T-T N=154	T-P N=50	P-T N=111	T-T N=92	T-P N=85	P-T N=86
Baseline Week 0	n	153	50	110	91	85	86
	Mean	180.52	174.27	175.38	196.81	199.63	199.09
	SD	77.93	71.81	77.46	91.21	86.27	100.19
	Range	25.3; 461.5	56.5; 361.2	57.0; 425.6	31.5; 427.3	28.1; 427.2	29.9; 447.4
Week 26	n	153	50	110	91	85	86
	Mean	145.73	143.52	179.91	166.02	177.05	196.63

	SD	70.04	71.85	83.24	89.32	88.11	106.17
	Range	15.4; 461.9	37.1; 309.6	30.3; 428.2	31.6; 446.5	20.6; 414.0	15.4; 461.9
	Change from Baseline (cm²)/ (SD)	-34.78 (42.4)	-30.75 (37.41)	4.53 (38.83)	-30.79 (47.10)	-22.58 (46.39)	-22.58 (46.39)
	Percent change (SD)	-18.45 (22.67)	-18.62 (20.35)	4.56 (24.33)	-14.87 (22.15)	-12.07 (23.55)	-1.40 (20.71)
Week 39							
Week 39	n	153	50	110	91	85	86
	Mean	148.08	166.48	158.72	165.76	197.47	180.14
	SD	76.79	72.71	81.67	80.20	90.19	106.99
	Range	10.7; 483.3	49.3; 361.2	34.2; 502.3	20.4; 420.7	26.0; 445.6	20.5; 492.7
	Change from Baseline (cm²)/ (SD)	-32.44 (40.76)	-7.79 (38.47)	-16.67 (37.66)	-31.04 (49.69)	-2.16 (47.42)	-18.95 (41.96)
	Percent change (SD)	-17.80 (21.26)	-2.87 (24.63)	-8.98 (20.37)	-13.92 (22.23)	0.21 (25.13)	-11.46 (21.13)
	LSM	-20.85	-6.08	---	-16.66	-2.88	---
	p-value	<0.001			<0.001		
Week 52							
Week 52	n	153	50	110	91	85	86
	Mean	150.54	176.00	165.71	194.12	158.07	184.71
	SD	74.07	81.70	87.01	100.17	81.03	91.32
	Range	14.1; 498.9	43.8; 321.4	18.8; 431.7	17.2; 450.0	26.0; 493.2	28.3; 457.6
	Change from Baseline (cm²)/ (SD)	-31.62 (45.46)	-5.38 (39.96)	-24.36 (41.87)	-41.06 (57.42)	0.04 (52.61)	-26.13 (47.12)
	Percent change (SD)	-17.53 (23.49)	-1.42 (23.89)	-12.72 (24.30)	-17.46 (23.09)	1.28 (27.69)	-13.96 (25.62)
	LSM	-21.34	-4.24	---	-20.66	-2.88	---
	p-value	<0.001			<0.001		

Source: ISE Table 5.2

Table 23 provides further ANCOVA analysis of the treatment difference from placebo in VAT for the individual Extension Phase Studies 10 and 12 (performed by the FDA statistical reviewer). In the T-T group, there was a relatively small percent change from baseline (+4.5% for Study 10 and -1.4% for Study 12), where as patients in the T-P groups experienced a significant increase in VAT percentage during the Extension Phase (+24.9% for Study 10 and +24.5% for Study 12). The LSM treatment differences from placebo were -20.4% for Study 10 and -25.8% for Study 12, both statistically significant.

Table 23 ANCOVA* results for VAT % change from Week 26 to Week 52 – Extension Phase of Pivotal Trials (Individual Studies, ITT Analysis)

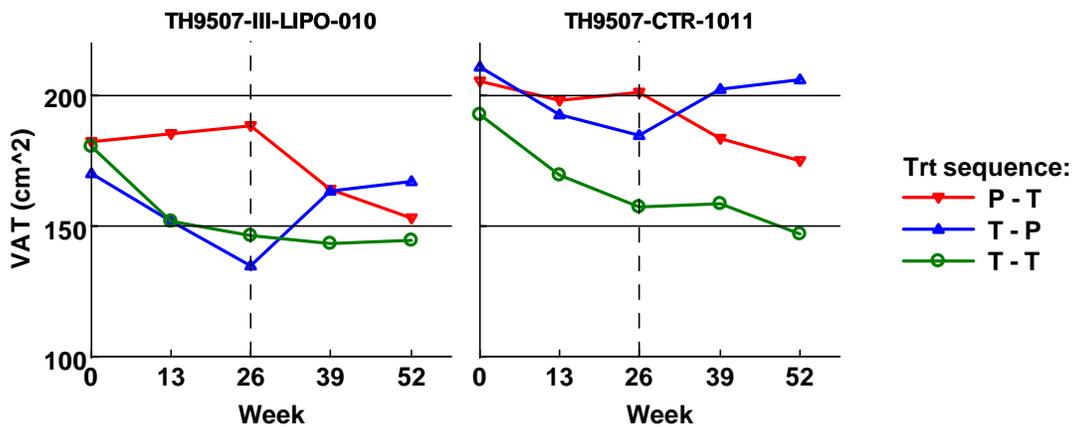
Study	T-T		T-P		Treatment Difference from Placebo LSM, (SE) [95% CI] P-value
	n	LSM	n	LSM	
10	154	+4.5% (2.4)	50	+24.9% (4.1)	-20.4% (4.8) [-29.8, -11.0] p<0.0001
12	92	-1.4% (5.2)	85	+24.5% (5.4)	-25.8% (7.6) [-40.7, -10.9] p=0.0008

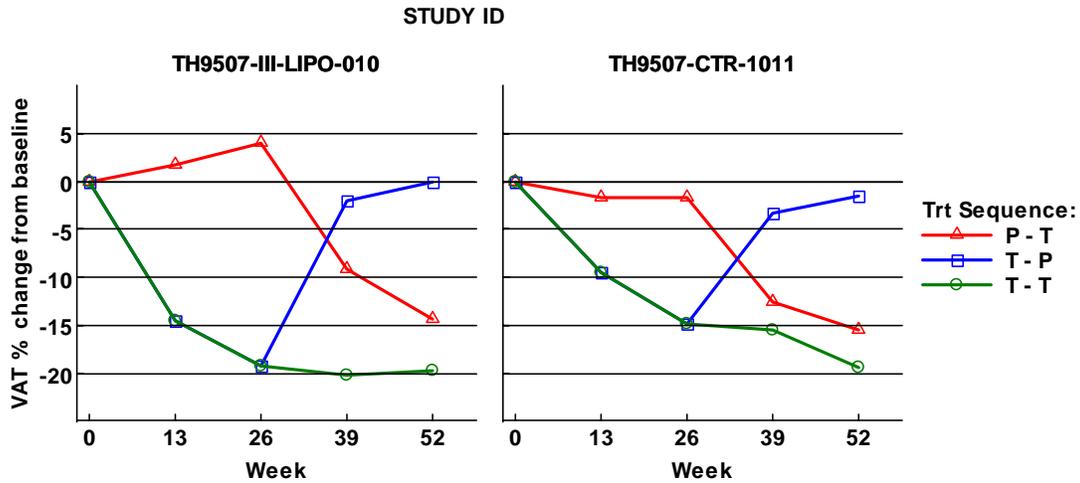
Source: FDA Statistical Review

*Analysis of covariance included treatment as fixed effect and Week 26 baseline as covariate

Figure 8 depicts the mean absolute (top) and percent (bottom) changes from baseline in VAT for Pivotal Trials 10 (Main and Extension Phases) and 11/12. This figure illustrates graphically that although at the end of 52 weeks the percent decrease is greatest among patients receiving tesamorelin for the entirety of the trial (i.e. T-T group), those patients in the T-P and P-T groups showed rapid decreases in VAT following the initiation of tesamorelin, which was sustained through 26 weeks of treatment. Furthermore, those patients in the T-P groups whose tesamorelin was discontinued exhibited a rapid and sustained return to baseline VAT values.

Figure 8 Mean % Changes in VAT from Week 0 to Week 52 –Pivotal Trials (Individual Trials 010 and 011)

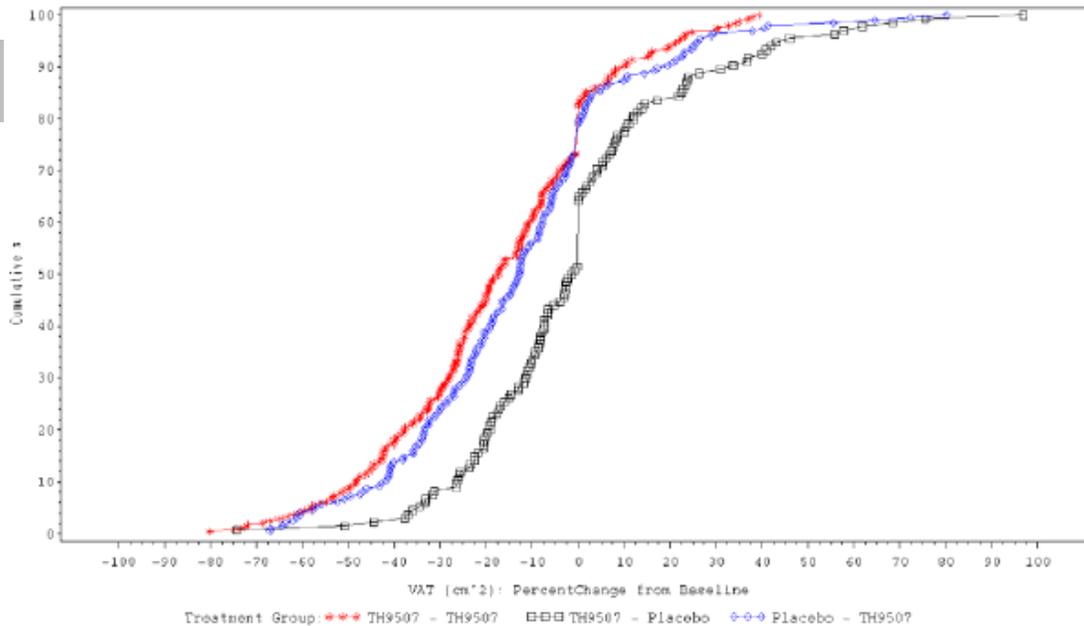




Source: FDA Statistical Reviewer

Figure 9 depicts the cumulative distribution function (CDF) of the percent change in VAT from baseline to 52, which graphically demonstrates that a higher proportion of patients in the T-T and P-T groups than in the T-P group showed a decrease in VAT over the 52-week treatment period.

Figure 9 Cumulative Distribution Function of the Percent Change in VAT by Treatment Group at Week 52 – Extension Phase of Pivotal Trials (Both Trials Combined)

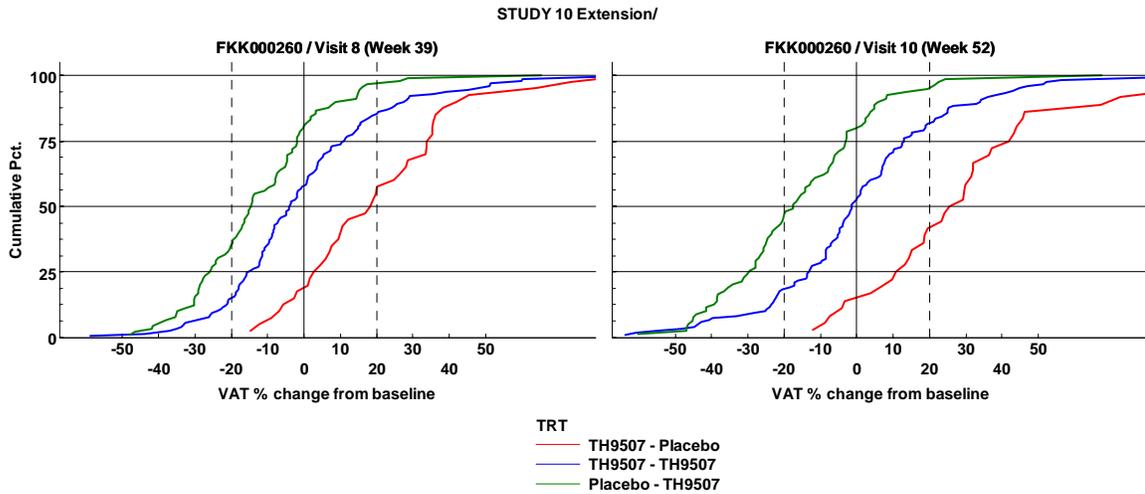


Source: ISE Figure 1

Figure 10 depicts the CDF of the percent change in VAT from Week 26 to Week 52 for the individual Pivotal Trials 10 and 12. These figures graphically demonstrate a

comparable percent change in VAT from baseline for patients in these two studies, with the largest percent change over this time period seen in the P-T group (with both P-T and T-T having a greater reduction in VAT compared to T-P).

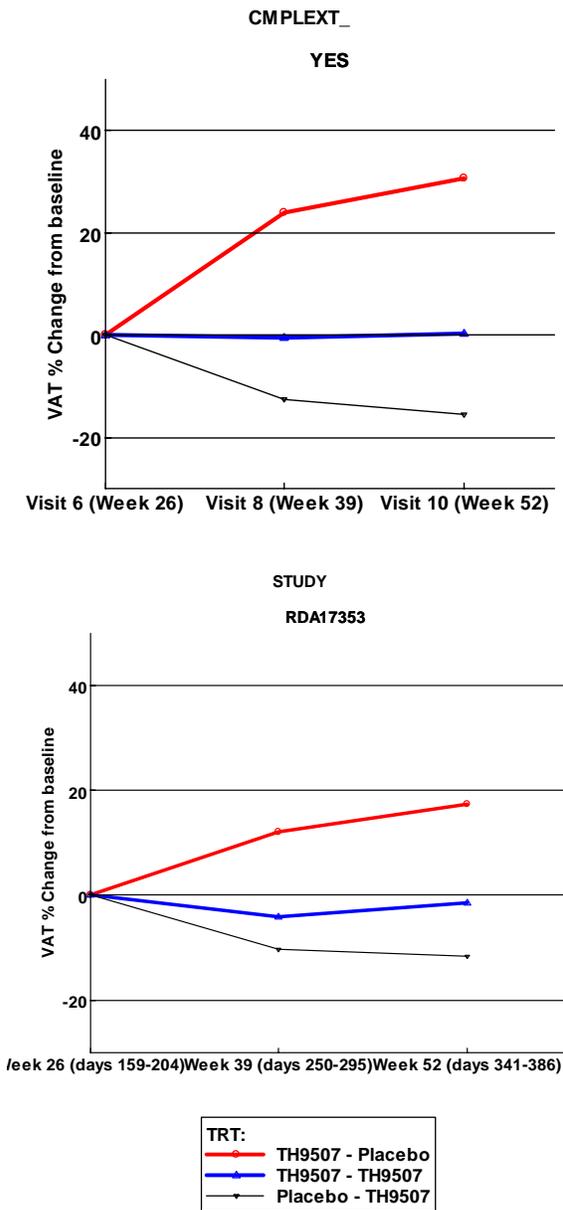
Figure 10 Cumulative Distribution Function of the Percent Change in VAT by Treatment Group from Week 26 to Week 52 –Extension Phase of Pivotal Trials (Individual Studies)



Source: Statistical Review

Figure 11 depicts the mean and median percent change from the time of re-randomization (Week 26) to Week 52 in the individual Studies 10-extension and 12 for completers only. The figure demonstrates that over the course of the Extension Phase, patients in the T-T group sustained their VAT reduction from the Main Phase; patients in the P-T group had a marked reduction in VAT after starting tesamorelin; and patients in the T-P group had a marked increase in VAT after stopping tesamorelin.

Figure 11 VAT Mean and Median % Change from Re-Randomization – Extension Phase of Pivotal Trials (Individual Studies)



Source: FDA Statistical Review

6.1.5 Analysis of Secondary Endpoints(s)

Secondary endpoint analyses were the change from baseline in the IGF-1 level, total cholesterol: HDL-C ratio, TG level, and patient reported outcomes (PROs): belly size evaluation, belly appearance distress, and belly profile.

Because of the large number of secondary endpoints, the Agency and applicant agreed to develop a hierarchy to rank key endpoints in order of importance (in hopes of minimizing Type I Error). Based on a communication with the Agency in December, 2007, the

applicant devised a “gatekeeper” strategy for analysis of the following endpoints: belly appearance distress change scores, triglycerides, total cholesterol: HDL-C ratio, and non-HDL-C (an endpoint that was added based on the Agency’s recommendation). These endpoints were ordered in significance (most to least significant) as listed in Table 9. They were to be considered for analysis only if:

- the primary endpoint was found to be statistically significant (which was the case given the VAT results), and if
- the secondary endpoint ordered in significance before it was found to be statistically significant.

As indicated in Table 24, the secondary endpoint rankings were different for Studies 10 and 11. During the December 2007 correspondence, the Agency requested the applicant change the gatekeeper analysis (re-ordering the rankings and adding a “supportive” analysis using non-HDL-C in place of triglycerides). Because Study 10 had already been completed, the changes were applied only to Study 11.

Table 24 Gatekeeper Approach to Studies 10 and 11

Secondary Endpoint	Ranking of Endpoint		
	Study 10	Study 11	
		Primary	Supportive
Belly appearance distress PRO (change from baseline)	1	1	1
Triglycerides Change from baseline to Week 26 in	2	1	NR
Total cholesterol:HDL-C ratio (change from baseline to Week 26)	3	2	2
Non-HDL-C (change from baseline to Week 26)	Not ranked	Not ranked	Supportive

Source: ISE Table 6

The results of this gatekeeper approach to efficacy are displayed in T, below. According to this approach, the efficacy analyses were supposed to stop at the primary efficacy level for Study 10 (because the changes in belly appearance distress PRO were not statistically significant) and at the level of belly appearance distress PRO in Study 11 (because the change in triglycerides relative to placebo was not statistically significant in the trial).

Table 25: Overview of Ranked Secondary Variables for Studies 10 and 11

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
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).

This review will present the secondary efficacy analyses results regardless of the gatekeeper strategy.

6.1.5.1 IGF-1 Levels

IGF-1 levels were determined centrally from fasting blood samples obtained at Week 0, 13, 26, 39, and 52 (or ET). In this section, IGF-1 results are presented as a marker of tesamorelin efficacy. Please see the safety section of this review for further detailed analyses of IGF-1 levels.

Main Phase

IGF-1 levels were measured centrally from fasting blood samples obtained at Weeks 0, 13 and 26. In this section, IGF-1 results are presented as a marker of tesamorelin efficacy. Please see the safety section of this review for a detailed safety analysis of IGF-1 levels. The Week 26 change from baseline in mean IGF-1 is presented by individual study and for the pooled data in Table 26. All analyses indicated a statistically significant elevation in mean IGF-1 at Week 26 ($p < 0.001$). The Week 13 findings were consistent with those described for Week 26.

Table 26 IGF-1 Change from Baseline to Week 26* -- Main Phase of Pivotal Trials

Visit	Study 010				Study 011				Combined Results			
	Tesamorelin N=273		Placebo N=137		Tesamorelin N=270		Placebo N=126		Tesamorelin N=543		Placebo N=263	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Baseline (ng/mL)	269	161.1 (59.0)	136	168.1 (75.0)	265	146.2 (65.9)	125	149.1 (59.4)	534	153.7 (62.9)	261	159.0 (68.5)
Change to Week 26 (ng/mL)	269	107.3 (112.8)	136	-16.3 (66.4)	265	108.5 (110.5)	125	2.3 (59.0)	534	107.9 (111.6)	261	-7.4 (63.5)
% Change to Week 26	269	80.3 (112.6)	136	-5.0 (29.4)	265	88.0 (88.4)	125	5.4 (39.2)	534	84.1 (101.3)	261	-0.04 (34.8)
P-value^a	<0.001				<0.001				<0.001			

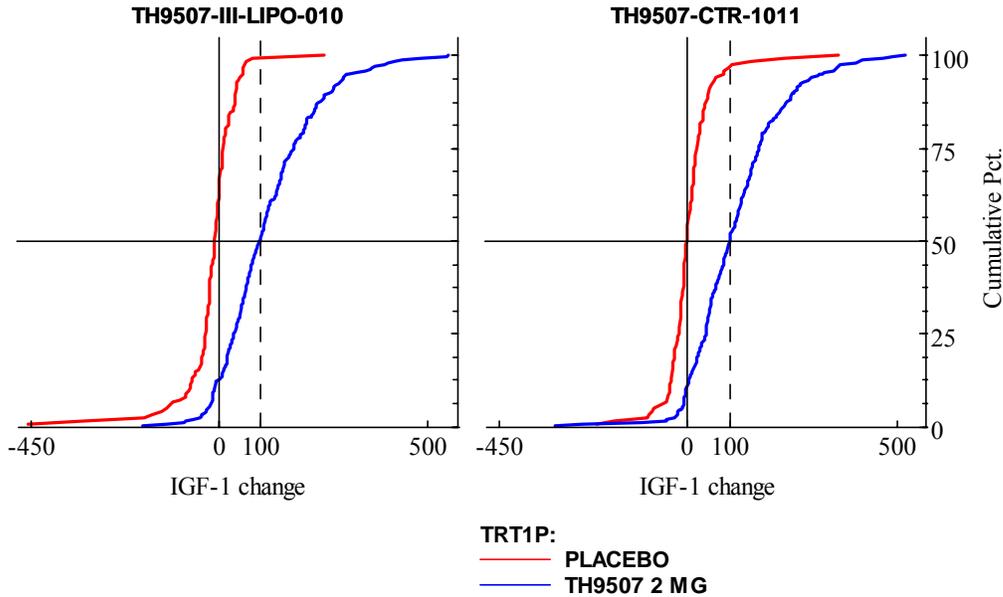
Source: ISE Table 11

*ITT Population

^a P-values are for treatment group difference in mean change from baseline. For the individual studies, the ANCOVA model is IGF-1 at baseline + treatment. For the combined studies, the ANCOVA model is IGF-1 at baseline + study + treatment.

Cumulative distribution graphs for IGF-1 changes at Week 26 show a clear separation between tesamorelin and placebo.

Figure 10 Cumulative Distribution of IGF-1 from Baseline to Week 26 – Main Phase (Individual Pivotal Studies)



Source: FDA Statistical Review

Extension Phase

In the Extension Phase IGF-1 levels were measured centrally at Weeks 39 and 52 (or ET)

The T-T group can be compared with the T-P group to assess sustained efficacy of tesamorelin over a 52-week period. In the pooled Extension Phase studies (shown in Table 27), mean baseline (Week 0) IGF-1 was 160.54 for the T-T group and 149.96 for the T-P group. At the start of the Extension Phase (after 26 Weeks of treatment with tesamorelin), mean IGF-1 had increased to 287.08 ng/mL (+ 93.94%) in the T-T group and to 273.28 ng/mL (+100.52%) in the T-P group. However, after 13 weeks of the Extension Phase (Week 39 of the trials), the mean IGF-1 change from baseline held steady in the T-T group (255.02 ng/mL, +73.15%), whereas patients in the T-P group had experienced a reversal of the IGF-1 increase they experienced in the Main Phase (mean IGF-1 138.92 ng/mL, change from baseline of -2.40%) This pattern held through week 52, with a mean IGF-1 increase of 63.07% and a decrease of 0.7% for T-T and T-P groups respectively (p<0.001).

The P-T group can be compared with the T-P group to assess efficacy of tesamorelin. In the pooled Extension Phase studies, mean baseline (Week 0) IGF-1 for P-T was 162.76, similar to the T-P group. At the start of the Extension Phase, mean IGF-1 had decreased by 3.32% in the P-T group; after 13 weeks of the Extension Phase (Week 39), the mean IGF-1 had increased by 61%, whereas those in the T-P group (as mentioned above) exhibited a decline in IGF-1 from baseline. At week 52, patients in the P-T group had a mean IGF-1 increase of 56% from baseline, comparable to those in the T-T group (p<0.001).

Table 27 Change in IGF-1 from Baseline – Extension Phase of Pivotal Trials (Both Trials Combined)

		Combined Results		
		T-T N=246	T-P N=135	P-T N=197
Baseline	n	240	133	195
	Mean (ng/mL)	160.54	149.96	162.76
	SD	63.52	61.41	73.14
	Range	30; 435	22; 406	31; 549
Week 26	n	240	133	195
	Mean (ng/mL)	287.08	273.28	148.44
	SD	127.67	108.36	59.63
	Range			
	Change from Baseline (cm²)/ (SD)	126.54 (114.53)	123.32 (102.45)	-14.31 (61.38)
	Percent change (SD)	93.94 (115.30)	100.52 (87.76)	-3.32 (30.71)
Week 39	n	240	133	195

	Mean (ng/mL)	255.02	138.92	247.42
	SD	122.09	48.60	112.83
	Range	36.0; 667.0	15.0; 255.0	42.0; 584.0
	Change from Baseline (cm²)/ (SD)	94.48 (106.82)	-11.05 (45.09)	84.67 (96.08)
	Percent change (SD)	73.15 (150.77)	-2.40 (27.63)	61.37 (67.74)
	LSM	96.9	-13.5	---
	p-value	<0.01		
Week 52				
	n	240	133	195
	Mean (ng/mL)	238.42	140.89	236.02
	SD	120.41	53.22	122.80
	Range	36.0; 667.0	13.0; 298.0	42.0; 716.0
	Change from Baseline (cm²)/ (SD)	77.88 (80.64)	-9.07 (51.82)	73.27 (112.65)
	Percent change (SD)	63.07 (152.16)	-0.73 (30.99)	56.00 (82.04)
	LSM	80.64	-12.20	---
	p-value	<0.01		

Source: ISE Table 7.2a

As shown in Table 28, the results of Studies 10-extension and 12 were generally similar, with patterns for the T-T, T-P, and P-T groups similar those seen in the pooled data above. The differences in mean change in IGF-1 from baseline (Week 0) between the T-T and P-T groups compared with T-P were statistically significant in both pivotal studies.

Table 28 Change in IGF-1 from Baseline – Extension Phase of Pivotal Trials (Individual Trials)

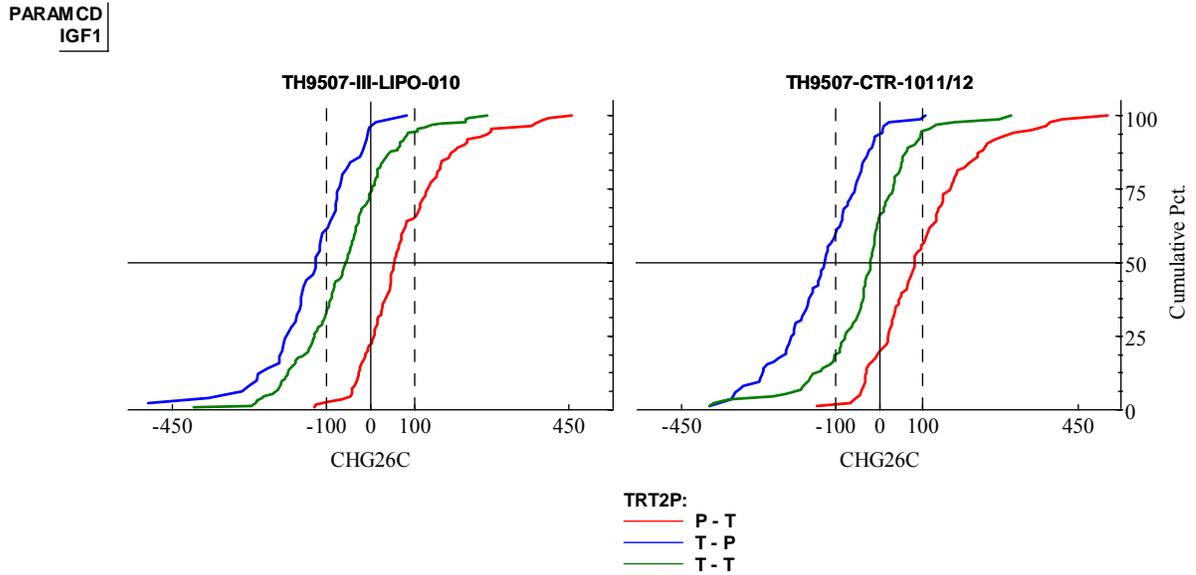
		Study 10-extension			Study 12		
		T-T N=154	T-P N=50	P-T N=111	T-T N=92	T-P N=85	P-T N=86
Baseline Week 0	n	151	49	110	89	84	85
	Mean	159.58	161.82	170.37	162.17	143.05	152.88
	SD	57.378	56.010	78.094	73.085	63.661	65.328
	Range	30.0; 377.0	56.0; 327.0	37.0; 549.0	33.0; 435.0	22.0; 406.0	31.0; 401.0
Week 26	n	151	49	110	89	84	85
	Mean	289.30	282.22	150.44	283.31	268.06	145.85
	SD	123.65	105.19	60.80	134.85	110.45	58.33
	Range	78.0; 746.0	92.0; 679.0	41; 428	54; 741	87; 528	47; 356
	Change from	129.72 (111.67)	120.41 (100.15)	-19.94 (66.43)	121.15 (119.69)	125.01 (104.32)	-7.04 (53.65)

	Baseline (ng/ml)/ (SD)						
	Percent change (SD)	98.11 (130.36)	85.86 (77.22)	-6.82 (26.23)	86.86 (84.00)	109.07 (92.73)	1.22 (35.34)
Week 39							
Week 39	n	151	49	110	89	84	85
	Mean	245.97	144.04	241.04	270.36	135.93	255.68
	SD	119.12	45.05	113.42	126.17	50.58	112.19
	Range	53.0; 667.0	64.0; 255.0	42.0; 549.0	36.0; 605.0	15.0; 240.0	45.0; 584.0
	Change from Baseline (ng/ml)/ (SD)	86.40 (107.04)	-17.78 (35.99)	70.66 (98.16)	108.19 (105.64)	-7.12 (49.42)	102.80 (90.71)
	Percent change (SD)	71.04 (181.45)	-8.25 (19.27)	49.36 (63.95)	76.72 (74.81)	1.02 (3110)	76.91 (69.69)
	LSM	85.34	-14.52	---	110.30	-9.36	---
	p-value	<0.001			<0.001		
Week 52							
Week 52	n	151	49	110	89	84	85
	Mean	229.05	146.98	228.69	254.30	137.35	245.49
	SD	118.86	52.53	117.74	122.03	53.61	129.14
	Range	40.0; 667.0	64.0; 298.0	42.0; 611.0	36.0; 613.0	13.0; 266.0	45.0; 716.0
	Change from Baseline (ng/ml)/ (SD)	69.48 (108.10)	-14.84 (49.72)	58.32 (100.16)	92.13 (113.32)	-5.70 (53.01)	92.61 (124.97)
	Percent change (SD)	59.62 (180.64)	-5.52 (26.45)	42.24 (69.91)	68.92 (84.89)	2.06 (33.19)	73.80 (92.93)
	LSM	68.42	-11.59	---	95.64	-9.42	---
	p-value	<0.001			<0.001		

Source: ISE Table 7.2a

Figure 13 depicts the CDF of the percent change in IGF-1 from Week 26 to Week 52 for the individual Pivotal Trials 10-extension and 12. These figures graphically illustrate an increase in IGF-1 for patients in the T-T and P-T groups, with the largest percent change over this time period seen in the P-T group (with both P-T and T-T having a greater reduction in VAT compared to T-P).

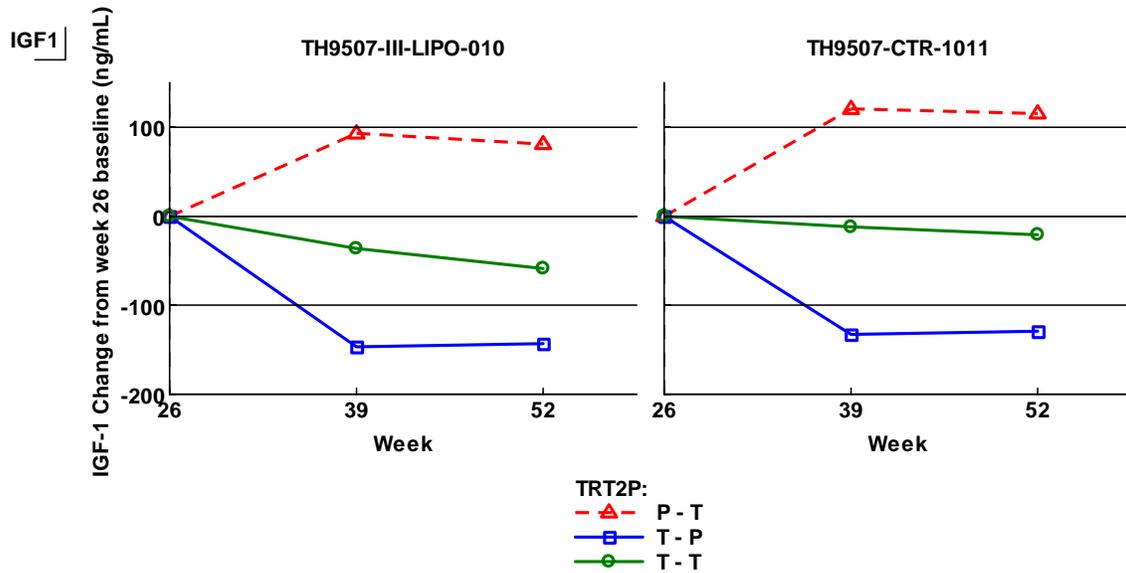
Figure 13 Cumulative Distribution of IGF-1 from Week 26 to Week 52 – Extension Phase (Individual Pivotal Studies)



Source: FDA Statistical Review

Figure 14 shows the mean IGF-1 change during Weeks 26-52 among the three treatment groups. Patients in the T-P group experienced a sharp decline in IGF-1 levels by Week 39, whereas those in the P-T group experienced a pronounced increase over that same time period. In both studies, patients in the T-T groups demonstrated a slow but steady decline in IGF-1 levels (although significantly less than in the T-P group).

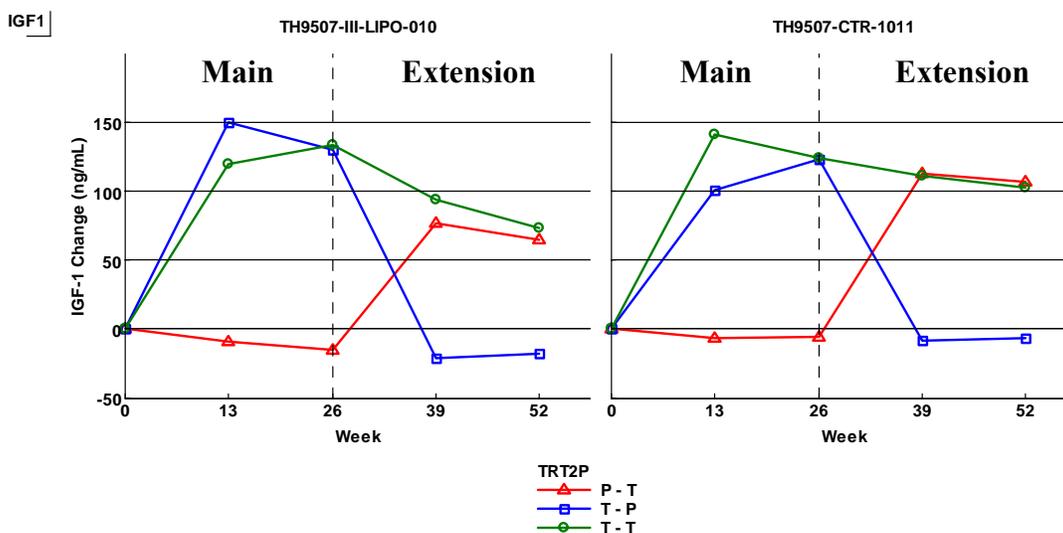
Figure 14 Mean IGF-1 Change from Week 26 to Week 52 – Extension Phase (Individual Pivotal Studies)



Source: FDA Statistical Review

Figure 15 demonstrates the change in IGF-1 among the three treatment groups during the entire 52-week trial course (Main and Extension Phases). The T-P treatment sequence in this figure shows at week 39, IGF-1 reversed to Week 0 levels after discontinuation at week 26. Patients in the P-T group demonstrated a rapid and sustained rise in IGF-1 after being switched from placebo to tesamorelin at Week 26. Patients in the T-T group demonstrated a sustained increase in IGF-1 levels through Week 26, then a slow but steady decline in levels during the Extension Phase.

Figure 15 Mean IGF-1 Change from Week 0 to Week 52 – Individual Pivotal Studies



Source: FDA Statistical Review

6.1.5.2 Patient-related Outcomes Related to Body Image

The effect of tesamorelin on patient-related outcomes (PROs) was assessed using the PHASE V® Outcomes Information System (OIS) by Phase V Technologies Inc. Patients (and for some PROs investigators as well) were asked to complete questionnaires at Weeks -4, 0, 26, and 52 or end of trial. PROs were reported across two domains: body image and health-related quality of life (HRQOL). The PROs related to body image (specifically, *belly size evaluation*, *belly appearance distress*, and *belly profile*) were considered secondary efficacy variables and the effect of tesamorelin on these endpoints are described next.

Main Phase

Belly Appearance Distress (BAD)

Subjects scored the distress related to their belly appearance using a body appearance distress scale (Figure 18). Scores ranged from 0 (“extremely upsetting”) to 100 (“extremely encouraging”) with a score of 50 being neutral and indicating “no feeling either way.” A positive change indicates patient improvement towards “encouragement.”

Figure 18 Body Appearance Distress Scale

Think about your “current appearance”. The following statements are about how you feel about certain aspects of your current appearance.

Scored	Patient Selects Phrase
0.0	Extremely Upsetting and Distressing
12.5	Very Upsetting and Distressing
25.0	Quite Upsetting and Distressing
32.5	A little Upsetting
50.0	No feeling either way
62.5	A little encouraging
75.0	Quite encouraging
87.5	Very Encouraging
100.0	Extremely Encouraging

Source: ISE

As calculated by the FDA Statistical Reviewer, the treatment difference between tesamorelin and placebo was not statistically significant (p=0.076) for Study 10, but was significantly greater for the tesamorelin group compared to placebo for Study 11 (p=0.022). This differs from the applicant’s assessment (statistically significant in both studies, with p=0.028 for Study 10 and p=0.022 for Study 11). Descriptive statistics for changes in BAD (from the FDA Statistical Review) are presented in Table 29.

Table 29 Descriptive Statistics of Belly Appearance Distress* – Main Phase (Individual Pivotal Studies)

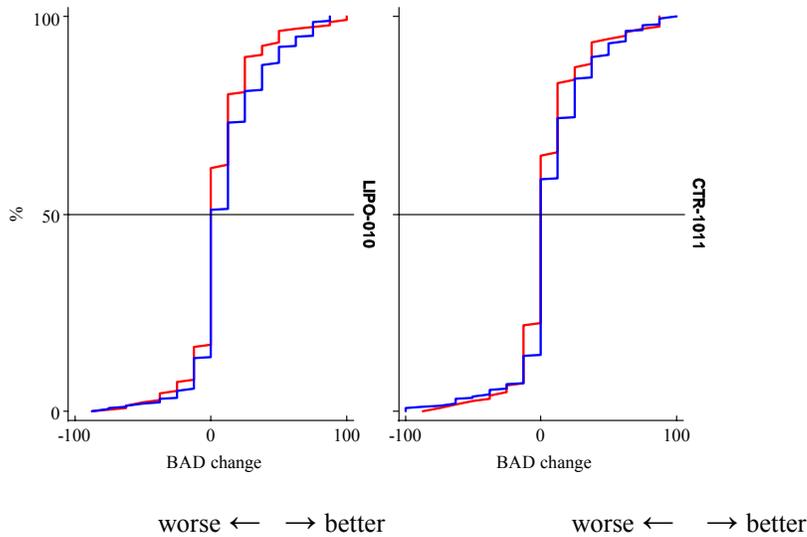
Study	Treatment Group	n	Evaluation	Mean	SD	Median	Min	Max
10	Placebo	137	Baseline	24.0	25.7	12.5	0.0	100.0
			Week 26	30.2	27.3	25.0	0.0	100.0
			Baseline- Wk 26*	6.2	25.8	0.0	-87.5	100.0
10	Tesamorelin	273	Baseline	22.1	22.2	12.5	0.0	100.0
			Week 26	33.8	25.9	25.0	0.0	100.0
			Baseline- Wk 26*	11.6	26.9	0.0	-87.5	87.5
11	Placebo	126	Baseline	20.2	22.1	12.5	0.0	100.0
			Week 26	25.4	25.1	25.0	0.0	87.5
			Baseline- Wk 26*	5.2	26.6	0.0	-87.5	87.5
11	Tesamorelin	268	Baseline	22.4	24.2	12.5	0.0	100.0
			Week 26	30.6	25.4	25.0	0.0	100.0
			Baseline- Wk 26*	8.3	29.0	0.0	-100.0	100.0

Source: FDA Statistical Review

*ITT population, LOCF analysis

Figure 19 depicts the FDA statistical findings graphically as cumulative frequency curves for Studies 10 and 11. There was only a small separation between drug and placebo for both studies.

Figure 19 Cumulative Distribution of Belly Appearance Distress from Baseline to Week 26* – Main Phase (Individual Pivotal Studies)



Source: FDA Statistical Review
 *ITT population, LOCF analysis

Belly size evaluation (BSE): Subjects were asked to use the Body Size Scale to compare their “current appearance” to their perceived “healthy look.” Compared to their “healthy look”, the patient’s current appearance (with respect to the amount or size of the specific body area) was scored as in Figure 16:

Figure 16 PRO Scoring for Perceived Belly Size
Compared to my “healthy look,” my current amount or size is...

<u>Score</u>	<u>Patient’s Answer</u>	
-100	A great deal less/very smaller or thinner	Far from healthy
-75	A lot less/much smaller or thinner	
-50	Somewhat less, smaller or thinner	
-25	A little less, smaller or thinner	
0	About right.....	On target
+25	A little more or bigger	
+50	Somewhat more or bigger	
+75	A lot more or much bigger	
+100	A great deal more or very much bigger	Far from healthy

Source: ISE

The difference in BSE scores from baseline to Week 26 between treatment groups was not statistically significant; the p-values as calculated by FDA Statistical Reviewer, Dr. Lee-Ping Pian, for tesamorelin to placebo comparisons were 0.75 for Study 10 and 0.21 for Study 11, respectively (0.98 and 0.21 as calculated by the applicant). Table 30 shows the descriptive statistics for BSE.

Table 30 Descriptive Statistics of Belly Size Evaluation[†] – Main Phase (Individual Pivotal Studies)

Study	Treatment Group	n	Evaluation	Mean	SD	Median	Min	Max
10	Placebo	137	Baseline	55.8	52.0	75.0	-100.0	100.0
			Week 26	35.4	55.0	50.0	-100.0	100.0
			Baseline- Wk 26*	13.1	31.4	0.0	-100.0	100.0
	Tesamorelin	273	Baseline	59.8	47.7	75.0	-100.0	100.0
			Week 26	35.3	54.9	50.0	-100.0	100.0
			Baseline- Wk 26*	14.6	30.1	0.0	-75.0	100.0
11	Placebo	126	Baseline	56.9	57.2	75.0	-100.0	100.0
			Week 26	47.6	53.7	75.0	-100.0	100.0
			Baseline- Wk 26*	11.7	25.2	0.0	-75.0	100.0
	Tesamorelin	268	Baseline	56.0	54.2	75.0	-100.0	100.0
			Week 26	33.4	58.0	50.0	-100.0	100.0
			Baseline- Wk 26*	14.6	27.6	0.0	-75.0	100.0

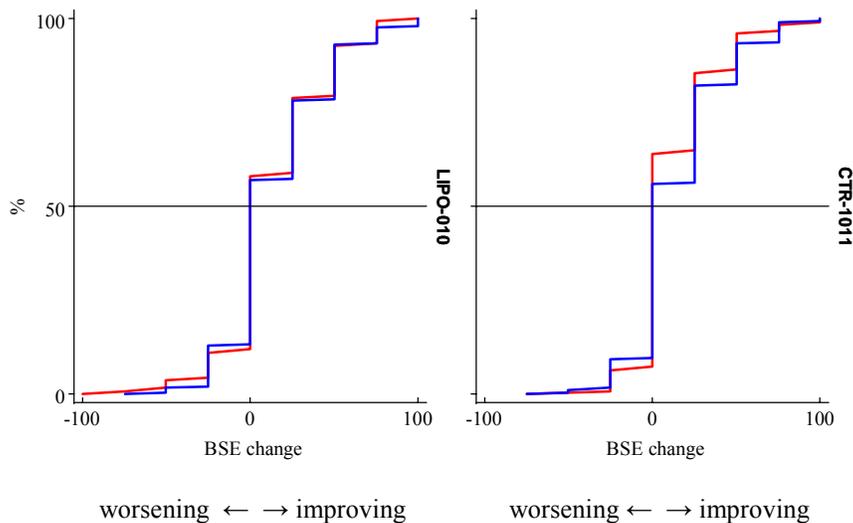
Source: FDA Statistical Review

[†]ITT population, LOCF analysis

*Corrected changed score = -(absolute(week 26)-absolute(baseline)) with positive score= improving and negative score=worsening

Figure 17 depicts the FDA statistical findings as a cumulative frequency distribution curve for BSE. There was none to minimal drug to placebo separation, depending on the study.

Figure 17 Cumulative Distribution of Belly Size Evaluation from Baseline to Week 26* – Main Phase (Individual Pivotal Studies)



Source: FDA Statistical Review

*ITT population, LOCF analysis

Belly Profile (BP)

For this PRO, patients selected one of six belly images, which ranged from 0 (normal) to 5 (most dysmorphic profile) in response to the questions: (1) “How do you think you look

today?"; (2) "How would you most like to look?"; and (3) "What is the smallest amount of improvement that you consider beneficial to your health and well-being?"

For this PRO, according to the FDA statistical review, tesamorelin demonstrated statistically significant reduction in belly dysmorphia over placebo only in Study 10 (p=0.031, compared with 0.075 for Study 11). These findings are in accordance with those of the applicant's calculations (p=0.042 and 0.075 for Studies 10 and 11, respectively). Table 31 displays the descriptive statistics from the FDA statistical review for responses to Belly Profile Question 1 in Studies 10 and 11.

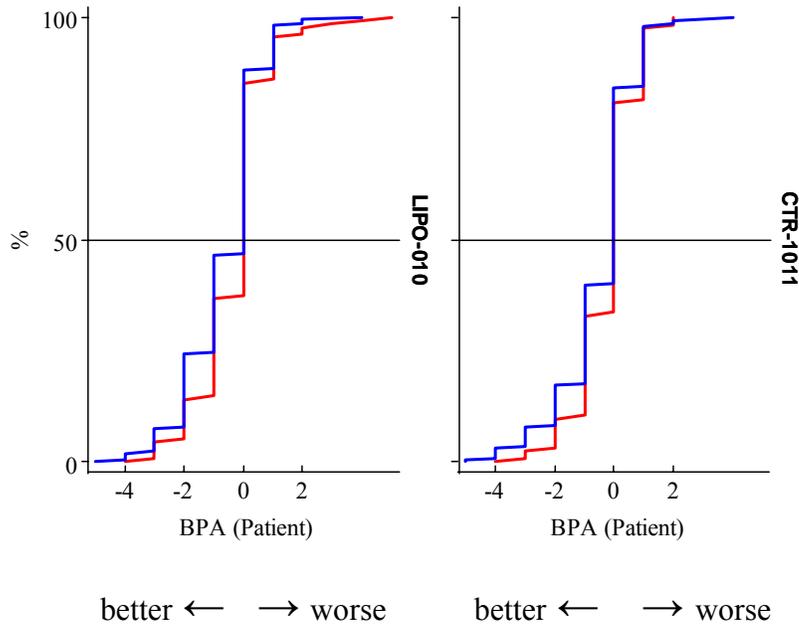
Table 31 Descriptive Statistics of Belly Profile (Question 1)* – Main Phase (Individual Pivotal Studies)

Study	Treatment Group	n	Evaluation	Mean	SD	Median	Min	Max
10	Placebo	137	Baseline	3.2	1.5	3.0	0.0	5.0
			Week 26	2.8	1.5	3.0	0.0	5.0
			Baseline- Wk 26*	-0.3	1.3	0.0	-4.0	5.0
	Tesamorelin	273	Baseline	3.3	1.3	3.0	0.0	5.0
			Week 26	2.6	1.4	3.0	0.0	5.0
			Baseline- Wk 26*	-0.7	1.2	0.0	-5.0	4.0
11	Placebo	126	Baseline	3.3	1.2	3.0	1.0	5.0
			Week 26	3.1	1.4	3.0	0.0	5.0
			Baseline- Wk 26*	-0.3	1.0	0.0	-4.0	2.0
	Tesamorelin	268	Baseline	3.2	1.4	3.0	0.0	5.0
			Week 26	2.7	1.6	3.0	0.0	5.0
			Baseline- Wk 26*	-0.5	1.3	0.0	-5.0	4.0

Source: FDA Statistical Review
 *ITT population, LOCF analysis

Figure 20 depicts the FDA statistical findings graphically as the changes in Belly Profile.

Figure 20 Cumulative Distribution of Belly Profile (Question 1) from Baseline to Week 26* – Main Phase (Individual Pivotal Studies)



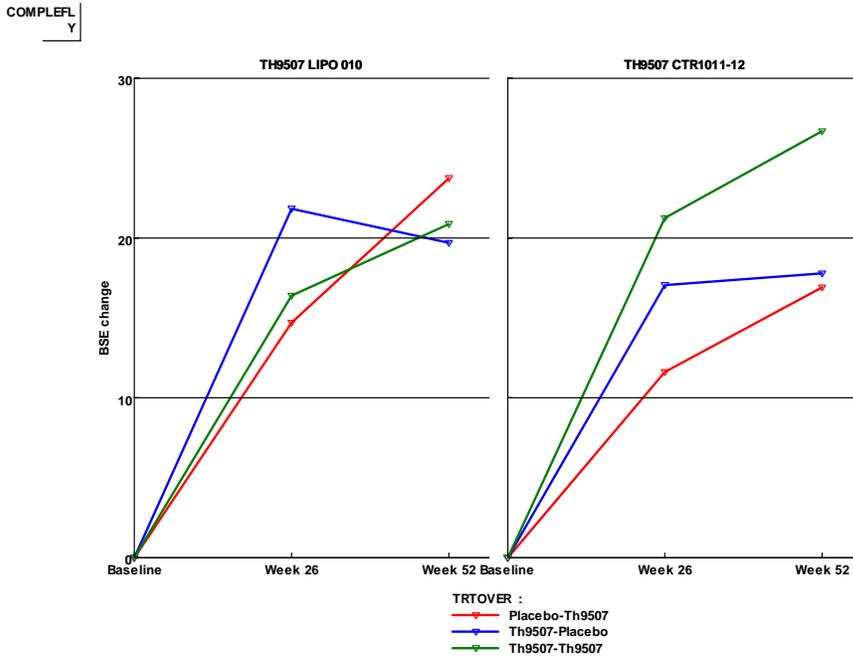
Source: FDA Statistical Review
 *ITT population, LOCF analysis

Extension Phase

Belly Size Evaluation

Figure 21 graphically represents the changes in BSE seen among completers of Studies 10-extension and 12 (with change in the “positive” direction indicating an improved self-evaluation). The data indicates that the improvement in BSE seen in both tesamorelin and placebo groups at Week 26 improved further during Weeks 26-52 in patients receiving tesamorelin (i.e., those in the T-T and P-T groups). Patients who were removed from tesamorelin therapy at Week 26 (i.e., those in the T-P group) experienced a modest decline in BSE for Study 10 and a modest improvement in Study 12 (although less than in the T-T or P-T groups).

Figure 21 Mean Change in BSE from Baseline at Weeks 26 and 52*



Source: FDA Statistical Review

Belly Appearance Distress

Table 32 displays the descriptive statistics for BAD and Figure A15 depicts these statistics graphically for Studies 101-extension and 12. The data in Table 32 indicates that the modest improvement in BAD seen in both tesamorelin and placebo groups at Week 26 improved further during Weeks 26-52 in patients receiving tesamorelin (i.e., those in the T-T and P-T groups). Patients who were removed from tesamorelin therapy at Week 26 (i.e., those in the T-P group) experienced a modest decline in BAD for Study 10 and no significant change Study 12.

Table 32 Descriptive Statistics of Belly Appearance Distress* – Extension Phase (Individual Pivotal Studies)

		Study 10-extension			Study 12		
		T-T N=154	T-P N=50	P-T N=111	T-T N=92	T-P N=85	P-T N=86
Baseline Week 0	n	151	49	110	89	84	85
	Mean	21.65	23.50	23.31	23.90	16.80	17.20
	SD	22.17	20.77	25.53	24.56	17.63	19.56
Week 26	n	151	49	110	89	84	85
	Mean	35.87	36.75	30.52	31.50	32.20	25.40
	SD	27.46	21.49	28.04	24.41	27.44	26.81
Week 52	n	151	49	110	89	84	85
	Mean	33.82	28.50	30.97	37.10	26.60	29.70
	Change from	12.17	5.00	7.66	13.20	9.90	12.50
		(26.51)	(22.16)	(25.63)	(33.83)	(24.25)	(29.52)

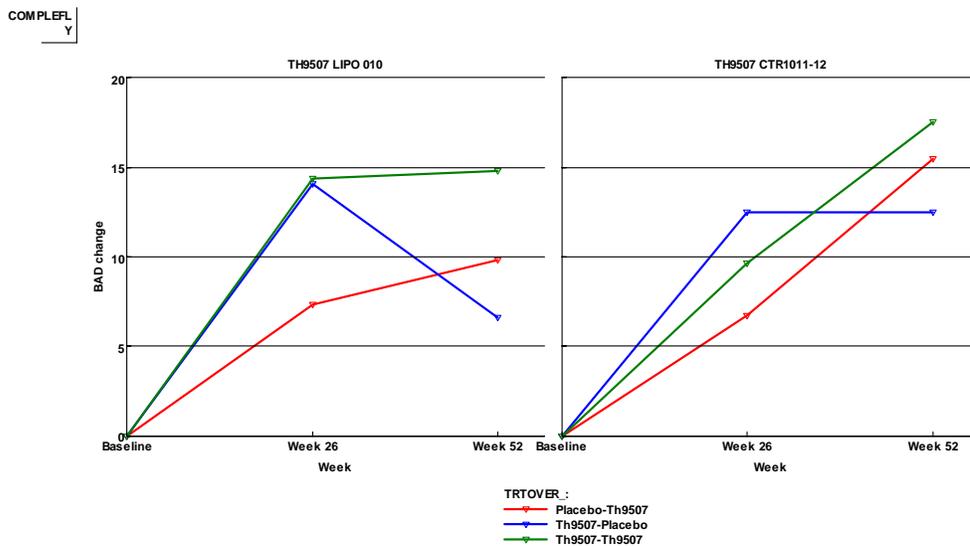
	Baseline (SD)						
	Percent change (SD)	71.04 (181.45)	-8.25 (19.27)	49.36 (63.95)	76.72 (74.81)	1.02 (3110)	76.91 (69.69)
	p-value	0.020			0.005		

Source: ISE, Table 18

*ITT population

As shown in Figure 22, in Study 10 (Main and Extension Phases), patients in the T-P group experienced a worsening of BAD score following re-randomization to placebo at Week 26, whereas those who were switched from placebo to tesamorelin (P-T) or who remained on tesamorelin for all 52 weeks (T-T) experienced a modest but continued improvement in BAD score. In Study 11, the same trends held for the P-T and T-T groups, but those in the T-P group did not have a notable change in BAD score after being switched from tesamorelin to placebo.

Figure 22 Mean Change in BAD from Baseline at Weeks 26 and 52*



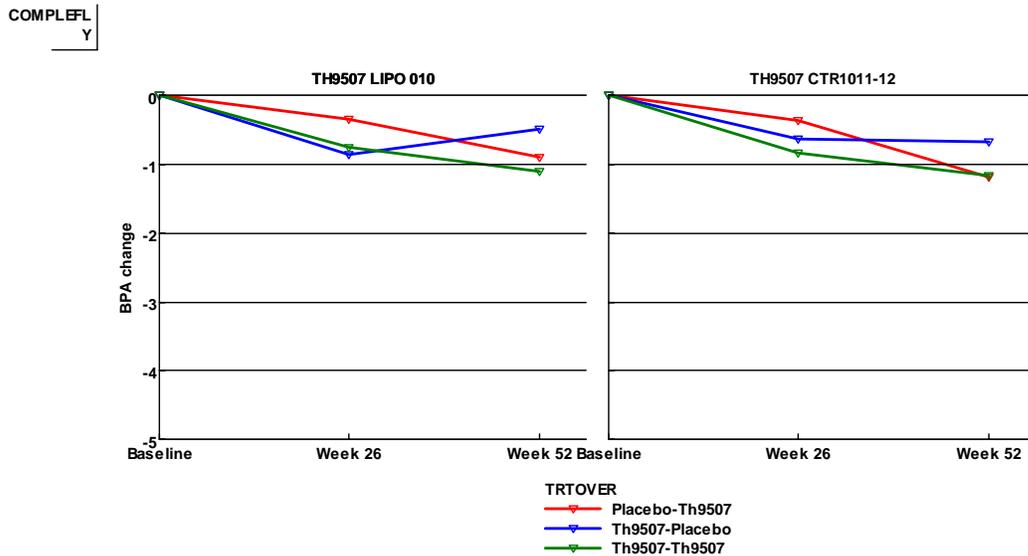
Source: FDA Statistical Review

*Completers only

Belly Profile

Figure 23 graphically represents the changes in BP seen among completers of Studies 10-extension and 12 (with change in the “negative” direction indicating an improved self-evaluation). The data indicates that the improvement in BP seen in both tesamorelin and placebo groups at Week 26 improved further during Weeks 26-52 in patients receiving tesamorelin (i.e., those in the T-T and P-T groups). Patients who were removed from tesamorelin therapy at Week 26 (i.e., those in the T-P group) experienced a modest decline in BSE for Study 10 and no significant change in Study 12.

Figure 23 Mean Change in BP from Baseline at Weeks 26 and 52*



Source: FDA Statistical Review
 *Completers only

6.1.5.3 Triglycerides

Triglycerides were measured from fasting blood samples which were analyzed centrally. Fasting blood samples were measured at Weeks 0, 6, 13, 26, 32, 39, and 52 (or ET). In addition, triglycerides were measured during screening to check study eligibility. On the days of drug dosing, sites were instructed to obtain blood samples prior to administering study drug.

Main Phase

Fasting triglycerides were measured at Weeks 0, 6, 13, 26 and were analyzed centrally. The statistical results were inconsistent between the two trials. In Study 10 tesamorelin was superior to placebo (mean reduction of 52.8 mg/dl relative to placebo, $p < 0.001$). In Study 11 the placebo-subtracted triglyceride reduction of 19.9 mg/dl did not reach statistical significance ($p = 0.1$). An ANCOVA analysis provided by the FDA statistical reviewer (using treatment, lipid lowering treatment (Y/N) as fixed effect and baseline TG as covariate) confirmed that the TG change from baseline was statistically significant in Study 10 but not in study 11 (Table 33).

Table 33 Triglyceride (mg/dL) Change from Baseline to Week 26 – Main Phase (Individual Studies)

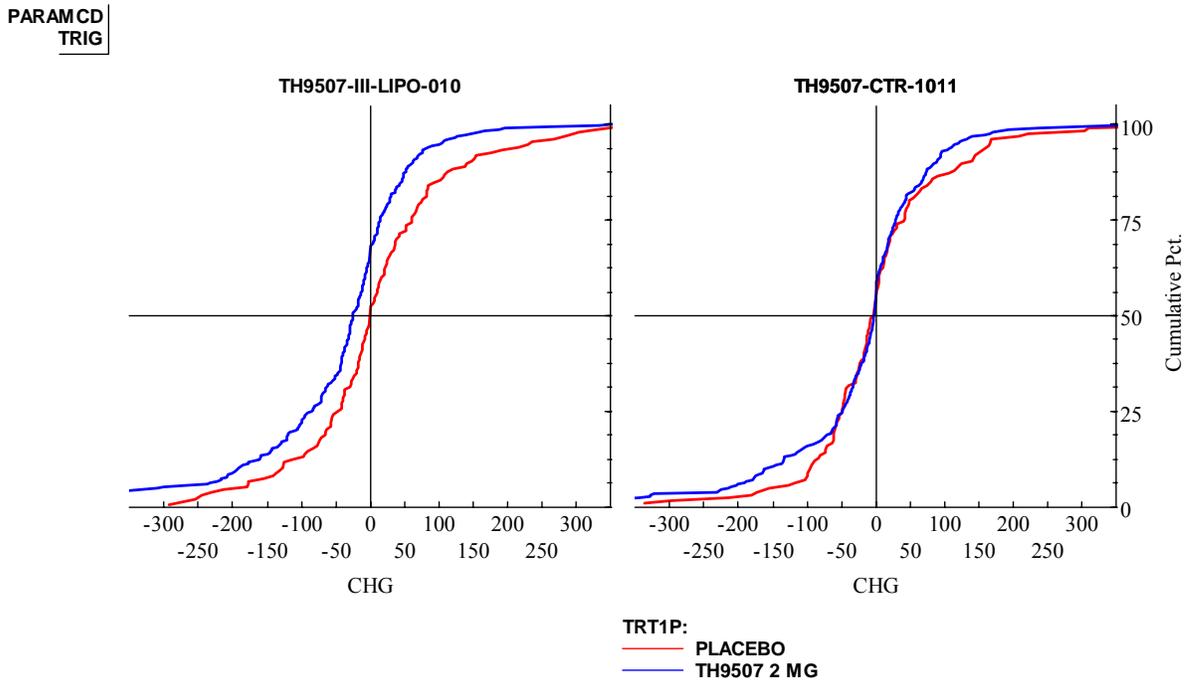
	Study 10			Study 11		
	Treatment		Difference from placebo*	Treatment		Difference from placebo*
	Tesamorelin N=273	Placebo n=137		Tesamorelin N=270	Placebo n=126	
Baseline mean (SD)	251.9 (188.1)	233.5 (145.0)		238.7 (261.3)	222.6 (143.9)	
LSM Change from baseline (SE)	-48.0 (6.6)	4.8 (9.3)	-52.8 (11.4) [-75.3, -30.4] p<0.001	-18.5 (6.9)	1.3 (10.0)	-19.9 (12.1) [-43.6, 3.9] p=0.10
Median change	-24.8	0		-2	-2	
Mean % change (SD)	-7.9 (40.5)	11.7 (57.1)	p<0.001	2.7 (44.9)	7.6 (46.4)	p=0.48
Median % change	-12.7	0		-1.6	-1.5	

Source: FDA Statistical Review

*ANCOVA model with treatment, lipid lowering treatment (Y/N) as fixed effect and baseline TG as covariate

Cumulative distribution curves provided by the FDA statistical reviewer (Figure 24) indicate clear separation between drug and placebo in Study 10 but not in Study 11.

Figure 24 Cumulative Distribution of TG Change from Baseline to Week 26* – Main Phase (Individual Studies)



Source: FDA Statistical Review

*ITT excluding patients with baseline carried forward

Extension Phase

Table 34 demonstrates that in Studies 10-extension and 12, the difference between the T-T and T-P treatment sequence was not significant in triglyceride change from baseline 26 to week 52 for either of the studies.

Table 34 TG (mg/dL) Change from Baseline to Week 52 – Extension Phase (Individual Studies)

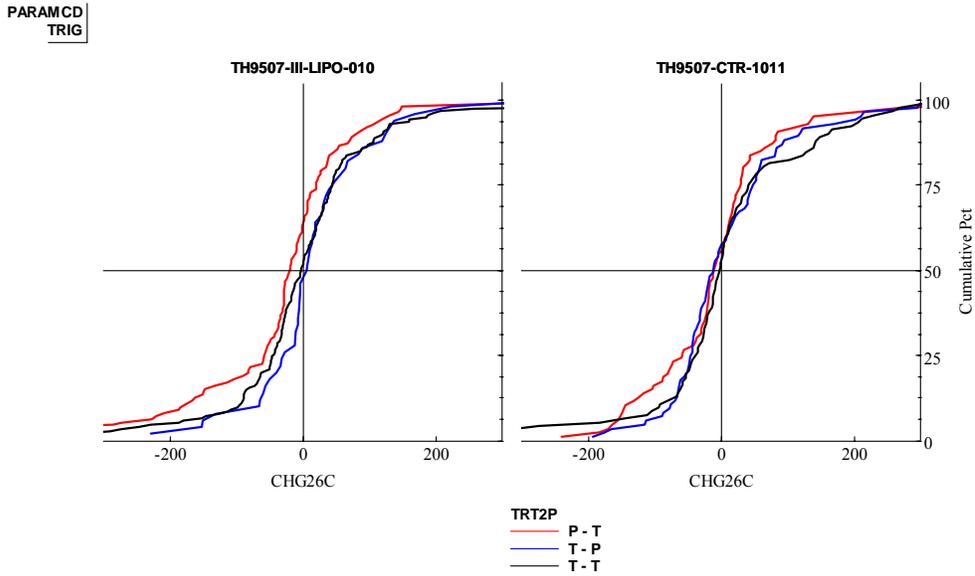
		Study 10-extension			Study 12		
		T-T N=154	T-P N=50	P-T N=111	T-T N=92	T-P N=85	P-T N=86
Baseline Week 0	n	151	49	110	89	84	85
	Mean	267.74	222.67	241.82	255.52	216.71	215.43
	SD	206.51	126.42	152.40	213.91	169.81	123.44
Week 26	n	151	49	110	89	84	85
	Mean	207.57	173.89	251.59	208.60	199.99	221.45
	SD	141.24	102.78	171.06	140.03	128.31	150.98
	Change from Baseline (SD)	-57.17 (157.41)	-48.78 (89.55)	9.77 (123.48)	-46.92 (166.90)	-16.72 (131.54)	6.02 (113.91)
Week 52	n	151	49	110	89	84	85
	Mean	210.75	189.35	216.83	218.54	219.27	216.31
	SD	156.89	110.49	140.83	165.01	233.69	160.84
	Change from Baseline (LSM)	-53.99 (-50.00)	-33.33 (-47.69)	-24.99	-36.98 (-26.49)	2.56 (-10.93)	0.88
	p-value	0.901			0.453		

Source: ISE, Table 18

[†]ITT population

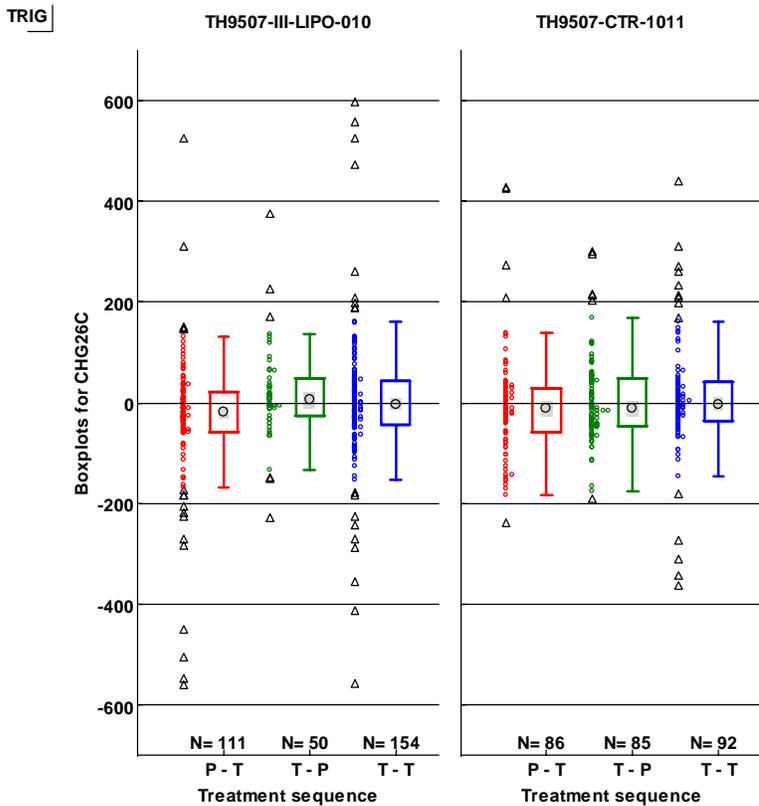
Figure 25 presents cumulative distribution for TG change and Figure 26 the boxplot for TG percent change from Weeks 26 to 52.

Figure 25 Cumulative distribution of TG change from Week 26 to Week 52* – Extension Phase (Individual Studies)



Source: FDA Statistical Review
 *ITT excluding patients with baseline carried forward

Figure 26 Boxplot of TG % change from Week 26 to Week 52* – Main Phase (Individual Studies)



Source: FDA Statistical Review
 *ITT excluding patients with baseline carried forward

6.1.5.4 Total Cholesterol: High-density Lipoprotein Cholesterol Ratio

Total cholesterol and HDL-C were measured from fasting blood samples which were analyzed centrally. Fasting blood samples were measured at Weeks 0, 6, 13, 26, 32, 39, and 52 (or ET). On the days of drug dosing, sites were instructed to obtain blood samples prior to administering study drug.

Main Phase

Total cholesterol and HDL-C were measured from fasting blood samples which were analyzed centrally. Measurements were performed at Weeks 0, 6, 13, and 26. As shown in Table 35 the treatment group difference in Study 10 achieved statistical significance $p < 0.001$ but this observation was not confirmed in Study 11 ($p < 0.094$).

Table 35 Total Cholesterol: HDL-C Ratio Change from Baseline to Week 26* -- Main Phase of Pivotal Trials

Visit	Study 10				Study 11				Combined Results			
	Tesamorelin N=273		Placebo N=137		Tesamorelin N=270		Placebo N=126		Tesamorelin N=543		Placebo N=263	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Baseline (ng/mL)	270	4.50 (1.34)	133	4.30 (1.24)	264	4.75 (1.69)	126	4.61 (1.61)	534	4.62 (1.53)	259	4.45 (1.44)
Change to Week 26 (ng/mL)	269	-0.31 (0.98)	136	0.21 (0.95)	265	-0.05 (1.01)	125	0.15 (0.92)	534	-0.18 (1.00)	261	0.18 (0.94)
P-value^a	<0.001				0.094				<0.001			

Source: ISE Table 8

*ITT Population

^a P-values are for treatment group difference in mean change from baseline.

Extension Phase

Total cholesterol and HDL-C were measured from fasting blood samples which were analyzed centrally. During the extension phase, fasting blood samples were measured at Weeks 32, 39, and 52 or ET (in addition to measurements at Weeks 0, 6, 13 and 26).

As shown in Table 36, the mean total cholesterol:HDL-C ratio increased slightly in the T-T, T-P, and P-T groups from Week 26 to Week 52 in Study 10-extension. In Study 12, the ratio decreased in the T-T group but increased in the T-P and P-T groups. These changes were not statistically significant.

Table 36 Total Cholesterol: HDL-C Ratio Change from Baseline to Week 52* -- Extension Phase of Pivotal Trials

	Study 10-extension			Study 12		
	T-T N=154	T-P N=50	P-T N=111	T-T N=92	T-P N=85	P-T N=86
Visit	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Baseline (ng/mL)	4.50 (1.46)	4.32 (1.10)	4.31 (1.24)	5.01 (1.68)	4.66 (1.55)	4.57 (1.42)
Change to Week 26 (ng/mL) / (SD)	-0.34 (1.06)	-0.32 (0.91)	0.26 (1.03)	-0.22 (1.23)	0.06 (1.03)	0.21 (0.97)
Change to Week 52 (ng/mL) / (LSM)	0.02 (0.02)	0.10 (0.07)	0.29	-0.23 (-0.12)	0.12 (-0.01)	0.06
P-value^a	0.706			0.524		

Source: ISE, Table 18

^aITT population

6.1.5.5 Non HDL-Cholesterol

Non-HDL-C was measured from fasting blood samples which were analyzed centrally. Fasting blood samples were measured at Weeks 0, 6, 13, 26, 32, 39, and 52 (or ET). On the days of drug dosing, sites were instructed to obtain blood samples prior to administering study drug.

Main Phase

Non-HDL-C was measured from fasting blood samples and was analyzed centrally. Fasting blood samples were collected at Weeks 0, 6, 13, and 26. The reduction observed in Study 10 reached statistical significance, but again this result was not confirmed in Study 11 (Table 37).

Table 37 Non-HDL-C Ratio Change from Baseline to Week 26* -- Main Phase of Pivotal Trials

	Study 10				Study 11				Combined Results			
	Tesamorelin N=273		Placebo N=137		Tesamorelin N=270		Placebo N=126		Tesamorelin N=543		Placebo N=263	
Visit	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Baseline (ng/mL)	272	150.02 (41.26)	134	147.24 (35.88)	264	147.03 (42.58)	126	144.75 (35.89)	536	148.55 (41.90)	260	146.03 (35.84)

Change to Week 26 (ng/mL)	272	-10.76 (31.30)	134	-0.77 (25.15)	264	1.08 (30.48)	126	5.50 (26.90)	536	-4.93 (31.43)	260	2.27 (26.15)
P-value^a	0.001				0.216				0.001			

Source: ISE, Table 8
^aITT population

Extension Phase

In the pooled Extension Phase studies, the difference in mean change from baseline to Week 52 in non-HDL-C between the T-T and T-P groups was statistically significant (p=0.034) with a mean decrease observed in the T-T group and a mean increase in the T-P group.

As shown in Table 38, the pattern of mean changes was generally similar for Studies 10 and 12; however, the difference in change from baseline to Week 52 was significant only in Study 12. In Study 10 Extension Phase, mean decreases were observed in the T-P group at Week 26 and Week 52, while mean increases were observed in Study 12.

Table 38 Non-HDL-C Ratio Change from Baseline to Week 52* -- Extension Phase of Pivotal Trials

	Study 10-extension			Study 12		
	T-T N=154	T-P N=50	P-T N=111	T-T N=92	T-P N=85	P-T N=86
Visit	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Baseline (ng/mL)	147.68 (44.14)	149.36 (35.42)	148.79 (35.56)	151.36 (44.52)	142.76 (38.02)	145.34 (33.52)
Change to Week 26 (ng/mL) / (SD)	-10.81 (31.21)	-12.56 (29.34)	-1.19 (26.26)	-2.51 (35.86)	5.71 (32.34)	6.93 (25.75)
Change to Week 52 (ng/mL) / (LSM)	-5.31 (-5.58)	-7.39 (-6.34)	-2.80	-10.10 (-6.59)	8.88 (4.82)	0.21
P-value	0.850			0.007		

Source: ISE, Table 18
^aITT population

6.1.6 Other Endpoints

Main Phase

Table 39 describes the changes from baseline to Week 26 in various parameters of body composition.

Table 39 Body Composition (Change from Baseline to Week 26) – Main Phase of Both Pivotal Studies

Visit	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)	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Trunk fat (kg)												
Baseline value	261	14.93 (5.598)	130	15.29 (5.755)	264	15.26 (5.312)	123	15.23 (5.055)	525	15.10 (5.454)	253	15.26 (5.416)
Change to Week 26	261	-1.00 (1.898)	130	0.38 (1.551)	264	-0.81 (2.099)	123	0.17 (1.528)	525	-0.90 (2.002)	253	0.28 (1.540)
P-value ^a	<0.001				<0.001				<0.001			
P-value ^b	<0.001/0.159											
LBM (kg)												
Baseline value	261	61.98 (10.122)	130	61.40 (9.558)	264	62.39 (10.324)	123	60.52 (11.207)	525	62.19 (10.216)	253	60.97 (10.381)
Change to Week 26	261	1.32 (2.398)	130	-0.24 (1.804)	264	1.21 (2.386)	123	-0.03 (1.908)	525	1.27 (2.391)	253	-0.14 (1.855)
P-value ^a	<0.001				<0.001				<0.001			
P-value ^b	<0.001/0.386											
Total fat (kg)												
Baseline value	261	22.93 (9.469)	130	23.91 (9.866)	264	23.62 (9.391)	123	23.34 (8.442)	525	23.27 (9.427)	253	23.63 (9.187)
Change to Week 26	261	-1.05 (2.581)	130	0.63 (2.301)	264	-0.91 (2.950)	123	0.29 (2.179)	525	-0.98 (2.771)	253	0.46 (2.244)
P-value ^a	<0.001				<0.001				<0.001			
P-value ^b	<0.001/0.225											
SAT (cm²)												
Baseline value	267	230.80 (127.417)	130	238.79 (133.006)	264	230.71 (120.312)	124	226.49 (112.159)	531	230.76 (123.819)	254	232.78 (123.182)
Change to Week 26	267	-3.24 (28.755)	130	2.33 (29.457)	264	-1.41 (34.085)	124	0.96 (27.844)	531	-2.33 (31.501)	254	1.66 (28.633)
P-value ^a	0.053				0.530				0.076			
P-value ^b	0.078/0.417											
VAT/SAT ratio												
Baseline value	267	1.27 (1.608)	130	1.18 (1.579)	264	1.27 (1.602)	124	1.25 (1.210)	531	1.27 (1.604)	254	1.22 (1.408)
Change to Week 26	267	-0.25 (0.654)	130	0.07 (0.587)	264	-0.23 (1.033)	124	0.03 (0.599)	531	-0.24 (0.863)	254	0.05 (0.592)
P-value ^a	<0.001				0.001				<0.001			
P-value ^b	<0.001/0.676											
Limb fat (kg)												
Baseline value	261	7.12 (4.284)	130	7.70 (4.742)	264	7.52 (4.700)	123	7.29 (3.979)	525	7.32 (4.498)	253	7.50 (4.384)
Change to Week 26	261	-0.03 (0.838)	130	0.22 (0.997)	264	-0.08 (1.004)	123	0.12 (0.898)	525	-0.05 (0.925)	253	0.17 (0.949)
P-value ^a	0.007				0.066				0.001			
P-value ^b	0.001/0.642											

Reference: Section 9, Table 6.1, Table 8.1.1, and Table 8.2.1, Table 8.3.1, Table 8.4.1, and Table 8.5.1.

^a P-values are for treatment group difference. For the individual studies, the ANCOVA model is variable at baseline + treatment. For the combined studies, the ANCOVA model is variable at baseline + study + treatment.

^b P-value is for treatment group difference. The ANCOVA model is variable at baseline + study + treatment + treatment group-by-study. / Study-by-treatment group p-value.

The main findings from Table 39 are listed next:

- The mean change from baseline in abdominal subcutaneous tissue (SAT) was not significantly different between tesamorelin and placebo subjects.
- The change from baseline in the VAT/SAT ratio was significantly different between tesamorelin and placebo subjects ($p < 0.001$), as was the primary efficacy endpoint, VAT.
- The mean change in total fat at both Weeks 13 and 26 was significantly different ($p < 0.001$) between tesamorelin and placebo patients; the mean changes from baseline at Weeks 13 and 26 were -0.93 and -0.98 kg, respectively, in the tesamorelin group and +0.26 and +0.46 kg, respectively, in the placebo group.
- The mean change from baseline in limb fat (total, lower limb, and upper limb fat) was statistically significantly different between the tesamorelin and placebo treatment groups at Week 26; however, this difference was not considered clinically significant.
- The mean change in trunk fat at both Weeks 13 and 26 was significantly different ($p < 0.001$); the mean changes from baseline at Weeks 13 and 26 were -0.82 and -0.90 kg, respectively, in the tesamorelin group and +0.14 and +0.28 kg, respectively, in the placebo group. The results of mean change from baseline in trunk fat for the PP population were generally similar to those described for the ITT population.
- The mean change from baseline in lean body mass (LBM) was statistically significantly different between the groups at each time point ($p < 0.001$); the tesamorelin group showed increased LBM, whereas the placebo group showed decreased LBM, at both Week 13 (+1.23 vs. -0.08 kg, respectively) and Week 26 (+1.27 vs. -0.14 kg, respectively).

Anthropometric Measurements

Waist and hip circumferences were measured at Weeks -4 (screening), 13, and 26. In summary:

- The mean waist circumference decreased from baseline in both treatment groups at Week 26, but a greater decrease was observed in the tesamorelin group; across both studies the mean change from baseline relative to placebo was approximately 1.5 cm ($p < 0.001$) and it was statistically significant for each study ($p < 0.001$ for Study 10, $p = 0.013$ for Study 11).
- The mean hip circumference increased in both arms in Study 10 ($p = 0.021$) and was not statistically different from placebo in Study 11 or in the pooled analysis.
- The mean waist:hip ratio was statistically significantly different in Study 11, in Study 10 and in the pooled analysis.

Table 40 Anthropometric Measurements (Change from Baseline to Week 26) – Main Phase of Both Pivotal Studies

Visit	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)	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Waist circumference (cm)												
Baseline value	273	104.22 (9.539)	137	104.64 (9.494)	270	104.98 (9.028)	126	104.43 (9.081)	543	104.60 (9.287)	263	104.53 (9.281)
Change to Week 26	273	-2.61 (4.906)	137	-0.80 (4.051)	270	-2.19 (5.434)	126	-0.82 (4.728)	543	-2.40 (5.175)	263	-0.81 (4.380)
P-value ^a	<0.001				0.013				<0.001			
P-value ^b									<0.001/0.575			
Hip circumference (cm)												
Baseline value	273	99.71 (8.532)	137	99.99 (9.314)	270	100.59 (8.375)	126	99.76 (9.264)	543	100.15 (8.457)	263	99.88 (9.273)
Change to Week 26	273	0.15 (3.719)	137	0.99 (3.232)	270	0.13 (4.026)	126	-0.10 (4.004)	543	0.14 (3.871)	263	0.47 (3.657)
P-value ^a	0.021				0.526				0.280			
P-value ^b									0.308/0.046			
Waist:hip ratio												
Baseline value	273	1.05 (0.063)	137	1.05 (0.065)	270	1.05 (0.071)	126	1.05 (0.072)	543	1.05 (0.067)	263	1.05 (0.069)
Change to Week 26	273	-0.03 (0.053)	137	-0.02 (0.043)	270	-0.02 (0.055)	126	-0.01 (0.047)	543	-0.03 (0.054)	263	-0.01 (0.045)
P-value ^a	0.046				0.002				<0.001			
P-value ^b									<0.001/0.382			

Reference: Section 9, Table 8.6.1

^a P-values are for treatment group difference. For the individual studies, the ANCOVA model is variable at baseline + treatment. For the combined studies, the ANCOVA model is variable at baseline +study + treatment.

^b P-value is for treatment group difference. The ANCOVA model is variable at baseline +study + treatment + treatment group-by-study. / Study-by-treatment group p-value.

Source: ISE Table 12

Extension Phase

Trunk fat

Table 41 shows that the mean change from baseline for trunk fat for both Studies 10-extension and 12 was statistically significantly different between the T-T and T-P groups at Week 52. For both studies, patients in both the T-T and P-T groups exhibited a decrease in mean trunk fat over the course of the Extension Phase, while those in the T-P group had a modest increase.

Table 41 Change in Trunk Fat from Baseline to Week 52 – Extension Phase (Individual Studies)

		Study 10			Study 12		
		T-T	T-P	P-T	T-T	T-P	P-T
Baseline	n	154	50	111	88	84	84
	Mean	14.7	15.3	15.3	13.8	15.9	14.6
	SD	5.69	5.27	5.81	4.00	5.72	4.81
Week 26	n	154	50	111	92	85	85
	Mean	13.5	14.3	15.9	13.1	15.0	14.8
	SD	6.01	5.44	6.10	4.22	6.24	5.15
Week 52	N	154	50	111	92	84	85
	Mean	13.6	15.7	14.7	13.0	16.2	13.9
	SD	6.04	5.36	6.04	3.87	6.46	5.34
Δ Mean (Δ LSM)		-1.23 (-1.20)	0.24 (+0.13)	-0.85	-0.83 (-0.88)	0.36(0.41)	-0.68
Trtmt Diff in LSM		-1.47			-1.19		
p-value		<0.001			<0.001		

Source: TH507-CTR-1012 Table 14.2.2.2.1; TH9507/III/LIPO/010 Table 71

Lean Body mass

Table 42 shows that in both Studies 10-extension and 12, LBM was preserved in patients in the T-T and P-T groups relative to T-P. In both studies, the LSM treatment difference for patients in the T-T group compared to the T-P group was statistically significant (though patients in the T-T group of Study 10 did have a mean LBM loss of 0.10 kg during the Extension Phase) This finding suggests that the LBM gained by tesamorelin-treated patients in the Main Phase is reversible with withdrawal of drug, and that this increase in LBM is sustained through a 52-week treatment period.

Table 42 Change in Lean Body Mass from Week 26 to Week 52 – Extension Phase

		Study 10			Study 12		
		T-T	T-P	P-T	T-T	T-P	P-T
Baseline	n	154	50	111	88	84	88
	Mean	62.1	62.8	61.8	63.8	63.0	61.2
	SD	10.1	10.5	9.4	9.16	9.51	11.0
Week 26	n	152	48	106	92	85	85
	Mean	63.67	65.21	61.59	65.08	64.69	61.12
	SD	10.18	10.994	9.274	9.692	9.355	10.787
Week 52	n	152	48	105	92	84	85
	Mean	63.57	63.43	63.49	65.15	62.97	62.76
	SD	10.42	11.02	9.48	9.36	9.21	10.69
Δ Mean (Δ LSM)		1.41 (1.47)	-0.07 (-0.134)	1.51	1.04 (1.15)	-0.25 (0.37)	1.30

Trtmt Diff in LSM	1.48		1.29	
p-value¹	<0.001		<0.001	

Source: TH507-CTR-1012 Table 14.2.2.6.1; TH9507/III/LIPO/010 Table 72

Total body fat

Table 43 shows change in total body fat from Week 26 to Week 52 in Studies 10-extension and 12. For both studies there was a decrease in total body fat for the T-T group over 52 weeks (and for the P-T group over the last 26 weeks), and the treatment difference between those receiving tesamorelin during the Extension period (T-T) and those in the T-P group was statistically significant.

Table 43 Change in Total Body Fat from Baseline to Week 52 – Extension Phase (Individual Studies)

		Study 10-extension			Study 12		
		T-T	T-P	P-T	T-T	T-P	P-T
Baseline	n	154	50	111	92	85	86
	Mean	22.5	23.2	23.6	21.1	23.9	22.1
	SD	9.67	8.50	9.56	7.21	9.30	8.21
Week 26	n	152	48	106	92	85	85
	Mean	21.19	22.05	24.57	20.38	22.83	22.39
	SD	10.05	8.59	10.13	7.53	9.69	8.56
Week 52	N	152	48	105	92	84	85
	Mean	21.39	23.67	22.78	19.85	23.89	21.16
	SD	10.13	8.34	9.60	6.99	9.92	8.93
Δ Mean (Δ LSM)		-1.24 (-1.21)	0.41 (0.311)	-0.818	-0.99 (-1.11)	0.29 (0.43)	-0.701
Trtmt Diff In LSM		-1.65			-1.28		
p-value¹		<0.001			<0.001		

Sources: TH9507/III/LIPO/010 Table 67; TH9507-CTR-1012 Table 14.2.2.5.1

Subcutaneous Adipose Tissue

As seen in Table 44, although the treatment difference for change from baseline to Week 52 in Abdominal SAT between the T-T and T-P groups for Study 10-extension was statistically significant, the results for Study 12 did not reach statistical significance. In Study 10-extension, patients in the T-T group exhibited a sustained decrease in SAT (mean loss of 7.79 cm²) and those in the P-T group had a mean decrease of 2.97 cm² from baseline and a decrease of 12.82 cm² from Week 26. In Study 12, patients in the T-T group had a net increase of 4.58 cm² from baseline to Week 52, and patients in the P-T group had a mean increase of 0.818 cm² over the course of the Extension Phase (increase of 0.24 from cm² Weeks 26 to 52).

Table 44 Abdominal SAT (cm²) Change from Baseline to Week 52 – Extension Phase

		Study 10-extension			Study 12		
		T-T	T-P	P-T	T-T	T-P	P-T
Baseline	n	150	49	105	90	83	85
	Mean	221	239	238	202	227	208
	SD	128	129	134	107	118	102
Week 26	n	152	49	109	92	85	85
	Mean	219.51	234.59	247.98	202.51	233.97	208.58
	SD	126.67	126.55	147.41	108.52	122.86	100.88
Week 52	n	151	49	105	91	85	85
	Mean	214.65	238.53	235.16	205.87	235.33	208.82
	SD	123.24	126.02	132.65	109.13	123.78	99.89
Δ Mean (Δ LSM¹)		-7.79 (-7.82)	-1.82 (-1.73)	-2.97	4.58 (3.86)	1.08 (1.87)	0.818
Trtmt Diff in LSM		-5.97			4.50		
p-value¹		0.14			0.71		

Table Provided by Sponsor

¹ For T-T vs. T-P comparisons within each study, the model is: Change in abdominal SAT from Week 26 = Week 26 SAT + treatment group

A separate ANOVA analysis provided by the Sponsor looking solely at the difference between Weeks 26 and 52 between the T-T and T-P groups did not reach statistical significance.

VAT/SAT ratio

As shown in Table 45, tesamorelin maintained its reduction of the VAT/SAT ratio over a 52-week treatment period. Based on ANCOVA analysis of the treatment difference in LSM, the mean change from baseline in VAT/SAT ratio was significantly different between the T-T and T-P groups during both the Extension Phase Studies 010 and 012. The T-T and P-T groups had similar responses, both exhibiting small decreases in VAT/SAT ratio over the course of the Extension Phase.

Table 45 VAT/SAT Ratio Change from Baseline to Week 52 – Extension Phase

		Study 10-extension			Study 12		
		T-T	T-P	P-T	T-T	T-P	P-T
Baseline	n	154	50	111	90	83	85
	Mean	1.43	1.04	1.26	1.45	1.42	1.36
	SD	1.89	0.99	1.72	1.28	2.29	1.28
Week 26	n	154	50	111	92	85	85
	Mean	1.11	0.79	1.35	1.18	1.02	1.41
	SD	1.39	0.61	2.16	1.04	0.855	1.70

Week 52	n	154	50	111	91	85	85
	Mean	1.14	1.01	1.20	1.11	1.58	1.17
	SD	1.44	0.91	2.28	0.929	4.38	1.38
Δ Mean (Δ LSM)		-0.28 (-0.27)	-0.02 (-0.08)	-0.048	-0.34 (-0.26)	0.19 (0.10)	-0.19
Trtmt Diff in LSM		-0.19			-0.36		
p-value		0.005			0.09		

Total limb fat

As shown in Table 46, changes in limb fat were small and not statistically significant different from baseline or from Week 26 in all three treatment groups for Studies 10-extension and 12.

Table 46 Change in Limb Fat from Baseline to Week 52 – Extension Phase (Individual Studies)

		Study 10-extension			Study 12		
		T-T	T-P	P-T	T-T	T-P	P-T
Baseline	n	154	50	111	88	84	84
	Mean	6.89	6.97	7.36	6.46	7.19	6.67
	SD	4.35	3.69	4.28	3.93	4.17	3.95
Week 26	n	154	50	111	92	85	85
	Mean	6.86	6.89	7.76	6.48	7.09	6.81
	SD	4.34	3.57	4.57	3.87	3.96	3.97
Week 52	N	154	50	111	92	84	85
	Mean	6.93	7.12	7.56	6.37	7.13	6.65
	SD	4.35	3.56	4.40	3.71	4.01	3.97
Δ Mean (Δ LSM)		0.004 (0.001)	0.15 (0.16)	0.03	-0.15 (-0.22)	-0.06 (0.004)	-0.007
Trtmt Diff In LSM		-0.15			-0.09		
p-value		0.258			0.138		

Source: TH507-CTR-1012 Table 14.2.2.2.1; TH9507/III/LIPO/010 Table 71

Anthropometric Measurements

Waist and hip circumferences were measured at Weeks -4 (screening), 13, 26, 39. and 52 (or end of trial). Table 47 describes the changes from baseline to Week 52 in anthropometric measurements. In summary, for the T-T and P-T groups compared with T-P, these show a small but statistically significant decrease in waist circumference for Study 10-extension (but not Study 12); a small but statistically significant decrease in waist:hip ratio for Study 12 (but not Study 12-extension); and non-significant decreases in hip ratio for both studies.

Table 47 Anthropometric Measurements (Change from Baseline to Week 52) – Extension Phase of Both Pivotal Studies

	Study TH9507/III/LIPO/010			Study TH9507-CTR-1012			Combined Results		
	Tesamorelin -Tesamorelin (N=154)	Tesamorelin -Placebo (N=50)	Placebo -Tesamorelin (N=111)	Tesamorelin- Tesamorelin (N=92)	Tesamorelin- Placebo (N=85)	Placebo- Tesamorelin (N=86)	Tesamorelin- Tesamorelin (N=246)	Tesamorelin- Placebo (N=135)	Placebo- Tesamorelin (N=197)
Waist circumference (cm)									
Baseline	103.77 (8.848)	105.10 (11.983)	104.92 (9.876)	103.81 (8.255)	105.62 (9.153)	103.80 (8.933)	103.79 (8.614)	105.43 (10.251)	104.43 (9.469)
Week 26	100.68 (10.176)**	101.97 (12.431)**	103.94 (11.008)	100.95 (8.859)**	103.29 (11.380)**	102.80 (12.008)	100.78 (9.687)**	102.80 (11.752)**	103.44 (11.440)**
Week 52	100.54 (10.261)**	104.32 (12.924)††	102.12 (10.636)**†††	100.06 (7.650)**	103.25 (11.154)**	100.84 (12.224)**†††	100.36 (9.356)**	103.65 (11.804)**	101.56 (11.344)**†††
Change from baseline									
Mean (SD)									
Week 26	-3.09 (4.958)	-3.13 (5.137)	-0.98 (4.288)	-2.86 (6.229)	-2.33 (5.248)	-1.00 (5.408)	-3.00 (5.457)	-2.63 (5.202)	-0.99 (4.796)
Mean (LSM)									
Week 52	-3.24 (-3.24)	-0.79 (-0.76)	-2.80	-3.75 (-3.66)	-2.37 (-2.47)	-2.96	-3.43 (-3.51)	-1.78 (-1.76)	-2.87
P-value ^a	=0.001			0.054			=0.001		
P-value ^b	<0.001/0.091								
Hip circumference (cm)									
Baseline	99.25 (8.251)	101.11 (10.686)	100.00 (8.883)	98.89 (7.020)	100.77 (8.282)	99.51 (9.814)	99.12 (7.801)	100.90 (9.208)	99.79 (9.280)
Week 26	99.47 (8.758)	101.83 (10.980)	100.89 (9.168)**	99.38 (7.831)	100.51 (9.035)	99.09 (9.851)	99.44 (8.407)	101.00 (9.781)	100.11 (9.490)
Week 52	99.03 (9.095)	101.66 (11.369)	100.45 (8.808)	99.13 (7.630)	100.32 (8.535)	99.51 (10.156)	99.07 (8.561)	100.82 (9.662)	100.04 (9.407)
Change from baseline									
Mean (SD)									
Week 26	0.22 (3.730)	0.72 (3.943)	0.90 (3.374)	0.49 (4.064)	-0.26 (3.970)	-0.42 (4.096)	0.32 (3.852)	0.10 (3.973)	0.32 (3.754)
Mean (LSM)									
Week 52	-0.22 (-0.15)	0.55 (0.32)	0.45	0.24 (-0.12)	-0.45 (-0.05)	-0.00	-0.05 (-0.13)	-0.08 (0.07)	0.25
P-value ^a	0.478			0.858			0.598		
P-value ^b	0.564/0.513								
Waist:hip ratio									
Baseline	1.05 (0.061)	1.04 (0.057)	1.05 (0.066)	1.05 (0.089)	1.05 (0.056)	1.05 (0.059)	1.05 (0.073)	1.05 (0.056)	1.05 (0.063)
Week 26	1.01 (0.070)**	1.00 (0.055)**	1.03 (0.072)**	1.02 (0.072)**	1.03 (0.071)**	1.04 (0.066)	1.01 (0.070)**	1.02 (0.067)**	1.03 (0.070)**
Week 52	1.02 (0.088)**	1.03 (0.064)††	1.02 (0.068)**†††	1.01 (0.071)**	1.03 (0.065)**	1.01 (0.080)**†††	1.02 (0.082)**	1.03 (0.065)**†††	1.02 (0.074)**†††
Change from baseline									
Mean (SD)									
Week 26	-0.03 (0.050)	-0.04 (0.054)	-0.02 (0.044)	-0.04 (0.073)	-0.02 (0.046)	-0.01 (0.047)	-0.03 (0.060)	-0.03 (0.049)	-0.01 (0.046)
Mean (LSM)									
Week 52	-0.03 (-0.03)	-0.01 (-0.01)	-0.03	-0.04 (-0.04)	-0.02 (-0.03)	-0.03	-0.03 (-0.03)	-0.02 (-0.02)	-0.03
P-value ^a	0.054			0.035			0.008		
P-value ^b	0.007/0.483								

Source: ISE, Table 21

6.1.6.1 Remaining “Other” Efficacy Endpoints

As the clinical significance of the following endpoints is less germane to this review, the following “other” efficacy endpoints will be mentioned only briefly. Unless otherwise noted, the findings for each of the following endpoints were not considered clinically significant.

Bone Markers

The effects of tesamorelin on osteocalcin and N-terminal telopeptides of Type-1 collagen levels were assessed from fasting blood samples obtained at Weeks 0, 26, and 52 (or ET). Samples were analyzed centrally by (b) (4).

Bone Mineral Content and Bone Mineral Density

BMC and BMD were assessed from whole-body DEXA scan performed at local facilities and analyzed at an outside facility. Although BMC and BMD data were recorded and analyzed at Weeks 13, 26, and 39, only data collected and analyzed at Weeks 0 and 52 were presented by the Sponsor (as per study protocol).

Low-Density Lipoprotein Cholesterol, Apolipoprotein A1, and Apolipoprotein B
LDL-C was calculated using the total cholesterol, HDL-C, and triglyceride measurements. Apolipoprotein A1 and Apolipoprotein B were measured from fasting blood samples which were analyzed at an outside location. Fasting blood samples were obtained at Weeks 0, 13, 26, 39, and 52 (or ET).

Inflammatory Markers

C-reactive protein (CRP), tumor necrosis factor-receptors I and II (TNF-RI and RII), adiponectin, tissue plasminogen activator (tPA) antigen and activity, and plasminogen activator inhibitor-I (PAI-1) antigen and activity were analyzed at an outside facility from blood samples. Samples were collected at Weeks 0, 26, and 52 (or ET).

Patient-Reported Outcomes Related to Body Image and Health-Related Quality of Life

As previously described, the effect of tesamorelin on PRO was assessed using the PHASE V OIS (With BSE, BAD, and BP considered Secondary Efficacy Endpoints). Patients and investigators completed questionnaires at Weeks -4, 0, 26, and 52 (or ET). The PRO related to body image and health-related quality of life were considered other efficacy variables and are listed below:

- Perceived Body Weight and Weight Concerns
- HRQOL – Perceived Health (Global Analogue Scale)
- HRQOL – Appearance-specific Symptom Interference
- HRQOL – Symptoms and Side Effects Distress
- HRQOL – Mental and Emotional Health
- HRQOL – General Health Perceptions
- HRQOL – Composite QOL
- HRQOL – Overall QOL

6.1.7 Subpopulations

6.1.7.1 Subgroup Analyses by Gender

Tables 48 and 49 summarize the treatment effect by gender at Weeks 13 and 26 in the Main Phase of each pivotal study using ANCOVA for analysis. Results from the subgroup analyses by gender showed that the percent change from baseline in VAT at Weeks 13 and 26 was similar for females across studies for identical timepoints but different for males (larger reductions from baseline in Study 10). Comparisons between changes in males and females were more discordant at Week 13 but more similar at Week 26. Of note, baseline VAT was significantly less in females compared with males in both pivotal trials.

Table 48 Gender Analysis of % Change in VAT at Weeks 13 and 26* – Study 10 (Main Phase)

Visit		Tesamorelin (N=273)			Placebo (N=137)			P- value
		n	Mean (SD)	LSM	n	Mean (SD)	LSM	
Baseline VAT (cm²)		272	178 (76.9)	---	136	171 (76.9)	---	---
Week 13	Actual value (cm²)	272	157 (76.9)	---	137	175 (82.2)	---	---
	% change (all patients)	272	-12.1 (17.5)	-12.6	136	3.0 (21.9)	2.1	<0.001
	% change in males	237	-12.7 (17.6)	-14.5	114	2.6 (22.8)	0.2	<0.001
	% change in females	35	-7.8 (15.9)	-8.9	22	4.7 (16.5)	3.1	0.009
Week 26	Actual value (cm²)	273	150 (74.1)	---	137	178 (85.0)	---	---
	% change (all patients)	272	-15.1 (20.8)	-17.8	136	5.0 (23.4)	2.3	<0.001
	% change in males	237	-15.3 (20.7)	-18.0	114	4.8 (24.2)	1.9	<0.001
	% change in females	35	-13.9 (21.9)	-16.7	22	6.1 (19.4)	4.3	0.001

Source: TH9507/III/LIPO/010 CSR – Table 25

*ITT Analysis, LOCF

Table 49 Gender Analysis of % Change in VAT at Weeks 13 and 26* – Study 11 (Main Phase)

Visit		Tesamorelin (N=270)			Placebo (N=126)			P- value
		n	Mean (SD)	LSM	n	Mean (SD)	LSM	
Baseline VAT (cm²)		268	186 (86.6)	---	126	195 (95.5)	---	---
Week 13	Actual value (cm²)	269	170 (83.3)	---	126	192 (95.3)	---	---
	% change	268	-8.57 (15.9)	-12.6	126	-0.36 (19.7)	-2.1	<0.001
	% change in males	226	-8.85 (16.5)	-10.5	105	-0.42 (20.9)	-2.34	<0.001
	% change in females	42	-7.05 (12.4)	-7.77	21	-0.06 (12.6)	-1.13	0.06
Week 26	Actual value (cm²)	269	166 (86.8)	---	126	194 (100)	---	---
	% change	268	-10.9 (21.2)	-13.8	126	-0.62 (18.9)	-2.6	<0.001
	% change in males	226	-10.9 (21.8)	-13.8	105	-0.05 (19.0)	-1.8	<0.001
	% change in females	42	-11.2 (18.4)	-13.3	21	-3.46 (18.6)	-5.1	0.127

Source: TH9507-CTR-1011 CSR – Table 14.2.1.6.1.1, Table 14.2.1.6.1.2, Table 14.2.1.6.1.3

*ITT Analysis, LOCF

6.1.7.2 Subgroup Analyses by Anti-tesamorelin IgG Antibody Status

For a complete analysis of the effect of Anti-tesamorelin antibody status on percent change in VAT, please see the Safety section of this review.

6.1.7.3 Other Subgroup Analyses

Several sensitivity analyses were conducted in order to evaluate the effect of covariates other than gender on the percent change from baseline in VAT during the Main Phase; such covariates included testosterone use, impaired glucose tolerance/Type 2 Diabetes, antiretroviral regimen, number of days on protease inhibitor, race, age, and country. The percent change from baseline in VAT remained significant between patients in the tesamorelin and placebo groups regardless of the status of any of the above covariates.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The sponsor has selected a daily dose of 2 mg tesamorelin based on clinical pharmacology data and results of Phase 2 studies. The main objective of dose selection was to determine the maximum dose of tesamorelin that can be administered, while keeping IGF-1 level within the physiological range of young adults and limiting the potential impact on glucose parameters. The 2 mg dose was selected for the following reasons:

- Clinical pharmacology data showed that daily administration of 2 mg tesamorelin was associated with an increase in levels of IGF-1, an integrated measure of GH and a surrogate endpoint of the biological activity of tesamorelin, within the physiological ranges expected for young adults.
- In Phase 2 studies, including the one in HIV-infected subjects with lipodystrophy, the 2 mg dose had a consistently superior effect on IGF-1 level, when compared to the 1 mg dose, and was overall well tolerated.
- The 2 mg dose was efficacious in reducing VAT and trunk fat in the target population and had a superior effect when compared to the 1 mg dose (Phase II Study TH9507/II/LIPO/008).
- The results from a Phase 1 study in healthy elderly subjects (Study TH9507/I/PKPD/009) suggested that increasing the dose of tesamorelin above 2 mg once daily (QD) could result in increased incidence of AEs.
- Finally, the 2 mg daily dose did not have an impact on glucose parameters (Phase 2 study TH9507/II/Diabetic/006).

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Within the efficacy review, please see sections referring to Extension Phase Studies 010 and 012 for a detailed analysis of the efficacy and/or tolerance effects of tesamorelin for periods up to 52 weeks' duration.

6.1.10 Additional Efficacy Issues/Analyses

Not applicable for this review.

7 Review of Safety

Safety Summary

The safety observations made during the Egrifta clinical program in HIV patients with lipodystrophy are in general consistent with those observed with rhGH in adults. This should not come as a surprise since the mechanism of action of Egrifta, like that of native GHRH, is to stimulate the pituitary release of GH. Specifically, most of the treatment-emergent adverse events that occurred in excess with Egrifta relative to placebo were either adverse reactions known to occur in association with rhGH therapy in adults (e.g. arthralgia, extremity pain, headache, peripheral edema, paraesthesia/hypoesthesia, musculoskeletal stiffness, myalgia, hyperglycemia, joint stiffness, and carpal tunnel syndrome), or injection site reactions (some associated with systemic reactions such as urticaria, hypersensitivity). The remainders of the TEAEs appear to be background adverse events.

SAEs were rare and there were no imbalances between tesamorelin and placebo control; in addition, most appeared to be background events. The few deaths reported seemed to be linked to co-existing morbidities rather than to tesamorelin's known mechanism of action. The adverse events that resulted in discontinuations were, as in the case of TEAEs, either adverse reactions known to occur in association with rhGH therapy in adults, injection site reactions, (including some systemic hypersensitivity), or background events. There was a clear imbalance in frequency of hypersensitivity reactions in the tesamorelin group relative to placebo and, as mentioned above, some of them resulted in trial discontinuation.

Several safety assessments deserve special consideration because of the broader safety implications. They are: IGF-1 response, glucose metabolism changes, and immunogenicity.

The 2 mg daily dose of Egrifta elevated the mean IGF-1 levels above the upper limit of normal. Despite some evidence that the IGF-1 levels return in the upper normal range by the end of the first year of treatment, this may not necessarily be the case given that one does not fully understand the effect that dropouts may have had on the mean IGF-1 values; in fact, an analysis of IGF-1 levels in completers that ignores the dropout values suggests that the IGF-1 levels may be expected to be higher than those observed. Regardless, under both scenarios a significant proportion of patients have IGF-1 SD scores above the upper limit of normal at Week 52 (1/3 over 2 SD and 1/5 over 3 SD). Males reach higher levels than women. The issue of IGF-1 elevation is of significance for two reasons. First of all, the Egrifta regimen is a fixed regimen and titration (including

down titration) has not been investigated from either an efficacy or safety perspective. Secondly, HIV patients are at higher risk of non-AIDS defining malignancies and Egrifta treatment is anticipated to be long-term (once discontinued, efficacy is lost rapidly).

With respect to Egrifta's effects on glucose metabolism, it should be mentioned that, although it did not affect in any clinically meaningful way the mean values for fasting blood glucose, fasting insulin, HOMA-IR and HbA1c, there was a consistent trend indicating that a higher percentage of patients experienced a shift of individual fasting glucose and HbA1c values from normal to impaired glucose tolerance/prediabetes or from these aforementioned categories to diabetes, when compared to placebo. There was also a statistically significant difference in the proportion of patients who developed diabetes mellitus in the tesamorelin group: Odds Ratio of 3.4 (95% CI: 1.3, 11.5) or 3.6 (95% CI: 1.5, 12.0) depending on whether baseline diabetes mellitus cases were excluded or not. During the Extension Phase of the trials there was no convincing evidence to indicate deterioration in the glucose status of patients who were continued on tesamorelin, while patients who were switched to placebo seemed to remain stable or slightly improve. Such observation, though, does not account for the potential effect of dropouts. Placing all these observations in a broader context, the potential adverse cardiovascular effect of glucose metabolism deterioration has to be considered in the overall benefit-risk ratio regarding long-term cardiovascular consequences of tesamorelin treatment. This is particularly relevant as the argument has been made that VAT reduction is expected to improve the cardiometabolic profile of patients with HIV.

Finally, about 50% of Egrifta-treated patients develop anti-tesamorelin antibodies, most of low titers. The presence of anti-tesamorelin antibodies does not appear to affect the IGF-1 or VAT response. Upon treatment discontinuation the percentage of antibody-positive patients declines to about 18 % within 6 months. Anti-tesamorelin antibodies cross-react with endogenous GHRH in 60% of patients tested. *In vitro* neutralizing antibodies against tesamorelin develop in up to 18% of patients, and neutralizing antibodies against human GHRH are present in up to 5% of patients. Somewhat limited data suggest that the observed *in vitro* neutralizing activity does not have an effect *in vivo* on IGF-1 or VAT changes.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety review focused on the Pivotal Trials 10 and 11 (Main Phase) and 10-extension and 12 (Extension Phase). All Phase 1-3 studies were reviewed for information on patient deaths. An earlier Phase 2 trial evaluating EGRIFTA in patients with a history of diet-controlled diabetes mellitus (006) was also reviewed with respect to the risk of worsening hyperglycemia.

7.1.2 Categorization of Adverse Events

Adverse events were coded with the Medical Dictionary for Regulatory Activities (MedDRA) by system organ class and preferred term. In the ISS, common adverse events were defined as adverse events that occurred with a crude incidence rate (percentage of treated subjects reporting the event) >1.0% in any treatment group. More common adverse events were defined as adverse events that occurred with a crude incidence rate >5.0% in any treatment group.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Pivotal trials 10 and 11 (Main Phase) and 10-extension and 12 (Extension Phase) studied the efficacy of 2 mg/day of EGRIFTA in the treatment of excess abdominal fat in patients with HIV lipodystrophy. Data from these trials was pooled in the ISS. Exposure to EGRIFTA in these trials lasted for as long as 1 year in some subjects (T-T) group; patients were exposed to placebo for no more than 6 months

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

7.2.2 Explorations for Dose Response

In the Pivotal Trials, only a 2 mg/day dose of EGRIFTA was evaluated.

7.2.3 Special Animal and/or In Vitro Testing

Refer to Dr. Lauren Murphee Mihalcik's review for details.

7.2.4 Routine Clinical Testing

Routine clinical testing was adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

The Sponsor's testing of EGRIFTA's metabolism, clearance, and potential for interaction has already been discussed in Section 4.4.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

There are no other GRF analogues currently available.

7.3 Major Safety Results

7.3.1 Deaths

Ten deaths were reported during the tesamorelin clinical program. Four of them occurred in the pivotal (HIV) trials and six in non-HIV trials (Table 50). In the HIV trials, two deaths were reported in Study 10- extension (one due to coronary artery arteriosclerosis and another to postsurgical hemorrhage with subsequent asphyxiation, both on tesamorelin) and two during Study 11 (metastatic lung adenocarcinoma in a patient treated with tesamorelin, and cardiac failure/arrhythmia in a placebo-treated patient).

Of the six deaths that occurred in non-HIV clinical studies, four were in an 8-week study of elderly patients recovering from hip fracture surgery (the events were due to myocardial infarction, cerebral ischemic event and pneumonia/cardiac failure for tesamorelin-treated patients, and myocardial infarction for a placebo patient), and two occurred in a 12-week study that enrolled patients with COPD (myocardial infarction and COPD exacerbation, both in tesamorelin-treated patients).

Overall, the number of events is very small overall and, therefore, drawing firm conclusions on the basis of this information would be speculative. In addition, it should be recognized that the patients enrolled in the above-mentioned studies have many age-related and disease-related co-morbidities placing them at risk for a terminal event as indicated by the fact that most events were cardiac in nature. Furthermore, they represent three different patient populations (HIV patients, COPD and elderly postsurgical patients) with different expected background of adverse events and findings that, when coming from a non-HIV patient population, may not be readily extrapolated to HIV-patients. Regardless, all but one of the events listed above were judged by the investigators to be “unrelated” to the study medication. The only case of death deemed “related” was a patient who received tesamorelin 2 mg/day for 96 days in one of the pivotal studies. This patient was discontinued prematurely from the study due to an injection site reaction; five months later he was diagnosed with lung cancer with brain and spine metastases and subsequently died.

Table 50 Deaths- pivotal HIV trials and non-HIV studies

Study	Age/Gender	Treatment (dose)	Adverse event	Duration of Exposure (days)	Investigator’s assessment (relationship to treatment)
Non-HIV Studies					
10	54/M	Tesamorelin (T-T) (2 mg/day)	Coronary artery arteriosclerosis	215	Unrelated
10	50/M	Tesamorelin (P-T) (2 mg/day)	Post-tonsillectomy and adenoidectomy hemorrhage and asphyxiation	264	Unrelated
11	49/M	Tesamorelin (2 mg/day)	Metastatic lung adenocarcinoma	95	Related
11	50/M	Placebo	Cardiac failure/arrhythmia	NA	Unrelated
Non-HIV Studies					
003	53/F	Tesamorelin (2 mg/day)	Increased bronchial secretion and dyspnea	73	Unrelated

003	72/M	Tesamorelin (1 mg/day)	Acute myocardial infarction	43	Unrelated
004	87/F	Tesamorelin (2 mg/day)	Acute myocardial infarction	5	Unrelated
004	89/M	Tesamorelin (2 mg/day)	Post-operative pneumonia, cardiac failure	10	Unrelated
004	81/F	Tesamorelin (2 mg/day)	Cerebral ischemic event	27	Unrelated
004	95/F	Placebo	Myocardial infarction	NA	Unrelated

Source: Summary of Clinical Safety, Table 17

T-T = tesamorelin 2 mg/day during Main Phase and tesamorelin during the Extension Phase.

P-T = placebo during Main Phase and tesamorelin 2 mg/day during the Extension Phase.

T-P = tesamorelin 2 mg/day during Main Phase and placebo during the Extension Phase.

003=Study TH9507/II/COPD/003 conducted in patients with COPD.

004 =Study TH9507/II/HF/004 conducted in elderly patients recovering from hip fracture surgery.

N.B. Unless otherwise specified, the descriptions of safety data that follow in this review will refer to the combined datasets for the Main Phase (Studies 10 and 11) or the Extension Phase (Studies 10-extension and 12). Within this context they will focus on tesamorelin-to-placebo comparisons.

7.3.2 Nonfatal Serious Adverse Events

Main Phase

During the Main Phase of the pivotal trials similar proportions of patients experienced adverse events that met the regulatory definition of severe adverse event (SAE)⁴: 3.7% in tesamorelin-treated groups and 4.2% in the placebo groups. Largely, there were similar percentages of SAEs during Weeks 0-13 (2% tesamorelin and 1.9% placebo) as during Weeks 14-26 (1.9 % tesamorelin and 2.7% placebo). Of the SAEs that occurred with higher frequency in the tesamorelin groups compared to placebo, sepsis was the only one reported by \geq two tesamorelin-treated patient patients (0.4% to be precise) and in no placebo patients. The SAEs that occurred in one tesamorelin patient (0.2%) and in no placebo patients were: anemia, congestive cardiac failure, diarrhea, obstruction of the small intestine, abdominal abscess, appendiceal abscess, viral bronchitis, perianal abscess, upper respiratory tract infection, humeral fracture, rib fracture, dehydration, arthralgia, decreased mobility, basal cell carcinoma, rectal cancer, cerebellar syndrome, peripheral neuropathy, trigeminal neuralgia, bipolar disorder, dependence, and benign prostatic hyperplasia.

No specific pattern of adverse events is emerging from the SAEs listed above. Most of the SAEs that occurred with higher frequency in the tesamorelin group are consistent with background adverse events that are expected to occur in a condition such as HIV with multiple medical and surgical complications. At least one (arthralgia) has been seen in association with rhGH therapy, a therapeutic agent whose mechanism of action and adverse event profile overlaps considerably with that of tesamorelin. A small imbalance

⁴ Per CFR 21, Section 314.80 serious adverse events are defined as “any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

of adverse events was observed in the system organ class (SOC) “infections and infestations” (0.9% tesamorelin and 0.4% placebo), although the reason for this observation is not clear.

Of the SAEs mentioned above, adverse events that were considered “related” to the study drug by the investigators were relatively few and had similar incidence rates in the tesamorelin and placebo groups (0.9% vs.0.8%). The only ones that occurred with a higher frequency in the tesamorelin group (1 patient or 0.2%) relative to placebo were: congestive heart failure, diarrhea, sepsis, and decreased mobility.

Extension Phase

A comparison of SAE incidence between patients re-randomized at the end of the Main Phase to either tesamorelin (T-T group) or placebo (T-P group) indicates that similar percentages of patients experienced such adverse events: 2.8% in the T-T group and 2.2% in the T-P group (and similar to the nonrandomized placebo-tesamorelin or P-T group: 3.0%). Nausea and vomiting were the most frequent SAEs in the T-T group (1.2% and 0.8%, respectively), none being observed in the T-P group. Adverse events that occurred in one patient (0.4%) in the T-T group and in none of the T-P group patients were: coronary artery arteriosclerosis, chest pain, pneumonia, abortion spontaneous, chorioretinopathy, cellulitis, mental status change. Only one adverse event (chorioretinitis) was considered by the investigator to be “related” to study drug; it occurred in one patient treated with tesamorelin (0.4%). As noted previously for drug-placebo comparisons during the Main Phase, there is no clear pattern of SAEs that can be specifically ascribed to tesamorelin on the basis of this dataset.

7.3.3 Dropouts and/or Discontinuations

Main Phase

During the Main Phase of the pivotal trials, the percentage of patients who discontinued the trial prematurely because of adverse events was slightly higher in the tesamorelin group (9.6%) than in the placebo group (6.1%). Adverse events that occurred in \geq two patients and with greater frequency in the tesamorelin group relative to the placebo group are presented in Table 51. Some of these adverse events represent known adverse reactions that occur in association to rhGH therapy in adults in general (e.g. arthralgia, extremity pain, headache, peripheral edema, paraesthesia/hypoesthesia, musculoskeletal stiffness, myalgia, hyperglycemia, joint stiffness, and carpal tunnel syndrome). Another group of adverse events capture tolerability events related to the site of injection under terms such as: erythema, pruritus, pain, urticaria, irritation, swelling, mass, and hemorrhage. Several adverse events such as urticaria, hypersensitivity, and pruritus raise the suspicion of systemic drug reactions (they are analyzed separately in Section 3.5.4 of this review). The rest of the adverse events listed may represent small imbalances of background adverse events that were severe enough to result in trial discontinuation.

Table 51 Adverse Events Leading to Trial Discontinuation - Main Phase of Pivotal Studies (Both Studies Combined)*

Adverse event	Tesamorelin N=543 n (%)	Placebo N=263 n (%)
Arthralgia	13 (2.4)	2 (0.8)
Headache	12 (2.2)	1 (0.4)
Extremity pain	6 (1.1)	2 (0.8)
Injection site erythema	10 (1.8)	0
Injection site pruritis	10 (1.8)	0
Nausea	7 (1.3)	1 (0.4)
Injection site pain	7 (1.3)	2 (0.8)
Peripheral edema	7 (1.3)	0
Injection site urticaria	6 (1.1)	0
Diarrhea	5 (0.9)	2 (0.8)
Injection site irritation	5 (0.9)	0
Fatigue	5 (0.9)	2 (0.8)
Hypoesthesia	5 (0.9)	1 (0.4)
Dyspnea	5 (0.9)	2 (0.8)
Paresthesia	4 (0.7)	1 (0.4)
Musculoskeletal stiffness	4 (0.7)	0
Rash	4 (0.7)	1 (0.4)
Myalgia	3 (0.6)	1 (0.4)
Back pain	3 (0.6)	0
Injection site swelling	3 (0.6)	0
Injection site swelling	3 (0.6)	0
Hyperglycemia	3 (0.6)	0
Urticaria	3 (0.6)	0
Injection site hemorrhage	2 (0.4)	0
Injection site mass	2 (0.4)	0
Injection site hemorrhage	2 (0.4)	0
Injection site mass	2 (0.4)	0
Nasopharyngitis	2 (0.4)	0
Creatine phosphokinase elevation	2 (0.4)	0
Hypertriglyceridemia	2 (0.4)	0
Decreased appetite	2 (0.4)	0
Joint stiffness	2 (0.4)	0
Carpal tunnel syndrome	2 (0.4)	0
Depression	2 (0.4)	0
Insomnia	2 (0.4)	0

*Included are adverse event that had a higher frequency in the tesamorelin combined group relative to placebo.

Source: ISS Table 1.4.4.1

Several adverse events occurred with low frequency. Specifically, adverse events that occurred in one patient in the tesamorelin group (0.2%) but in none of the placebo group were: palpitations, tachycardia, hypoacusis, eye swelling, visual disturbance, dyspepsia, flatulence, gastroesophageal reflux disease, gingival swelling, hematochezia, lip swelling, oral disorder, swollen tongue, vomiting, chest discomfort, injection site rash, malaise, edema, pain, abdominal abscess, appendiceal abscess, ear infection, gingival infection, herpes simplex, rhinitis, sepsis, repetitive strain injury, wound, hyperinsulinemia, hematuria, hepatic enzyme elevation, liver function test abnormality, proteinuria, weight gain, dehydration, hypercholesterolemia, joint ankylosis, joint swelling, decreased

mobility, muscular weakness, musculoskeletal pain, neck pain, plantar fasciitis, dysgeusia, neuralgia, peripheral neuropathy, vasovagal syncope, frustration, stress, dysuria, renal pain, decreased urine flow, breast enlargement, allergic sinusitis, exertional dyspnea, generalized pruritis, skin exfoliation, and hypertension.

Extension Phase

During the extension phase of the pivotal trials, the percentage of patients who discontinued the trial prematurely because of adverse events was slightly lower in the T-T group (2.0%) than in the T-P group (4.4%). The only adverse events that occurred in \geq two patients and with greater frequency in the T-T group relative to the T-P group was urticaria, which occurred in two patients (0.8%). Several adverse events occurred with low frequency. Adverse events that occurred in at least one patient in the T-T group (0.4%) but not in the placebo group are presented in Table 52. These include: lymphadenopathy, coronary artery arteriosclerosis, diarrhea, injection site irritation, hypersensitivity, tachycardia, increased prostatic specific antigen, arthralgia, dizziness, depression, insomnia, macular rash. None amounts to a safety signal.

Table 52 Adverse Events Leading to Trial Discontinuation - Extension Phase (Both Studies Combined)

Adverse event	Tesamorelin (T-T*) N=246 n (%)	Placebo (T-P**) N=135 n (%)
Urticaria	2 (0.8)	0
Lymphadenopathy	1 (0.4)	0
Coronary artery arteriosclerosis	1 (0.4)	0
Diarrhea	1 (0.4)	0
Injection site irritation	1 (0.4)	0
Hypersensitivity	1 (0.4)	0
Tachycardia	1 (0.4)	0
Increased prostatic specific antigen	1 (0.4)	0
Arthralgia	1 (0.4)	0
Dizziness	1 (0.4)	0
Depression	1 (0.4)	0
Insomnia	1 (0.4)	0
Macular rash	1 (0.4)	0

Source: ISS Table 1.4.4.1e

* Included are adverse events having a higher frequency in the tesamorelin group relative to placebo.

**T-T = tesamorelin during the Main Phase and tesamorelin during the Extension Phase.

*** T-P = tesamorelin during the Main Phase and placebo during the Extension Phase.

7.3.4 Significant Adverse Events

Adverse events leading to study discontinuation have already been discussed in Section 7.3.3., and SAEs leading to discontinuation were described in Section 7.3.2.

7.3.5 Submission Specific Primary Safety Concerns

7.3.5.1 Cancer

As shown in Table 53, 17 patients experienced cancer TEAEs in the tesamorelin program (15 occurred in pivotal studies and 2 in non-pivotal studies). Within the pivotal studies, eight cases occurred during the Main Phase (five in the tesamorelin group and three in the placebo group) and seven during the Extension Phase (four in the P-T group, two in the T-P group, and one in the T-T group). The incidence of cancer in the Main Phase was similar between tesamorelin and placebo patients (0.9% vs. 1.1%). The incidence of cancer AEs in the Extension Phase was 1.5% in the T-P group, 2.0% in the P-T group and 0.4% in the T-T group. There was no specific pattern of cancers to differentiate tesamorelin from placebo.

Table 53 Cancer Adverse Events

Study	Age/Gender	Treatment (dose)	Type of Cancer	Duration of Drug Exposure (days)	Investigator's assessment (relationship to treatment)
Pivotal Studies: Main Phase					
10	60/M	Tesamorelin (2 mg/day)	Rectal cancer*	151	Unrelated
10	57/M	Tesamorelin (2 mg/day)	Basal cell carcinoma*	44	Unrelated
10	45/M	Tesamorelin (2 mg/day)	Prostatic neoplasm	177	Unrelated
11	53/M	Tesamorelin (2 mg/day)	Lung neoplasm	106	Unrelated
11	49/M	Tesamorelin (2 mg/day)	Basal cell carcinoma	113	Unrelated
11	39/F	Placebo	Breast cancer in situ*	-	Unrelated
11	40/M	Placebo	Hodgkin's disease*	-	Related
11	48/M	Placebo	Basal cell carcinoma	-	Unrelated
Pivotal Studies: Extension Phase					
10	50/M	T-T	Basal cell carcinoma	348	Unrelated
10	64/F	P-T	Basal cell carcinoma	160	Unrelated
10	55/M	P-T	Kaposi's sarcoma	33	Unrelated
10	51/M	P-T	Lung neoplasm	174	Unrelated
10	58/M	T-P	Basal cell carcinoma	182	Unrelated
10	43/M	T-P	Anal cancer*	186	Unrelated
12	38/M	P-T	Hodgkin's disease*	84	Related [#]
Non-pivotal Studies					
004	84/F	Tesamorelin (2 mg/day)	Tracheal cancer*	21	Unrelated
007	71/M	Tesamorelin (1 mg/day)	Prostatic neoplasm	57	Unrelated

Source: Summary of Clinical Safety Table 20

*Also reported as an SAE.

[†]Narrative unavailable.

[#]Investigator judged there was a possibility of causal relationship to placebo

T-T = tesamorelin 2 mg/day during Main Phase and tesamorelin during the Extension Phase.

P-T = placebo during Main Phase and tesamorelin 2 mg/day during the Extension Phase.

T-P = tesamorelin during Main Phase and placebo 2 mg/day during the Extension Phase.

Because of the suspected link between high IGF-1 levels and the risk of tumorigenesis, at the Division’s request the applicant has provided all IGF-1 values for the 17 patients who developed cancer during the clinical trials. A review of these data indicates that most patients with cancer tended to have IGF-1 values that fell within the normal range (≤ 2 SDS). Only three of them had IGF-1 levels that were > 2 SDS during the studies: one in T-T group (basal cell carcinoma), one in T-P (basal cell carcinoma) and one in P-T (lung neoplasma).

7.3.5.2 Injection Site Reactions

Overall, the proportion of patients experiencing at least one injection site-related adverse event was higher in tesamorelin-treated subjects compared to those receiving placebo (24.5% and 14.4%, respectively). Table 54 shows the incidence of individual injection site reactions for the Main Phase of the Pivotal Trials.

Table 54 Administration Site Adverse Events – Main Phase of Pivotal Studies (Both Studies Combined)*

Adverse event	Tesamorelin N=543 n (%)	Placebo N=263 n (%)
Injection site erythema	46 (8.5)	7 (2.7)
Injection site pruritis	41 (7.6)	2 (0.8)
Injection site bruising	40 (7.4)	27 (10.3)
Injection site pain	22 (4.1)	8 (3.0)
Injection site irritation	16 (2.9)	3 (1.1)
Injection site hemorrhage	9 (1.7)	1 (0.4)
Injection site urticaria	9 (1.7)	1 (0.4)
Injection site swelling	8 (1.5)	1 (0.4)
Injection site reaction	7 (1.3)	2 (0.8)
Injection site rash	6 (1.1)	0

*Included are adverse events occurring in $\geq 1\%$ that had a higher frequency in the tesamorelin combined group relative to placebo
Source: ISS Table 1.4.2.1

During the Extension phase, the AE incidence was 6.1% for the T-T group and 4.4% for the T-P groups.

7.3.5.3 Adverse Events Known to be Related to Growth Hormone

The applicant conducted an analysis of AEs known to be related to GH (Table 55). Consistent with observations made in the TEAE and patient discontinuation summaries, the incidence of such events was higher in tesamorelin-treated subjects compared to those receiving placebo (25.6% and 13.7%, respectively).

Table 55 GH-Related Adverse Events – Main Phase of Pivotal Studies (Both Studies Combined)*

Adverse event	Tesamorelin N=543 n (%)	Placebo N=263 n (%)
Extremity pain	33 (6.1)	12 (4.6)
Peripheral edema	33 (6.1)	6 (2.3)
Myalgia	30 (5.5)	5 (1.9)
Parasthesia	26 (4.8)	6 (2.3)
Hypoesthesia	23 (4.2)	4 (1.5)
Musculoskeletal stiffness	9 (1.7)	1 (0.4)
Joint stiffness	8 (1.5)	2 (0.8)
Carpal tunnel syndrome	8 (1.5)	0
Peripheral neuropathy	6 (1.1)	3 (1.1)
Joint swelling	6 (1.1)	0

*Included are adverse events occurring in $\geq 1\%$ that had a higher frequency in the tesamorelin combined group relative to placebo
Source: ISS Table 1.4.2.1

The difference was smaller during the extension phase: 11.4% in the T-T group and 7.4% in the T-P group (Table 56).

Table 56 GH-Related Adverse Events – Extension Phase of Pivotal Studies (Both Studies Combined)*

Adverse event	T-T N=246 n (%)	T-P N=135 n (%)
Extremity pain	8 (3.3)	1 (0.7)
Peripheral edema	5 (2.0)	0
Parasthesia	4 (1.6)	2 (1.5)
Peripheral neuropathy	4 (1.6)	2 (1.5)
Hypoesthesia	4 (1.6)	1 (0.7)
Myalgia	3 (1.2)	0
Joint stiffness	2 (0.8)	0
Musculoskeletal stiffness	2 (0.8)	0
Carpal tunnel syndrome	2 (0.8)	0

*Included are adverse events occurring in ≥ 1 subject that had a higher frequency in the tesamorelin combined group relative to placebo
Source: ISS Table 1.4.2.2

7.3.5.4 Hypersensitivity Reactions

Twenty-eight patients were identified as having developed hypersensitivity reactions; 27 were treated with tesamorelin and only one patient received placebo. Among the 28 cases of hypersensitivity reaction, 22 were spontaneously reported and six additional cases were identified during the data review. Tesamorelin was discontinued in all 22 subjects who spontaneously reported a reaction and resulted in resolution of symptoms, either spontaneously or with anti-histamines. One of the 6 patients who were identified by the applicant during the post-study review reported worsening of symptoms over the course of the study. In this case, the patient first experienced injection site erythema, pruritis, injection site swelling, and urticaria during the first month of the study, which progressed to systemic symptoms (swollen tongue, sweating) 15 weeks later. Among tesamorelin-treated subjects, most hypersensitivity reactions were preceded by significant reactions at

the injection site and were associated with systemic reactions (12/27) including nausea (5), palpitation/tachycardia (4), light-headedness/dizziness (4), hot flush/flushing (3), sweating (3), dyspnea (1), headache (2), abnormal vision (2), weakness (1) and tongue edema (1).

During the Main Phase of the Pivotal Trials, 12 subjects receiving tesamorelin (2.2%) had a hypersensitivity reaction resulting in discontinuation. During the Extension Phase, three subjects in the T-T group (1.2%), 6 in the P-T group (3.0%) and none in the T-P group had a hypersensitivity reaction resulting in discontinuation. Most of the hypersensitivity cases (24/27, 89%) occurred within the first six months of exposure to tesamorelin.

7.3.5.5 IGF-1

Main Phase

IGF-1 measurements were performed at baseline, Week 13 and Week 26. Mean baseline IGF-1 SD scores were within the low normal range: -0.31 for the tesamorelin and -0.21 for the placebo group, respectively. Small differences in mean baseline IGF-1 levels existed between Study 10 (SD score close to 0.00) and Study 11 (SD score of about -0.4). The vast majority of patients had IGF-1 levels below the upper limit of normal (i.e. < 2 SD), with only 6% of patients displaying IGF-1 SD scores above the normal range (i.e. > 2 SD) at baseline.

At Week 26, the mean IGF-1 SD score increased above the upper limit of normal (2.39) in the tesamorelin group while for the placebo groups it remained in the normal range and below the study population mean (-0.45). Changes at Week 13 were consistent with those seen at Week 26 (Table 57). The percentage of patients with IGF-1 SDS values above the upper limit of normal increased from 6.2 % at baseline to 47.4 % in the tesamorelin group and remained virtually unchanged in the placebo group (6.1 % at baseline and 5% at Week 26). Moreover, the percentage of patients with SD scores above 3 standard deviations increased from 1.5% at baseline to 35.6% in the tesamorelin group with no real change in the placebo group (3.8% at baseline and 2.5% at week 26).

Also of interest is the potential effect of non-compliance on the IGF-1 data. For instance, in Study 10 non-compliance (defined in the protocol as actual administration of <80% of scheduled doses) was found in 26.2 % of patients, while in Study 11 it was 39.5%. This observation indicates that in compliant patients IGF-1 levels may be even higher.

Table 57 Mean IGF-1 SDS - Main Phase of Pivotal Studies (Both Studies Combined)

		Tesamorelin	Placebo
Baseline	N	534	261
	Mean (SD); range	-0.31 (1.32); -3.1, 5.9	-0.21 (1.54) -2.9, 5.3
	SDS > +2 (%)	33 (6.2)	16 (6.1)
	SDS > +3 (%)	8 (1.5)	10 (3.8)
Week 13	N	456	217
	Mean (SD); range	2.49 (2.78); -2.6, 16.2	-0.26 (1.48); -3.0, 6.6
	SDS > +2 (%)	224 (49.1)	13 (6.0)
	SDS > +3 (%)	155 (34.0)	9 (4.1)
Week 26	N	405	202
	Mean; range	2.39 (2.85); -2.5, 14.0	-0.45 (1.26); -2.8, 3.5
	SDS > +2 (%)	192 (47.4)	10 (5.0)
	SDS > +3 (%)	144 (35.6)	5 (2.5)

Source: ISS Table 1.5.2.1.1

A breakdown by gender of the IGF-1 data is provided in Table 58. A significantly greater number of males compared to females enrolled in the study (457 vs. 77 in the tesamorelin group; 219 vs. 42 in the placebo group). At baseline the mean IGF-1 SD score was lower in females than males (approx. -0.7 females vs. -0.2 males). Regardless of gender, most patients had IGF-1 SD scores below the upper limit of normal with only a few exceeding it. At Week 13, the mean SD score for males receiving tesamorelin increased to 2.70 compared with only 1.13 for females. At Week 26, the means were similarly higher in males (2.62) versus females (0.94). Furthermore, a higher proportion of males had SD scores above 2 or 3 standard deviations when compared to females. Specifically, 52.4 % and 51.0% of males in the tesamorelin group had an SDS score >2 at Weeks 13 and 26, respectively, compared with only 27.9% and 24.1% of females; 37.0% and 38.2% of males had SDS scores >3 at Weeks 13 and 26, respectively, compared to only 14.8% and 18.5% of females. This, coupled with higher changes from baseline seen in males, indicates a clear gender-specific IGF-1 response with tesamorelin.

These data also indicate that the peak IGF-1 level is reached in both genders by Week 13 (the earliest post-baseline assessment). Given the known pharmacodynamic profile of IGF-1 following the administration of exogenous rhGH, it is very likely that such levels may be reached well before Week 13 (even within days) suggesting that patients are exposed to the levels of IGF-1 observed at Weeks 13 and 26 throughout most of the six-month trial.

Table 58 Mean IGF-1 SDS by Gender – Main Phase of Pivotal Studies (Both Studies Combined)

		Male		Female	
		Tesamorelin	Placebo	Tesamorelin	Placebo
Baseline	N	457	219	77	42
	Mean (SD)	-0.22 (1.34)	-0.13 (1.56)	-0.83 (1.09)	-0.60 (1.41)
	Range	-3.1, 5.9	-2.9, 8.3	-3.0, 2.8	-2.4, 3.8
	SDS > +2 (%)	32 (7.0)	13 (5.9)	1 (1.3)	3 (7.1)
	SDS > +3 (%)	7 (1.5)	8 (3.7)	1 (1.3)	2 (4.8)
Week 13	N	395	186	61	31
	Mean (SD)	2.70 (2.81)	-0.15 (1.48)	1.13 (2.12)	-0.91 (1.36)
	Range	-2.6, 16.2	-3.0, 6.6	-1.9, 7.8	-2.5, 4.0
	Change from baseline	2.92	-0.02	1.96	-0.31
	SDS > +2 (%)	207 (52.4)	11 (5.9)	17 (27.9)	2 (6.5)
	SDS > +3 (%)	146 (37.0)	8 (4.3)	9 (14.8)	1 (3.2)
Week 26	N	351	172	54	30
	Mean (SD)	2.62 (2.87)	-0.34 (1.23)	0.94 (2.19)	-1.06 (1.29)
	Range	-2.5, 14.0	-2.8, 3.8	-2.4, 6.9	-2.6, 3.7
	Change from baseline	2.84	-0.21	1.77	-0.31
	SDS > +2 (%)	179 (51.0)	9 (5.2)	13 (24.1)	1 (3.3)
	SDS > +3 (%)	134 (38.2)	4 (2.3)	10 (18.5)	1 (3.3)

Source: ISS Tables 1.5.2.1.9, 1.5.2.1.10

Extension Phase

During the extension phase the mean IGF-1 SDS decreased in the T-T group from 2.66 at Week 27 to 2.13 at Week 39 and 1.70 at Week 52. This change happened in the context of a concomitant reduction in the number of patients who contributed measurements to this analysis from 236 at Week 27 to 190 at Week 52.

The percentage of patients in the T-T group with IGF-1 measurements above 2 SD decreased from 50% at Week 27 to 33.7% at Week 52, as did that of patients with IGF-1 SD score >3, from 39.8% to 22.6 %, respectively. However, despite the reduction in mean IGF-1 levels and the decrease in the percentage of patients with above normal IGF-1 levels at Week 52, as many as 1/3 patients had IGF-1 levels > 2 SD and more than 1/5 had levels > 3 SD after one year of treatment. In contrast, patients in the T-P group who completed 52 Weeks of treatment had a reduction in mean IGF-1 SD score from 2.27 at Week 27 to values close to those recorded at the trial initiation (-0.58). All the findings described above are summarized in Table 59.

Finally, the patients in the P-T group (not included in Table 59), reproduced to a large extent the findings of the tesamorelin group during the Main Phase of the trials. Although the mean IGF-1 SDS values did not go above the upper limit of normal (-0.42 at baseline and 1.69 at end of the 6 months of treatment), the percentage of patients with values > 2 SD increased from 5.2% at baseline to 41.1 % at end-of-trial, as did the percentage of patients with values > 3SD which increased from 2.6% to 29.1% for the same duration of treatment.

Table 59 Mean IGF-1 SDS - Extension Phase of Pivotal Studies (Both Studies Combined)

		T-T	T-P
Week 27	N	236	132
	Mean (SD); range	2.66 (3.02); -2.5, 14.0	2.29 (2.50); -1.9, 12.4
	SDS > +2 (%)	118 (50.0)	64 (48.5)
	SDS > +3 (%)	94 (39.8)	42 (31.8)
Week 39	N	215	114
	Mean (SD); range	2.13 (2.73); -2.7, 11.8	1.92 (2.61); -3.1, 10.1
	SDS > +2 (%)	98 (45.6)	1 (0.9)
	SDS > +3 (%)	71 (33.0)	0
Week 52	N	190	93
	Mean; range	1.70 (2.82)	-0.58 (1.12)
	SDS > +2 (%)	64 (33.7)	5 (5.4)
	SDS > +3 (%)	43 (22.6)	1 (1.1)

Source: ISS Table 1.5.2.1.3.

An analysis of IGF-1 levels by gender is presented in Table 60. Patients of both genders in the T-T group experienced a lowering of mean IGF-1 SDS scores over the course of the Extension Phase (from 2.87 at Week 27 to 2.26 at Week 39 and 1.87 at Week 52 in males; from 0.89 to 1.01 to 0.38 for the same timepoints in females). Similar trends were noted for the proportion of patients in the T-T group with SDS scores >2 or >3.

However, a sizeable proportion of male patients maintained above-normal IGF-1 SD scores at Week 52: 36.3 % had SDS > 2 and 25.5% > 3 SDS. In contrast only 13.6% of females had a SD score > 2 SD and none > 3 SD for the same timepoint.

Table 60 Mean IGF-1 SDS by Gender – Extension Phase of Pivotal Studies (Both Studies Combined)

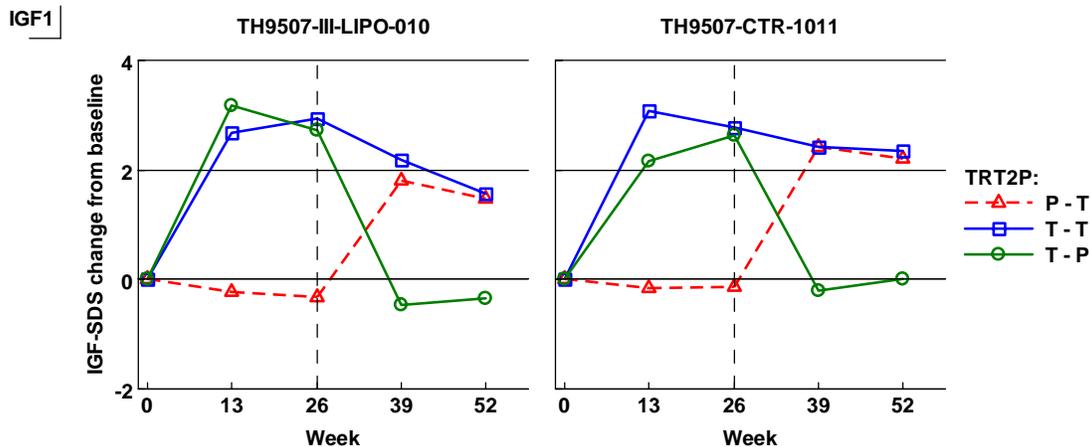
		Male		Female	
		T-T	T-P	T-T	T-P
Week 27	N	211	116	25	16
	Mean (SD)	2.87 (3.05)	2.45 (2.57)	0.89 (2.00)	1.06 (1.51)
	Range	-2.5, 14.0	-1.7, 12.4	-2.1, 5.5	-1.9, 4.4
	SDS > +2 (%)	113 (53.6)	60 (51.7)	5 (20.0)	4 (25.0)
	SDS > +3 (%)	90 (42.7)	40 (34.5)	4 (16.0)	2 (12.5)
Week 39	N	192	99	23	15
	Mean (SD)	2.26 (2.78)	-0.59 (1.03)	1.01 (2.01)	-1.02 (0.57)
	Range	-2.7, 11.8	-2.9, 2.3	-1.7, 5.3	-2.2, 0.0
	SDS > +2 (%)	91 (47.4)	1 (1.0)	7 (30.4)	0
	SDS > +3 (%)	65 (33.9)	6 (26.1)	0	1 (3.2)
Week 52	N	168	80	22	13
	Mean (SD)	1.87 (2.92)	-0.51 (1.19)	0.38 (1.38)	-0.98 (0.43)
	Range	-2.7, 12.2	-2.9, 3.0	-1.5, 2.9	-1.9, -0.3
	SDS > +2 (%)	61 (36.3)	5 (6.3)	3 (13.6)	0
	SDS > +3 (%)	43 (25.6)	1 (1.3)	0	0

Source: ISS Table 1.5.2.1.11.

Analyses of IGF-1 SD scores restricted to Extension Phase completers

Since the reduction in mean IGF-1 levels at Week 52 could have been confounded by the fact that some patients discontinued the trial for various reasons (and some of them may have had excessively high IGF-1 levels), the FDA statistical reviewer has conducted several analyses that exclude dropouts and focus only on the patients who had received treatment and had trial participation through Week 52. These patients are presented in Figure 27, which presents the mean IGF-1 SD scores in Studies 10 and 11/12 side-by-side. The element of immediate interest in the graph is the blue line that describes the mean IGF-1 SDS for patients who received tesamorelin through Week 52 and completed the trial. The trends observed are very similar to those described previously in that the mean IGF-1 SDS increased above the upper limit of normal, peaked at Month 6, and decreased subsequently. There were, however, some quantitative differences. In Study 10, the mean (SD) IGF-1 SDS at Week 52 was 1.6 (2.2) with a range between -3.5 and 10.5; in Study 12 it was higher at 2.3 (2.8) with a similar range (-3.1 to 11.6), suggesting an average value for the two studies combined close to 2 SD at Week 52 and higher than observed in Table 32.

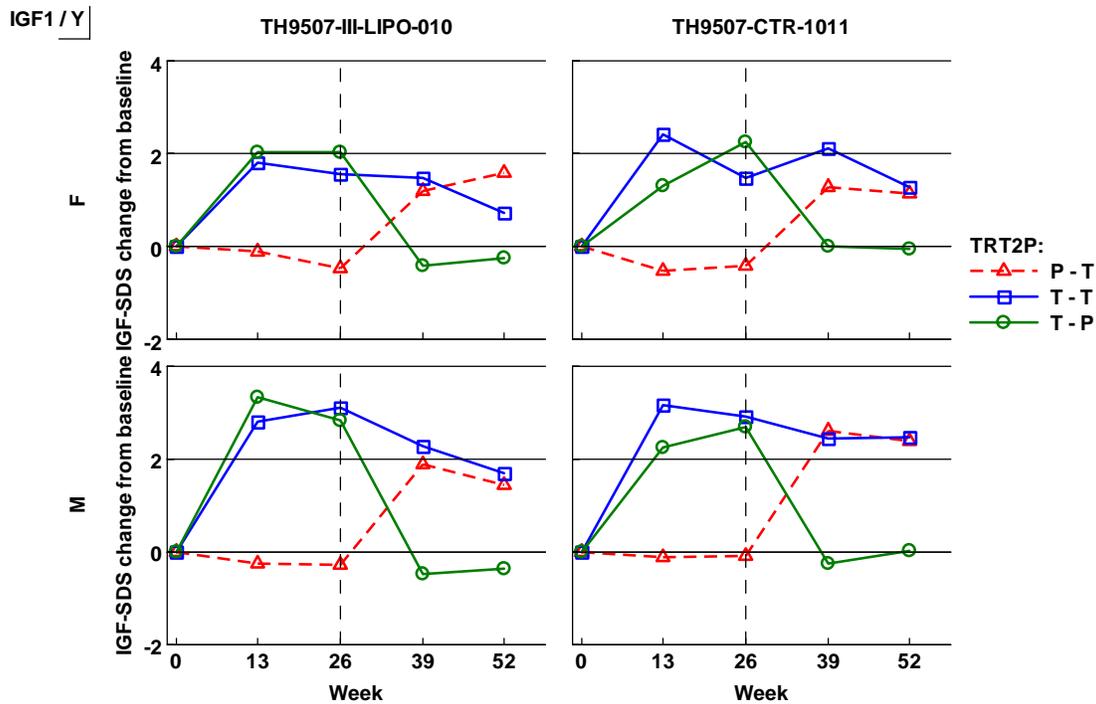
Figure 27 Mean IGF-1 Standard Deviation score (SDS) Over Time by Treatment Sequence – Extension Phase Completers



Source: FDA Statistical Review

When the IGF-1 SDS analyses conducted on the extension-phase completers were broken down by gender, the pattern observed was similar to that previously described. For female patients the mean (SD) scores at Week 52 were in the upper range of normal: 0.7 (1.3) with a range between -1.4 and 3 in Study 10; and 1.3 (1.1) with range of 0.2 to 2.9 in Study 11. For males the mean values at Week 52 were higher when compared to females and they also had a wider range. The mean (SD) was 1.7 (2.3) with a range of -3.5 to 10.5 in Study 10, and 2.5 (2.9) with a range of -3.1 to 11.6 in Study 11. This information is displayed graphically in Figure 28. As before, the blue line represents the group of interest (the T-T group). Females are represented in the upper two panels and males in the lower two panels.

Figure 28 Mean IGF-1 Standard Deviation Score (SDS) Over Time by Gender and Treatment Sequence – Extension Phase Completers



In summary, treatment with a fixed tesamorelin daily regimen of 2 mg had the following effect on serum IGF-1 levels:

- It increased the mean serum IGF-1 SD score above the upper limit of normal at 6 months (observation made in two independently conducted studies). The changes occurred as early as 13 weeks of treatment (the earliest timepoint measured in the trial), but given the pharmacodynamic characteristics of the drug they are likely to have occurred earlier. Almost half of the patients treated had IGF-1 SD scores above the upper limit of normal and more than 1/3 had levels greater than +3 SD. Female patients had a lesser IGF-1 SD elevation, while male patients experienced an even larger increase in mean serum IGF-1.
- Patients who continued tesamorelin for 52 weeks had mean IGF-1 levels in the upper normal range but even in this group of patients as many of 1/3 had SD scores above upper limit of normal and about 1/5 had levels greater than 3 SD; a larger proportion of males had above upper limit elevations when compared to females. An analysis including only extension phase completers suggests that patients who dropped out may have confounded the results and that IGF-1 levels may be expected to be even higher than those recorded at the end of the 52 week trials.
- Since a significant percentage of patients were not fully compliant with the treatment, it is likely that treatment-compliant patients may reach even higher IGF-1 SD scores; this finding is a safety concern given the fact that evidence is

- accumulating that HIV patients are at higher risk of non-AIDS defining malignancies.
- Discontinuation of tesamorelin resulted in a decrease in serum IGF-1 to baseline levels. However, discontinuation of tesamorelin also results in a reaccumulation of VAT.

7.3.5.6 Glucose, Insulin, and Glycosylated Hemoglobin

Both Studies 10 and 11 were fairly inclusive with regard to glucose metabolism status; they excluded only patients with fasting blood glucose (FBG) levels >150 mg/dl or if patients were previously treated with insulin, oral hypoglycemic or sensitizing agents. Consequently, the trials enrolled a mixture of patients, some with normal FBG, others with glucose intolerance, and some with mild diabetes managed on diet and exercise.

Glucose metabolism assessments included FBG, fasting insulin (FI), homeostasis model assessment-insulin resistance (HOMA-IR) and hemoglobin A1c (HbA1c), all performed at baseline, Week 6, Week 13, Week 26 (during the Main Phase), and Week 39, 45 and 52 (during the Extension Phase). In addition, a 2-hour oral glucose tolerance test (OGTT) was performed at baseline and last timepoint of the study for both the Main Phase and the Extension Phase.

The applicant has used several working definitions for glucose intolerance or diabetes. For the sake of clarity and simplicity this review will use applicant's "Definition 1" which best approximates that of the American Diabetes Association (ADA). According to Definition 1:

- Glucose intolerance is defined as a fasting plasma glucose of 100-125 mg/dL or a 2-hour plasma glucose of 140-199 in an OGTT (thus joining the impaired fasting glucose and impaired glucose tolerance in a single working definition).
- Diabetes mellitus is defined as a fasting plasma glucose ≥ 126 or a plasma glucose ≥ 200 mg/dl in a 2-hour OGTT.

To these predefined categories, this review will also add post hoc analyses of HbA1c using the 2010 ADA definitions (HbA1c of 5.7-6.4% defining pre-diabetes and $\geq 6.5\%$ defining diabetes mellitus).

Mean changes in Fasting Blood Glucose, HbA1c, Insulin, and HOMA-IR

Main Phase

There were no clinically significant changes in mean values for fasting plasma glucose, fasting serum insulin, HOMA-IR, and HbA1c during the Main Phase. A statistically significant, but not clinically relevant, mean change in HbA1c was observed in the tesamorelin group (0.15% vs. 0.04% placebo; $p=0.0004$). The mean changes from baseline for the above-mentioned assessments are summarized in Table 61.

Table 61 Change in FBG, Insulin, HOMA-IR, and HbA1c from Baseline to Week 26 – Main Phase of pivotal studies (Both Studies Combined)

	Tesamorelin (N=543)	Placebo (N=263)	P-value
FBG (mg/dL) – baseline Mean (SD)	98.21 (14.38)	98.10 (15.96)	
FBG (mg/dL) – change from baseline Mean (SD) LSM	2.65 (15.89) 2.68	0.70 (16.58) 0.70	0.0962
Insulin (µIU/mL) – baseline Mean (SD)	21.94 (29.24)	18.85 (13.65)	
Insulin (µIU/mL) – change from baseline Mean (SD) LSM	0.03 (29.29) 0.84	1.43 (21.93) -0.24	0.4992
HOMA-IR – baseline Mean (SD)	5.53 (8.30)	4.49 (4.23)	
HOMA-IR – change from baseline Mean (SD) LSM	-0.02 (8.50) 0.20	0.44 (7.09) -0.02	0.6474
HbA1c %– baseline Mean (SD)	5.26 (0.50)	5.28 (0.48)	
HbA1c % – change from baseline Mean (SD) LSM	0.14 (0.40) 0.15	0.02 (0.36) 0.04	0.0004

Source: ISS, Tables 107, 108, 109, and 110.

Extension Phase

Similar observations were made during the Extension Phase for comparisons between the two re-randomized groups (T-T and T-P: Table 62).

Table 62 Change in FBG, Insulin, HOMA-IR, and HbA1c from Baseline to Week 26 – Extension Phase of Pivotal Studies (Both Studies Combined)

	T-T (N=246)	T-P (N=135)	P-value
FBG (mg/dL) – baseline Mean (SD)	97.11 (13.09)	102.23 (16.86)	
FBG (mg/dL) – change from baseline Mean (SD) LSM	1.87 (14.48) 0.84	-2.02 (28.24) -0.13	0.6819
Insulin (µIU/mL) – baseline Mean (SD)	19.46 (20.22)	25.91 (31.38)	
Insulin (µIU/mL) – change from baseline Mean (SD) LSM	-0.41 (19.52) -2.04	-6.88 (30.60) -3.38	0.3588
HOMA-IR – baseline Mean (SD)	4.78 (5.74)	7.26 (10.95)	
HOMA-IR – change from baseline Mean (SD)	-0.04 (5.59)	-2.46 (11.12)	

LSM	-0.70	-0.98	0.5350
HbA1c %- baseline Mean (SD)	5.23 (0.50)	5.27 (0.47)	
HbA1c %- change from baseline Mean (SD) LSM	0.07 (0.37) 0.09	0.08 (0.54) 0.07	0.6789

Source: ISS, Tables 111, 112, 113, and 114.

Shifts in FBG

Main Phase

Table 63 depicts the changes in the relative proportions of patients with normal FBG, glucose intolerance (i.e. IFG/IGT), and diabetes mellitus at specific timepoints during the Main Phase. At baseline, the two groups had virtually identical proportions of patients with normal FBG (53%), glucose intolerance (38%) and DM (7-8%). The percentage of patients with glucose intolerance increased in the tesamorelin group from 38.9% at baseline to 45.6%, 44.9%, 53.8%, and 43.6% during subsequent measurements (Week 6 through Week 26). In contrast, the percentages of patients with glucose intolerance in the placebo group remained, with one exception at Week 19, about the same (39.9%, 33.5%, 48.7%, and 38.1%). The percentage of patients with DM increased minimally on treatment in the tesamorelin group and was only slightly higher than that in the placebo arm.

Table 63 Proportion of Patients with Normal BG, IFG/IGT, or DM at Baseline and Week 26 – Main Phase of Pivotal Studies (Both Studies Combined)

	Status	Tesamorelin N=543 n (%)	Placebo N=263 N (%)
Baseline	Normal	290 (53.7)	140 (53.8)
	IFG/IGT	210 (38.9)	99 (38.1)
	DM	40 (7.4)	21 (8.1)
Week 6	Normal	109 (47.8)	64 (54.2)
	IFG/IGT	104 (45.6)	47 (39.9)
	DM	15 (6.6)	7 (5.9)
Week 13	Normal	228 (48.7)	142 (64.3)
	IFG/IGT	210 (44.9)	74 (33.5)
	DM	30 (6.4)	5 (2.3)
Week 19	Normal	85 (38.5)	54 (46.2)
	IFG/IGT	119 (53.8)	57 (48.7)
	DM	17 (7.7)	6 (5.1)
Week 26	Normal	193 (47.3)	108 (53.5)
	IFG/IGT	178 (43.6)	77 (38.1)
	DM	37 (9.1)	17 (8.4)

Sources: LIPO-010 Table 14.3.4.5.1c. LIPO-011 Table 14.3.4.5.1c

Normal = FBG < 100 mg/dL, or OGTT < 140

IGT = 100 mg/dL ≤ FBG ≤ 125, or 140 ≤ 2-hr OGTT ≤ 199

DM = FBG > 125, or OGTT > 199

Table 64 looks at shifts during the Main Phase in terms of the number of times individual patients shifted into a “worse” category of glycemic control compared with their baseline evaluation. As an example, if a patient started in the “normal” blood glucose category and had two subsequent evaluations that were in a more severe category (either IFG/IGT or DM), that was considered two shifts. Importantly, this analysis was conducted only in the subgroup of patients who completed the trial in an attempt to remove the effect of incomplete data contributed by dropouts. The data shows that compared with placebo, patients in the tesamorelin group tended to shift more often with 14.1% experiencing two shifts (compared with 12.4% of placebo patients) and 17.3% experiencing ≥ 3 shifts (compared with 7.5% of placebo patients). In contrast, fewer tesamorelin-treated patients did not have any shifts (49.2%), as opposed to 60.8% of placebo-treated patients.

Table 64 Shifts* in FBG – Main Phase of Pivotal Trials (Both Trials Combined), Completers Only

Number of Shifts	Tesamorelin N=370	Placebo N=186
0	182 (49.2)	113 (60.8)
1	72 (19.5)	36 (19.4)
2	52 (14.1)	23 (12.4)
≥ 3	64 (17.3)	14 (7.5)

*Defined as number of times patient had FBG in a higher category compared to baseline during Main Phase

Extension Phase

Table 65 depicts the relative percentage of patients with normal BG, impaired glucose tolerance, or DM using again applicant’s Definition 1. Because of the baseline imbalance between the T-T and T-P group, descriptive comparisons may be more informative when made within the same treatment group. Patients in the T-T group did not tend to shift into a more severe category during the extension phase (50.6% and 52.7% had normal glucose tolerance at Weeks 26 and 52, respectively). Furthermore, the data indicates that in comparison with the T-T group, a greater percentage of patients in the T-P group shifted into a category of improved glucose tolerance: while 39.4% had normal glucose tolerance at Week 26, this increased to 50.5% at Week 52. This shift was most pronounced shortly after discontinuation of tesamorelin (with an increase in percentage of patients with normal glucose tolerance from 39.4% to 52.1% from Weeks 26 to 32) and remained steady from Weeks 39-52.

Table 65 Proportion of Patients with Normal BG, IFG/IGT, or DM – Extension Phase of Pivotal Studies (Both Studies Combined)

	Status	T-T N=246 n (%)	T-P N=135 n (%)
Week 26	Normal	121 (50.6)	52 (39.4)
	IFG/IGT	101 (42.3)	67 (50.8)
	DM	17 (7.1)	13 (9.8)
Week 32	Normal	98 (44.1)	61 (52.1)
	IFG/IGT	113 (50.9)	54 (46.2)
	DM	11 (5.0)	2 (1.7)
Week 39	Normal	116 (51.3)	63 (53.4)

	IFG/IGT	99 (43.8)	50 (42.4)
	DM	11 (4.9)	5 (4.2)
Week 45	Normal	102 (47.2)	57 (54.8)
	IFG/IGT	102 (47.2)	43 (41.3)
	DM	12 (5.6)	4 (3.9)
Week 52	Normal	107 (52.7)	50 (50.5)
	IFG/IGT	85 (41.9)	40 (40.4)
	DM	11 (5.4)	9 (9.1)

Sources: LIPO-010 Table 14.6.4.5.1c LIPO-012 Table 14.3.4.5.1c

Normal = FBG < 100 mg/dL, or OGTT < 140

IGT = 100 mg/dL ≤ FBG ≤ 125, or 140 ≤ 2-hr OGTT ≤ 199

DM = FBG > 125, or OGTT > 199

Table 66 looks at shifts during the Extension Phase in terms of the number of times individual patients shifted into a “worse” category of glycemic control compared with their baseline evaluation. For example, if a patient started in the “normal” blood glucose category and had two subsequent evaluations that were in a more severe category (either IFG/IGT or DM), that was considered two shifts. In an attempt to remove the partial data contributed by dropouts, this analysis was conducted only in the subgroup of patients who completed the trial. The data shows that compared with T-P, T-T patients tended to shift more often with 13.7% experiencing two shifts (compared with 8.4% of T-P patients) and 12.6% experiencing ≥3 shifts (compared with 3.6% of T-P patients). Fewer T-T patients (57.1%) did not have any shifts over the course of the Extension Phase, as opposed to 68.7% of T-P patients.

Table 66 Shifts* in FBG – Extension Phase of Pivotal Trials (Both Trials Combined)

Number of Shifts	T-T N=182	T-P N=83
0	104 (57.1)	57 (68.7)
1	30 (16.5)	16 (19.3)
2	25 (13.7)	7 (8.4)
≥3	23 (12.6)	3 (3.6)

Baseline extension: latest available value prior to re-randomization and up to Week 13

*Defined as number of times patient had FBG in a higher category compared to baseline during Extension Phase

Source: Sponsor’s Table

Shifts in Hemoglobin A1c

Main Phase

Table 67 shows the proportion of patients at baseline, Week 13, and Week 26 in the tesamorelin and placebo groups with HbA1c levels considered in the “normal,” “pre-diabetes,” or “diabetes mellitus” range as per the 2010 ADA recommendations. At baseline, similar percentages of patients were in each category in the tesamorelin and placebo groups. By Week 13 and 26, there were more patients in the diabetes category in the tesamorelin group (5.4% and 6.6%, respectively) when compared to placebo (1.9% and 2.5%, respectively). The differences in the pre-diabetes category were minimal.

Table 67 Proportion of Patients with Normal BG, Pre-Diabetes, or DM (based on HbA1c) – Main Phase of Pivotal Studies (Both Studies Combined)

	Status	Tesamorelin N=543 n (%)	Placebo N=263 n (%)
Baseline	Normal	414 (79.0)	200 (78.4)
	Pre-Diabetes	99 (18.9)	52 (20.4)
	DM	11 (2.1)	3 (1.2)
Week 13	Normal	322 (71.9)	167 (79.1)
	Pre-Diabetes	102 (22.8)	40 (19.0)
	DM	24 (5.4)	4 (1.9)
Week 26	Normal	277 (70.1)	149 (74.9)
	Pre-Diabetes	92 (23.3)	45 (22.6)
	DM	26 (6.6)	5 (2.5)

Normal = A1c < 5.7%

Pre-Diabetes = 5.7% ≤ A1c < 6.5%

DM = A1c ≥ 6.5%

Source: Table From Sponsor

Table 68 looks at shifts in HbA1c during the Main Phase in terms of the number of times individual patients (completers only) shifted into a “worse” category of glycemic control compared with their baseline evaluation. In other words, if a patient started in the “normal BG” category and had two subsequent evaluations that were in a more severe category (either pre-diabetes or DM), that was considered two shifts. The data shows that compared with placebo, patients in the tesamorelin group tended to shift more often, with 17.5% experiencing one shift (compared with 13.9% of placebo patients) and 9.0% experiencing two shifts (compared with 3.1% of placebo patients). In contrast fewer tesamorelin-treated patients did not have any shifts over the course of the Main Phase (73.5%), as opposed to 83.0% of placebo-treated patients.,

Table 68 Shifts* in HbA1c – Main Phase of Pivotal Trials (Both Trials Combined): Patients With Datapoints Across All Timepoints

Number of Shifts	Tesamorelin N=389	Placebo N=194
0	286 (73.5)	161 (83.0)
1	68 (17.5)	27 (13.9)
2	35 (9.0)	6 (3.1)

Data are presented as n (%)

*Defined as number of times patient had HbA1c in a higher category compared to baseline during Main Phase

Normal: A1c < 5.7%

Pre-Diabetes: 5.7% ≤ A1c < 6.5%

DM: A1c ≥ 6.5%

Statistical analysis of patients who developed diabetes during the trial using the 2010 ADA HbA1c definition

In response to a request from the clinical team, the FDA statistical reviewer compared the number of patients who developed an HbA1c level ≥ 6.5% during the Main Phase in the tesamorelin and placebo arms; she used an Exact test applied to the safety population for the Week 26 timepoint using last-observation-carried-forward data. The analysis was

stratified by study and indicates that tesamorelin “was statistically significantly different than placebo in the percentage of patients with diabetes (p=0.004) after 26 weeks of treatment.” Similar results were obtained when excluding patients with baseline HbA1c \geq 6.5%. The Odds Ratio (95%CI) was 3.6 (1.5, 12.0) without exclusion of baseline cases and 3.4 (1.3, 11.5) after excluding patients with baseline HbA1c \geq 6.5%.

Extension Phase

Table 69 shows the proportion of patients at Week 26, Week 39, and Week 52 in the T-T and T-P groups with HbA1c levels considered in the “normal,” “pre-diabetes,” or “diabetes mellitus” range. There were no striking differences between groups. Within the T-T group there were no major changes from baseline to timepoint (except for a reduction in the percentage of patients with diabetes at the Week 52 timepoint). The T-P group showed a trend toward reduction of the percentage of patients with prediabetes or DM.

Table 69 Proportion of Patients with Normal BG, Pre-Diabetes, or DM (based on HbA1c) – Extension Phase of Pivotal Studies (Both Studies Combined)

	Status	T-T N=246 n (%)	T-P N=135 n (%)
Week 26	Normal	180 (73.2)	97 (71.9)
	Pre-Diabetes	54 (22.0)	31 (23.0)
	DM	12 (4.9)	7 (5.2)
Week 39	Normal	166 (78.3)	89 (80.9)
	Pre-Diabetes	37 (17.5)	18 (16.4)
	DM	9 (4.2)	3 (2.7)
Week 52	Normal	146 (74.5)	75 (79.8)
	Pre-Diabetes	47 (24.0)	15 (16.0)
	DM	3 (1.5)	4 (4.3)

Baseline extension: latest available value prior to re-randomization and up to Week 13

Normal = A1c < 5.7%

Pre-Diabetes = 5.7% \leq A1c < 6.5%

DM = A1c \geq 6.5%

Source: Table From Sponsor

Table 70 looks at shifts in HbA1c during the Extension Phase in terms of the number of times individual patients (completers only) who shifted into a “worse” category of glycemic control compared with their baseline evaluation. As an example, if a patient started in the normal HbA1c category and had 2 subsequent evaluations that were in a more severe category (either pre-diabetes or DM), that was considered 2 shifts. The data do not indicate any major differences between groups.

Table 70 Shifts* in HbA1c – Extension Phase of Pivotal Trials (Both Trials Combined): Patients With Datapoints Across All Timepoints

Number of Shifts	T-T N=187	T-P N=88
0	171 (91.4)	80 (90.9)
1	15 (8.0)	6 (6.8)
2	1 (0.5)	2 (2.3)

Data are presented as n (%)

Baseline extension: latest available value prior to re-randomization and up to Week 13

*Defined as number of times patient had HbA1c in a higher category compared to baseline during Main Phase

Normal: A1c < 5.7%

Pre-Diabetes: 5.7% ≤ A1c < 6.5%

DM: A1c ≥ 6.5%

Source: Table From Sponsor

Glucose metabolism – Summary and Conclusions:

During the Main Phase of the trials:

- There were no clinically meaningful changes in mean values for fasting blood glucose, fasting insulin, HOMA-IR and HbA1c at Week 26 between tesamorelin- and placebo-treated patients.
- At post-baseline evaluations, there was a trend of worsening glucose status in individual patients treated with tesamorelin as indicated by the larger proportions of patients who shifted from normal fasting blood glucose or HbA1c to abnormal values (in the range of glucose intolerance, prediabetes, or DM) relative to placebo.
- There was a statistically significant difference in the proportion of patients who developed DM in the tesamorelin group relative to placebo: Odds Ratio (95%CI) of 3.4 (1.3, 11.5) or 3.6 (1.5, 12.0) depending on whether baseline DM cases were excluded or not.

During the Extension Phase of the trials there were no convincing data to indicate deterioration in the glucose status in patients who were continued on tesamorelin, while patients who were switched to placebo seemed to remain stable or slightly improve. This observation has to take into consideration that the potential effect of dropouts is not known.

7.3.5.7 Immunogenicity

Immunogenicity testing

Immunogenicity testing during the Phase 3 trials aimed primarily at establishing whether patients treated with tesamorelin developed anti-tesamorelin antibodies, if such antibodies cross-react with endogenous GHRH, and whether they develop neutralizing capacity. The algorithm for immunogenicity testing is depicted in Figure 27. The applicant indicates that, regardless of treatment assignment, all patients enrolled in the Phase 3 clinical trials were tested for the presence of anti-tesamorelin antibodies (blood samples for immunological assessments were collected at baseline, weeks 6, 13, 26 for

the Main Phase, weeks 32, 39 and 52 or at early termination for the Extension Phase⁵). All antibody-positive subjects were also assessed to see if they cross-reacted to endogenous GHRH.

Patients who were found to be anti-tesamorelin antibody positive were tested for neutralizing activity against both tesamorelin and endogenous GHRH using an *in vitro* bio-assay⁶. Anti-tesamorelin neutralizing antibody testing was not performed in all antibody positive patients and not at all timepoints when such antibodies were measured (see above) but only in the following:

- All patients from the T-T group who were anti-tesamorelin antibody-positive at Week 52 (or at end of trial); testing was done for the Week 52 or end-of-trial timepoint.
- All patients from non T-T groups (i.e. T-P and P-T) who were anti-tesamorelin antibody positive following 26 weeks of actual tesamorelin treatment; thus, testing was done on samples at Week 26 for the T-P group and Week 52 for the P-T group.

It appears that the applicant was concerned with performing the antibody testing at the time of the longest exposure to tesamorelin and that this is the unifying concept for the above-described testing plan; simpler said, all patients were tested at the last timepoint of tesamorelin treatment. In the process not all patients randomized to tesamorelin in the Main Phase were tested at the same time: those who were re-randomized to tesamorelin were tested at Week 52 while those re-randomized to placebo were tested on a sample obtained at Week 26.

Anti-GHRH neutralizing antibody testing was performed in the following group of patients:

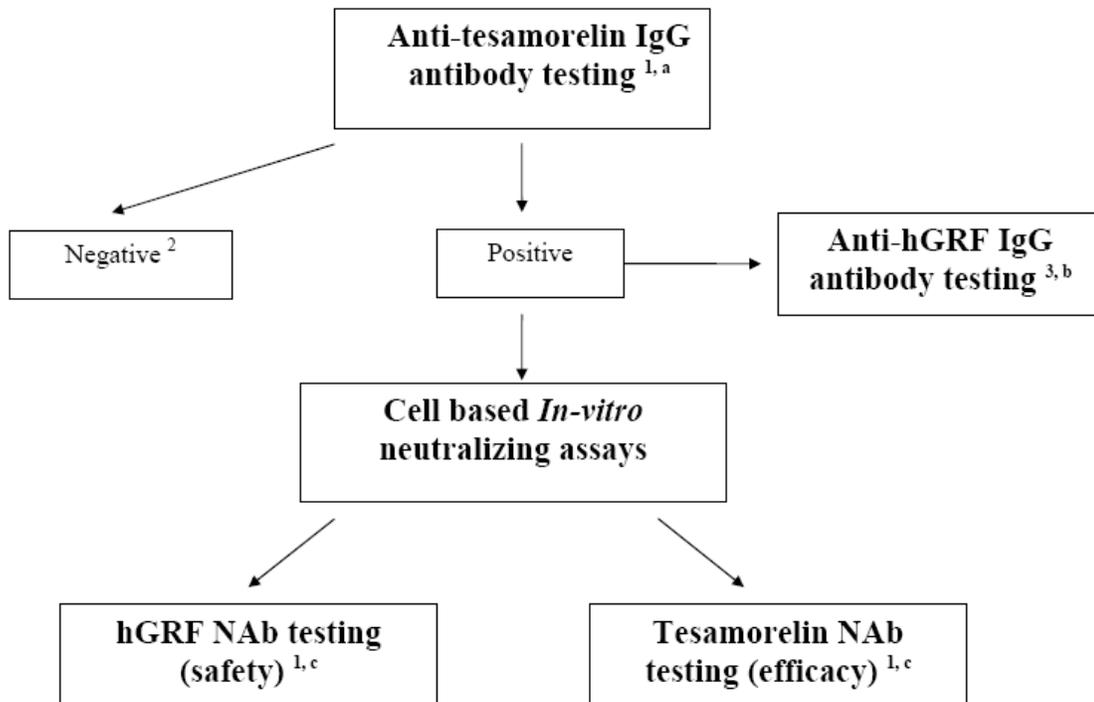
- All patients who were treated with tesamorelin for 52 weeks (T-T group) who were anti-tesamorelin antibody-positive at Week 52 (or at end of trial); testing was done only for the Week 52 (or end-of-trial) timepoint.
- All patients from non T-T groups (i.e. T-P and P-T) who were anti-tesamorelin antibody positive following 26 weeks of actual tesamorelin treatment; thus, testing was done on samples at Week 26 for the T-P group and Week 52 for the P-T group.
- All patients who had received tesamorelin for 6 months, were re-randomized to placebo (T-P group) and who, after a total of 52 weeks on trial (six months on treatment and 6 months off treatment) were still anti-tesamorelin antibody positive; for this group testing was done on paired samples: Week 26 and Week 52.
- All patients who experienced a hypersensitivity reaction during the trial and who were anti-tesamorelin antibody positive at the last visit.

⁵ Study 12 had an additional timepoint at Week 32.

⁶ Neutralizing activity was tested via an *in-vitro* cell based assay developed from a cell-line that expresses human GHRH receptors. In this cell line, as under physiological conditions, GHRH binds to the GHRH receptors and initiates a series of intracellular events that includes induction of cyclic adenosine monophosphate (cAMP) production. When this assay is performed in the presence of serum containing neutralizing antibodies, the cAMP response is blunted. Since both GHRH and tesamorelin bind to the receptor, either of them can be used in the assay and thus neutralizing antibodies to either of them can be detected.

Of note, the timepoints selected for testing of anti-GHRH neutralizing antibodies were not entirely the same as those previously described for anti-tesamorelin neutralizing antibodies. While all patients in the T-T and P-T groups were tested at Week 52, and all patients in the T-P group were tested at Week 26 (if anti-tesamorelin antibody positive), patients in the T-P group had an additional testing algorithm. If these patients were found to have positive anti-tesamorelin antibodies at Week 52, then they were tested for anti-GHRH neutralizing antibodies at both Weeks 26 and 52.

Figure 29 General Immunogenicity Analysis Scheme for Pivotal Trials



Source: Sponsor's Figure from Immunogenicity Report

Anti-tesamorelin Antibodies

Main Phase

Percentage of patients who developed anti-tesamorelin antibodies

All patients who participated in the Phase 3 pivotal studies were assessed for the presence of anti-tesamorelin antibodies⁷ (Table 71). At baseline, the majority of patients were anti-tesamorelin antibody negative (97.7% in the tesamorelin and 97.2% placebo group, respectively); of the few patients who were anti-tesamorelin antibody positive at baseline,

⁷ The assay was an ligand binding assay (ELISA) where 96-well plates were coated with tesamorelin and, after exposure to test serum anti-tesamorelin antibodies were detected with a goat anti-human horseradish peroxidase. The assay had a screening step (described above), followed by a confirmatory step using drug competition with an excess concentration of tesamorelin. Step 3 consisted in a establishing the titers using a scheme based on sequential dilution: aamples were first diluted 1/25 which is why 25 is the lowest titer in the assay. The applicant presented titers as "low" (25-200) and "high" (≥ 400) "based on the literature".

the vast majority had low titers and only one per group had “high” titers (defined as ≥ 400). By Week 26, nearly half of all patients in the tesamorelin group (49.5%) became anti-tesamorelin antibody positive, compared with only 3% in the placebo group. Of the patients in the tesamorelin group who tested positive for anti-tesamorelin antibodies, the majority (49%) had “low” titers (0-50); 32% had titers of 100-200 (labeled also as “low” by the applicant) and 18.8% had titers ≥ 400 .

Table 71 Antibody Status and Titers at Baseline and Week 26 – Main Phase of Pivotal Studies (Both Studies Combined)

		Tesamorelin N=543	Placebo N=263
Baseline	Absent	511 (97.7%)	246 (97.2)
	Present	11 (2.1)	7 (2.8)
	0-50 (Low)	9 (1.7)	5 (2.0)
	100-200 (Low)	1 (0.2)	1 (0.4)
	≥ 400 (High)	1 (0.2)	1 (0.4)
Week 26	Absent	206 (50.5%)	196 (97.0)
	Present	202 (49.5)	6 (3.0)
	0-50 (Low)	99 (49.5)	5 (83.3)
	100-200 (Low)	65 (32)	1 (16.7)
	≥ 400 (High)	38 (18.8)	0

Source: ISS Table 129

VAT reduction by antibody status and antibody titer

To assess the clinical impact of anti-tesamorelin antibodies, the changes in VAT in antibody-positive and antibody-negative patients were compared (Table 72). The mean percent VAT change from baseline was similar for patients receiving tesamorelin regardless of antibody status and not statistically different.

Table 72 Percent Change in VAT as a Function of anti-Tesamorelin Antibody Status – Main Phase of Pivotal Studies (Both Studies Combined)

	Tesamorelin N=543	
	Antibody positive	Antibody negative
Baseline VAT (cm ²)		
N	11	508
Mean	178.13	182.22
(SD)	(75.33)	(82.27)
Week 26 VAT (cm ²)		
N	200	206
Mean	150.19	162.54
(SD)	(79.43)	(83.24)
% VAT change		
N	200	206
Mean	-15.47	-16.40
(SD)	(22.20)	(22.51)
LSM	-18.4	-19.4
P-Value ^a	0.662	

Source: ISE Tables 5.7b, 5.17

*LSM provided in Table is the exponentiation of the LSM from the statistical model minus one, expressed as a percentage, ie (exp (LSM from model)-1)x100

^aP-value for LSM change from baseline to Week 26 (between group).

Comparisons of VAT change between the subgroups of antibody-positive patients by titers (low to high) indicate that such changes are comparable regardless the magnitude of antibody titer elicited. Specifically the Week 26 percent change in VAT (least square mean) for titers of 0-50, 100-200, and ≥ 400 was -12.2, -14.6, and -11.4, respectively.

The applicant also conducted a comparison of VAT change between antibody-positive and antibody-negative patients who met the prespecified definition of responders (i.e. patients who experienced a decline in VAT at Week 26 of $\geq 8\%$ relative to their baseline value). These results are presented in Table 73. According to this analysis similar percentages of non-responders (“failure” to respond by this criterion) were in the antibody-positive (33.5%) and antibody-negative groups (29.1%). It is interesting to note that although in pivotal Study 10, the percentages of non-responders is similar in antibody-positive and antibody-negative patients (26.0% vs. 30.5%, respectively), there is a greater disparity in Study 11 (41.7% of antibody-positive patients were non-responders, compared to 27.7% of antibody-negative subjects).

Table 73 VAT Responder Status at Week 26 as a Function of anti-Tesamorelin IgG Antibody Status Among Tesamorelin-Treated Patients - Main Phase of Pivotal Studies (Both Studies Combined)

	Responder n (%)	Non-Responder n (%)
Antibody Positive (N=200)	133 (66.5)	67 (33.5)
Antibody Negative (N=206)	146 (70.9)	60 (29.1)
P-Value	0.392	

Source: ISE Table 5.5

IGF-1 changes by antibody status and antibody titer

Table 74 presents the changes in IGF-1 levels according to antibody status. The results indicate that the IGF-1 percent change from baseline was virtually identical for antibody-positive and antibody-negative patients (123.04 ng/mL vs. 125.93 ng/mL).

Table 74 Change in IGF-1 as a Function of anti-Tesamorelin Antibody Status – Main Phase of Pivotal Studies (Both Studies Combined)

	Tesamorelin N=543	
	Antibody positive	Antibody negative
Baseline IGF-1 (ng/ml)		
N	534	534
Mean	153.70	153.70
(SD)	(62.89)	(62.89)
Week 26 IGF-1 (ng/ml)		
N	202	206
Mean	275.78	281.31
(SD)	(129.11)	(118.68)
IGF-1 change (ng/ml)		
N	197	203
Mean	123.04	125.93
(SD)	(124.56)	(101.37)
LSM	123	126

P-Value^a	0.85
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Source: ISE Tables 5.7b, 5.17

*LSM provided in Table is the exponentiation of the LSM from the statistical model minus one, expressed as a percentage, ie (exp (LSM from model)-1)x100

^aP-value for LSM change from baseline to Week 26 (between group)

The changes from baseline were also similar among the patients with different antibody titers: 120.21 ng/ml, 120.95 ng/ml, and 133.32 ng/ml for patients with titers of 0-50, 100-200, and ≥ 400 , respectively.

Extension Phase

Tesamorelin-tesamorelin (T-T) group

As shown in Table 75, at Week 26 slightly less than half of all patients in the T-T group (45.2%) had anti-tesamorelin antibodies. At Week 52, there was virtually no change from the Week 26 observation, as nearly half of all patients in the T-T group (47.4%) still had anti-tesamorelin antibodies. In contrast, among patients who received tesamorelin for 26 weeks and subsequently were re-randomized to placebo, the percentage of antibody-positive patients declined to 18.3% (from 55.6% at Week 26). In the T-T group most patients had low titers of antibody and 10.7% had titers ≥ 400 at Week 52. Similarly, most antibody-positive patients in the T-P group had low titers at Week 52 with only 5.8% having titers ≥ 400 .

Table 75 IgG Antibody Status and Titers at Weeks 26 and 52 – Extension Phase of Pivotal Studies (Both Studies Combined)

		T-T N=246	T-P N=135
Baseline n (%)	Absent	239 (98)	126 (96.9)
	Present	3 (1.2)	4 (3.1)
	0-50 (Low)	3 (100)	3 (75)
	100-200 (Low)	0	0
	≥ 400 (High)	0	1 (25)
Week 26 n (%)	Absent	131 (54.8)	59 (44.4)
	Present	108 (45.2)	74 (55.6)
	0-50 (Low)	59 (54.6)	32 (43.4)
	100-200 (Low)	30 (27.8)	30 (40.5)
	≥ 400 (High)	19 (17.6)	12 (16.1)
Week 52 n (%)	Absent	103 (52.6)	76 (81.7)
	Present	93 (47.4)	17 (18.3)
	0-50 (Low)	64 (68.8)	10 (58.8)
	100-200 (Low)	19 (20.4)	5 (29.4)
	≥ 400 (High)	10 (10.7)	1 (5.8)

Source: ISS Table 130

The percentage of VAT reduction was similar between antibody positive and antibody-negative patients in the T-T group (-18.9% vs. -20.2% descriptively and -24.1 % vs. -23.4% using least square means). This was the case for IGF-1 changes as well (79.5 ng/ml for antibody-positive and 88 ng/ml for antibody-negative patients; least square means: 86.1 ng/ml vs. 88.2 ng/ml). The IGF-1 change by antibody titer was virtually the same for the 0-50 and 100-200 groups (56.6 ng/ml vs. 54.3 ng/ml, respectively) and, in

fact, higher for the ≥ 400 group (82.1); as the number of patients in each subgroup decreased, not surprisingly one can expect more variability of the data.

Placebo-tesamorelin (P-T group)

This treatment arm is of interest because it represents tesamorelin-naïve patients and one can expect an immunogenicity response similar to that seen through Week 26 in the tesamorelin group in the Main Phase. Indeed, after six months of tesamorelin treatment (Week 52 of the trial) 60.2% of patients had anti-tesamorelin antibodies; most patients had low titers of antibody and 11.5% had titers ≥ 400 .

The percent change in VAT at this timepoint was -15.8 for antibody positive patients and -11.9% for antibody negative patients with LSM of -20.2% versus -14.8%, respectively. The IGF-1 changes were slightly higher in antibody-positive patients (93.6 ng/ml vs. 76.5 ng/ml in the antibody negative group) but the LSM were not very different (91.1 ng/ml vs. 88.2 ng/ml). The IGF-1 changes in subgroups of antibody titers did not show a concerning trend; with the number of patients getting smaller with each subsequent subgroup, and there is more variability in data.

Neutralizing Antibodies to Tesamorelin

Refer to the beginning of this section for a description of the selection criteria for testing. In the T-T group, 122/246 (49.6%) patients were positive for anti-tesamorelin antibodies at Week 52. Of these patients, 24/246 (9.7%) were found to be positive for anti-tesamorelin neutralizing activity *in vitro*; most had low antibody titers: 13 of them had titers of 25; seven patients had titers of 50; two patients had titers of 200; and only two patients had titers of ≥ 400 .

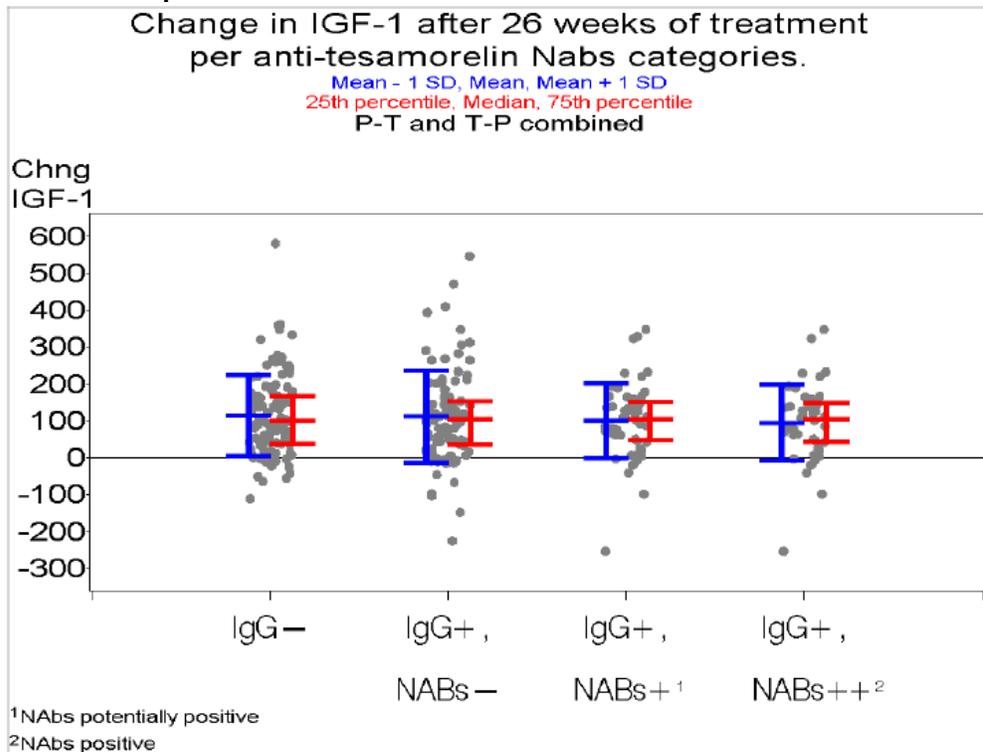
For patients in the non-T-T groups (i.e. T-P and P-T groups combined) 171/297 (58%) were anti-tesamorelin antibody-positive at the end of 6 months of treatment. Of these, 54/297 (18%) were also found to have anti-tesamorelin neutralizing antibodies *in vitro*; most had low titer antibodies: 35 had titers of 25; eight patients had titers of 50; four patients had titers of 200; and three subjects had titers of ≥ 400 .

A description of the time-course of developing neutralizing antibodies cannot be made because the applicant has tested for neutralizing antibody activity only at a single timepoint in the trial (Week 52 for the T-T arm after 26 weeks of treatment with tesamorelin for the other arms). Neither can one tell, in absence of sequential data in the same patient, whether these positive, mostly low-titer samples would be consistently positive in the same patient if tested sequentially; or would be seen inconsistently in various other patients instead, because of assay specificity. The applicant's suggestion that the "results suggest that prolonged treatment [52 weeks] with tesamorelin does not lead to an increase in tesamorelin neutralizing antibodies compared to those receiving drug for 26 weeks" is not substantiated by the data since there are no data points presented at Week 26 in the T-T arm to compare them with the Week 52 timepoint within the same arm; extrapolating the results of the combined T-P and P-T arms does not seem appropriate.

In support of the contention that anti-tesamorelin neutralizing antibodies do not have a significant impact on the activity of tesamorelin, the applicant has provided a series of graphs presenting descriptive data (means, SD, percentile, individual datapoints) regarding IGF-1 changes at Weeks 26, and Week 52, as well as the effect on VAT reduction at the same timepoints. The graphs include for comparison data in patients who did not develop anti-tesamorelin antibodies, along with data in patients with anti-tesamorelin antibodies (with or without neutralizing antibodies).

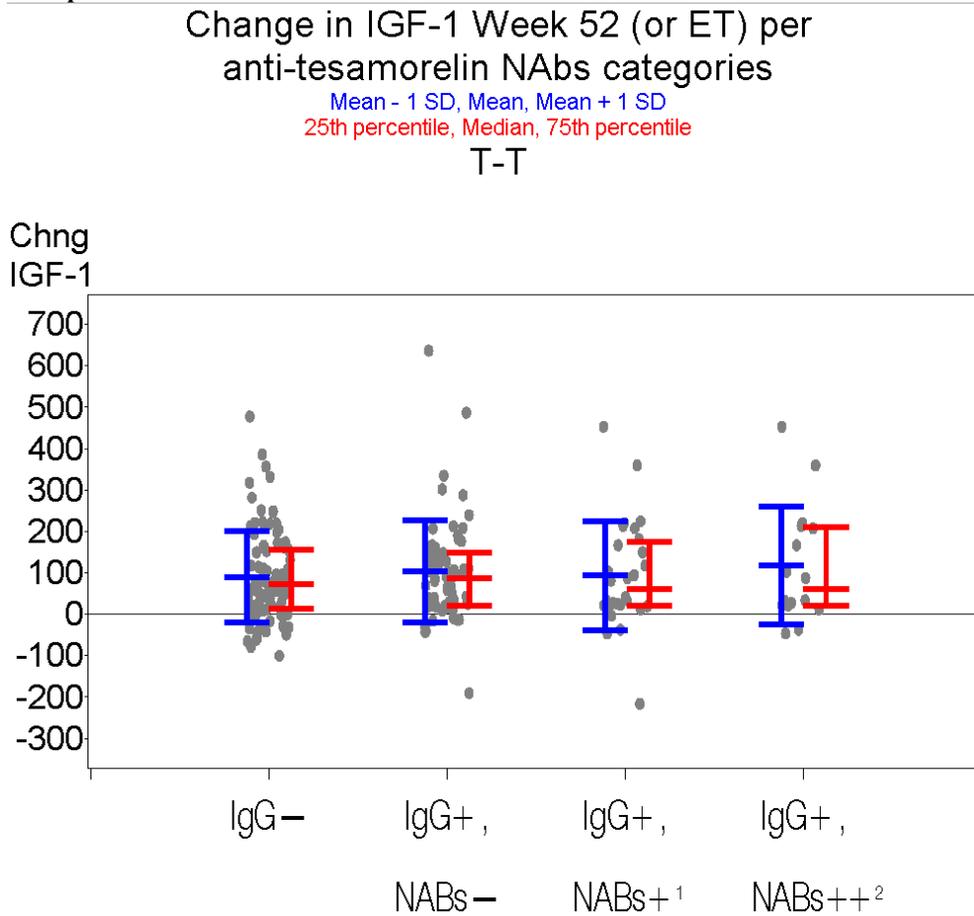
Figures 30 and 31 below show the effect of tesamorelin neutralizing antibodies on IGF-1. These figures illustrate the IGF-1 profiles for patients who did not develop anti-tesamorelin antibodies (“IgG-”) along with patients who developed anti-tesamorelin antibodies but not neutralizing antibodies (“IgG+, NABs-”) and patients who developed both anti-tesamorelin antibodies and neutralizing antibodies (“potentially positive” or “IgG+,NABs+” and “positive” “IgG+,NABs++”). Figure 30 presents data collected for the P-T and T-P arms combined and Figure 31 for the T-T arm only. Qualitatively, these indicate similar IGF-1 profiles for patients with and without neutralizing antibodies.

Figure 30 Change in IGF-1 After 26 Weeks of Treatment Based on Tesamorelin NAb Status – T-P and P-T Groups



Source: Sponsor's Figure from Immunogenicity Report

Figure 31 Change in IGF-1 After 52 Weeks of Treatment Based on Tesamorelin NAb Status – T-T Group



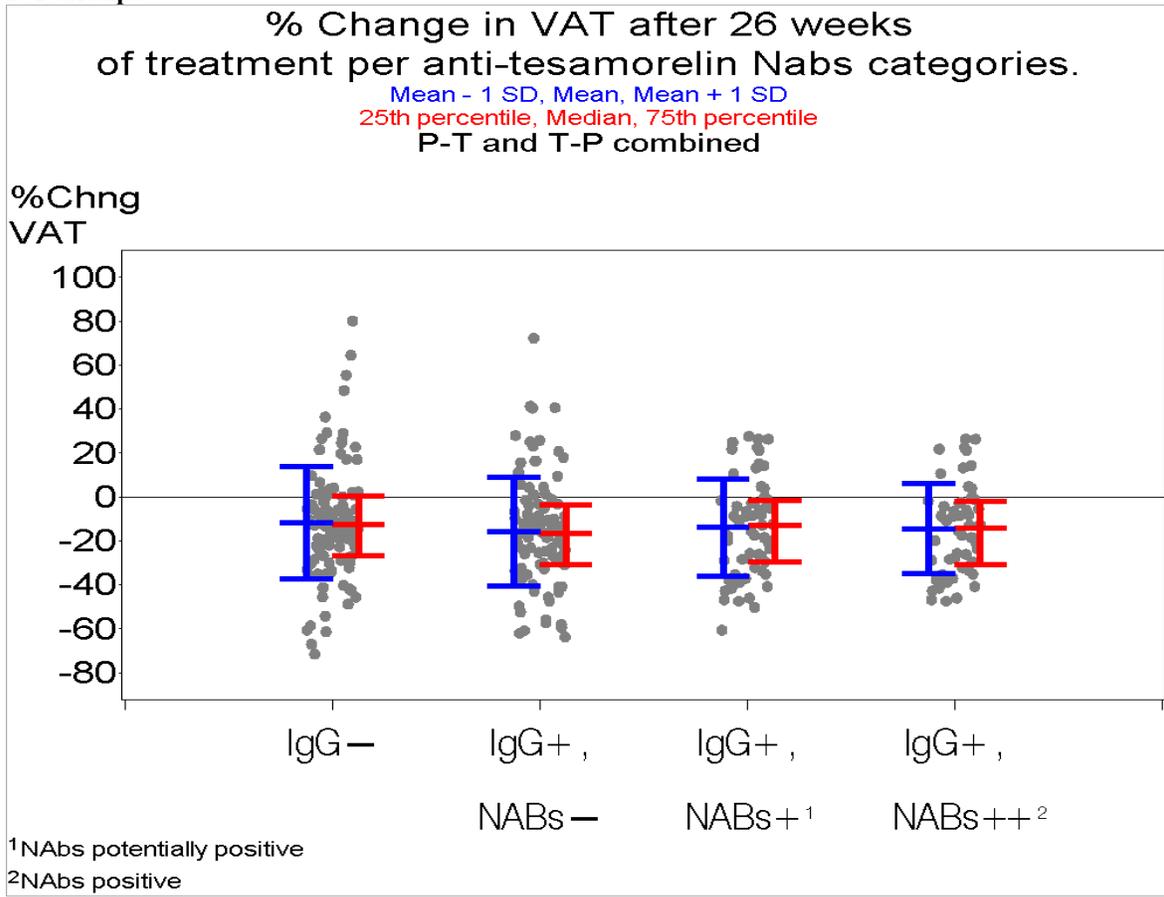
¹NABs potentially positive

²NABs positive

Source: Sponsor's Figure from Immunogenicity Report

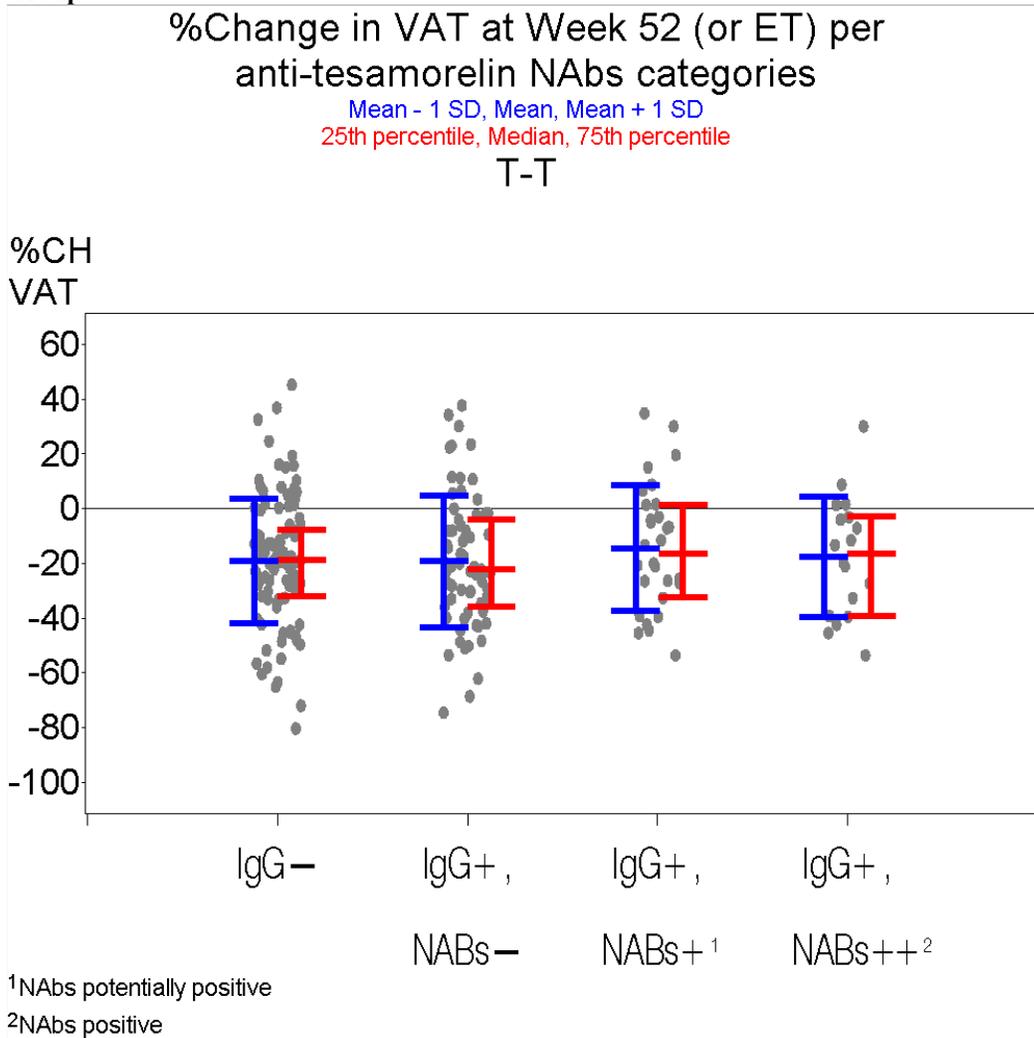
Figures 32 and 33 illustrate the VAT profiles for patients who did not develop anti-tesamorelin antibodies (“IgG-“) along with patients who developed anti-tesamorelin antibodies but not neutralizing antibodies (“IgG+, NABs-“) and patients who developed both anti-tesamorelin antibodies and neutralizing antibodies (“potentially positive” or “IgG+,NABs” and “positive” “IgG+,NABs++”). Figure 32 presents data collected for the P-T and T-P arms combined and Figure 33 for the T-T arm only. Qualitatively, the graphs indicate similar VAT profiles for patients with and without neutralizing antibodies.

Figure 32 Change in VAT After 26 Weeks of Treatment Based on Tesamorelin NAb Status – T-P and P-T Groups



Source: Sponsor's Figure from Immunogenicity Report

Figure 33 Change in VAT After 52 Weeks of Treatment Based on Tesamorelin NAb Status – T-T Group



Source: Sponsor's Figure from Immunogenicity Report

Anti-tesamorelin Antibodies – Cross Reactivity with human GHRH

Patients who developed anti-tesamorelin antibodies were tested for cross-reactivity with human GHRH⁸. This was done on blood samples collected during the last study visit; in situations in which the last sample was not the sample with the highest titer, the latter was also tested⁹. The results are presented in Table 76 by study. The cross reactivity was consistently seen at approximately 60% for each individual study.

⁸ The anti-human GHRH antibody assay was virtually identical to the one use for anti-tesamorelin antibodies, except that the plates were coated with human GHRH and human GHRH was used (rather than tesamorelin) for the competitive binding in the confirmatory stage. Titers were not measured, the goal being to identify the “incidence rate of cross-reactivity of anti-tesamorelin [...] positive subjects”. Samples were analyzed for “time points with highest anti-tesamorelin [...] titer (best chance to detect cross-reactivity) from anti-tesamorelin IgG positive subjects”

⁹ The applicant also states that: “Since study 012 is the Extension of study 011, cross-reactivity with hGRF was tested only for the positive samples from subjects that had not been tested in TH9507-CTR-1011. Only the samples with the highest titer were tested.”

Table 76 Anti-Tesamorelin Antibody Cross-Reactivity with human GHRH – Individual Pivotal Studies

	Study 10 N=248	Study 11 N=139	Study 12 N=69
Anti-human GHRH antibody positive n (%)	149 (60%)	86 (62%)	39 (56%)
Anti-human GHRH antibody negative n (%)	99 (40%)	53 (38%)	30(44%)

Source: Sponsor's Immunogenicity Report

Neutralizing Antibodies to human GHRH

Refer to the beginning of this section for selection of patients for testing. Patients in the T-T group were evaluated only for the 52 week timepoint; therefore no conclusions can be drawn on the temporal development of neutralizing antibodies. In the T-T group 122/246 (49.6%) patients were anti-tesamorelin antibody positive at Week 52. Of these patients, 12/246 (5%) were found to have anti-GHRH neutralizing antibodies in vitro at this timepoint, all with lowest titer (25).

The T-P group included patients who received tesamorelin during the Main Phase and at Month 6 were re-randomized to placebo. At Week 52, patients from this group were tested for the presence of anti-tesamorelin antibodies and those who were antibody-positive were tested for the presence of anti-GHRH neutralizing antibodies on samples from Week 26 and Week 52. At Week 52, 29/135 patients (21%) were anti-tesamorelin antibody positive. Of these 29 patients, 4/135 (3%) had anti-GHRH neutralizing antibodies at Week 26 (3 patients with titers of 25 and one patient with a titer of 100). By Week 52, only 2/135 (1.5%) of these patients had anti-GHRH neutralizing antibodies (one with a titer of 25 and one with a titer of 200).

It should be mentioned that the only instance where neutralizing antibody testing was done at two successive timepoints was in the group just described (T-P group, at Week 26 and Week 52 in a subgroup of patients who were anti-tesamorelin positive at Week 52). The number of patients with positive samples is too small to draw any conclusions (of the 4 patients who had anti-GHRH neutralizing antibodies at Week 26, 2 were negative at Week 52).

In the T-P and P-T groups combined 171/297 (58%) of patients were anti-tesamorelin antibody-positive at the end of treatment (i.e. Week 26 for T-P patients and Week 52 for P-T patients). Of these patients, 12/297 (4 %) were also found to be anti-GHRH neutralizing antibody positive.

In support of the contention that anti-GHRH neutralizing antibodies do not have a significant impact on the activity of tesamorelin, the applicant has provided a series of graphs presenting descriptive data (means, SD, percentiles, individual datapoints) regarding IGF-1 changes at Weeks 26 and 52. These graphs (Figures 34 and 35) illustrate IGF-1 profiles for the antibody-negative and antibody-positive patients (including patients with neutralizing anti-GHRH antibodies). Figure 34 depicts the

change in IGF-1 after 26 weeks of treatment (P-T and T-P groups), while Figure 35 depicts changes after 52 weeks (T-T group). Overall, these graphs suggest qualitatively that the changes in IGF-1 were similar in the anti-neutralizing antibody group and in the groups without neutralizing antibodies (or without any antibodies for that matter). It should be emphasized that the number of patients with anti-GHRH neutralizing antibodies was very small.

Figure 34 Change in IGF-1 After 26 Weeks of Treatment Based on hGRF NAb Status – T-P and P-T Groups

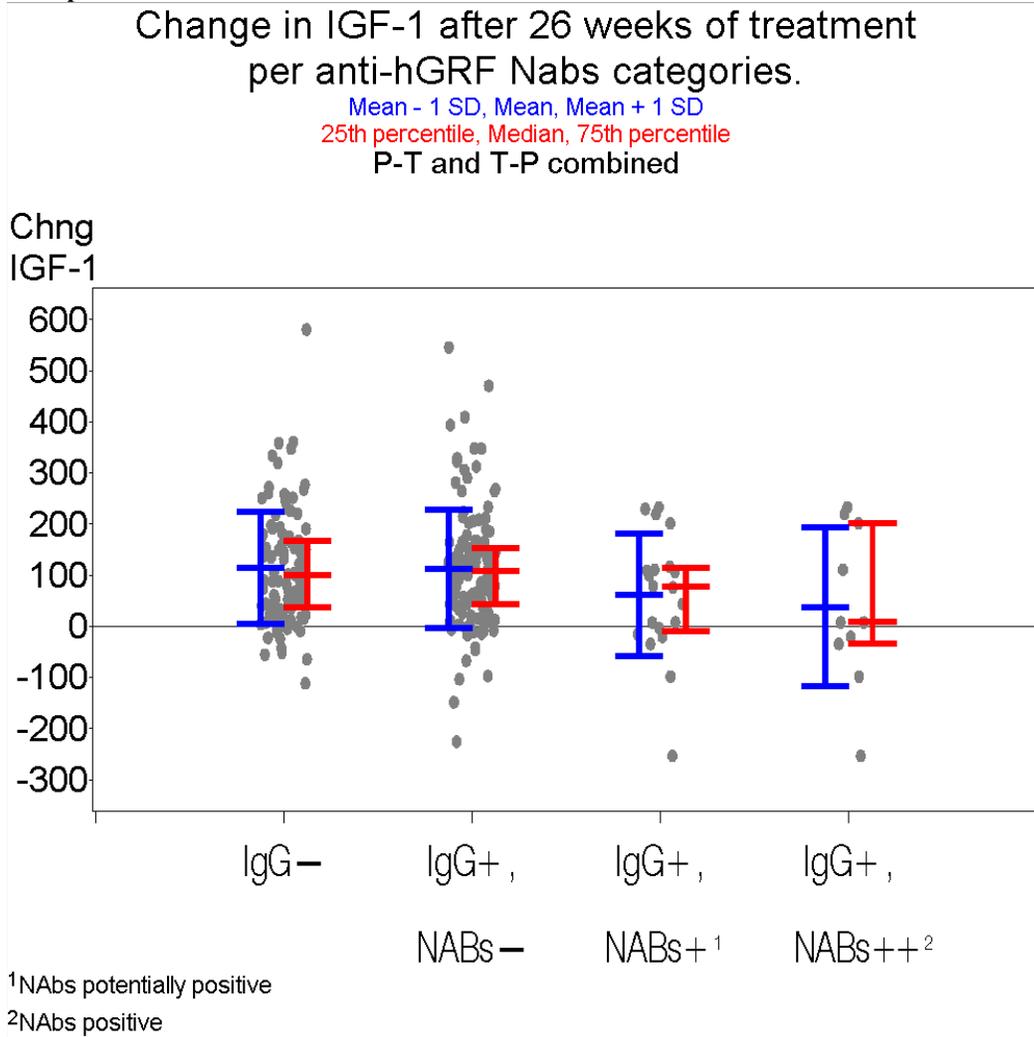
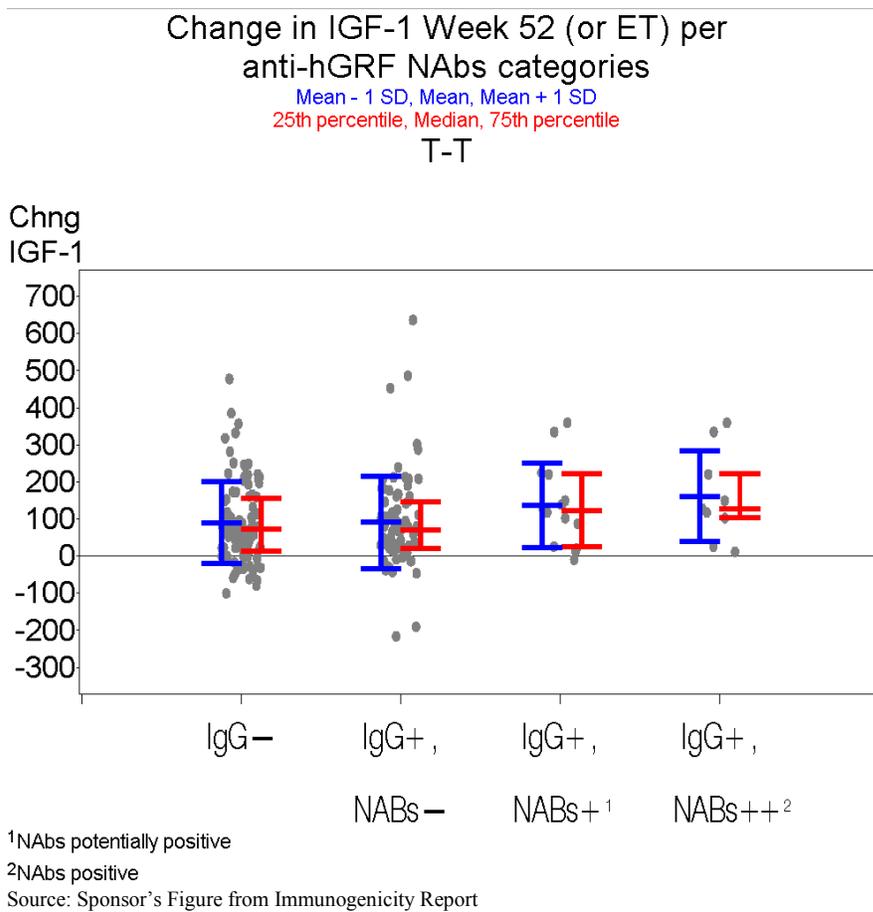


Figure 35 Change in IGF-1 After 26 Weeks of Treatment Based on hGRF NAb Status – T-P and P-T Groups



Summary/conclusions:

In summary, treatment with a fixed tesamorelin daily regimen of 2 mg had the following effect on the development of anti-tesamorelin antibodies:

- Approximately 50% of patients developed anti-tesamorelin antibodies at the end of the 26-week treatment period, with a minority (9.3%) developing high titers (i.e., ≥ 400).
- For patients who continued tesamorelin for an additional 26 weeks, about the same percentage of patients were antibody-positive at Week 52 (45.2% at Week 26 and 47.4% at Week 52).
- For patients who discontinued tesamorelin at the end of the Main Phase, the percentage of patients with anti-tesamorelin antibodies declined from 55.6% at Week 26 to 18.3% at Week 52.
- Comparisons of change from baseline in VAT and IGF-1 between anti-tesamorelin antibody-positive and antibody-negative patients did not show any evidence that the antibodies have any functional consequences.
- Anti-tesamorelin antibodies cross-reacted with endogenous GHRH in approximately 60% of patients.

- In vitro neutralizing antibodies to tesamorelin developed in a subgroup of patients with anti-tesamorelin antibodies (in one group 9.7% at Week 52, in another group 18% following six months of treatment). Most patients had low titers but there were exceptions. Overall, the presence of in vitro anti-tesamorelin neutralizing antibodies did not seem to impact on IGF-1 elevation or VAT reduction.
- In vitro anti-GHRH neutralizing antibodies were observed in a minority of patients with anti-tesamorelin antibodies (5% in a group at Week 52, 4% in a group treated for 26 weeks and tested only at the end of treatment, and 1-3% in another group treated for 26 weeks and tested both at Weeks 26 and 52). As in the case of anti-tesamorelin neutralizing antibodies they were associated with low titers and did not seem to impact IGF-1 or VAT response.

Due to the nature of antibody testing implemented in the Phase 3 program, there is limited information on the temporal development of any of the neutralizing antibodies.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Main Phase

Overall, a similar percentage of patients reported at least one treatment-emergent adverse event (TEAE) in each group (78.3% tesamorelin and 71.1% placebo) during the Main Phase of the pivotal trials. Most adverse events were categorized as moderate in intensity (44.9% tesamorelin and 44.5% placebo) or mild (60.8% tesamorelin and 52.1% placebo). The percentage of TEAEs classified as severe were also comparable between the treatment and control groups (9.8% tesamorelin and 11.8% placebo).

Table 77 lists the TEAEs that occurred more commonly in the tesamorelin group relative to placebo and had a frequency higher than 1%. As observed in the analysis of patient dropouts, a larger percentage of adverse events known to occur in association with rhGH therapy were encountered in the tesamorelin group. They include (in order of decreasing frequency), arthralgia, extremity pain, peripheral edema, myalgia, paresthesia/hypoesthesia, musculoskeletal pain, musculoskeletal stiffness, carpal tunnel syndrome, joint stiffness, hypertension and joint swelling. Injection site reactions represented another group of adverse events that were clearly encountered in excess in the tesamorelin group, and were captured under terms such as erythema, pruritis, pain, irritation, hemorrhage, urticaria, and swelling.

Given the above mentioned increase in frequency of injection site reactions, it is worth noting that there was also an imbalance in adverse events suggestive of systemic allergic reactions such as rash (3.7% tesamorelin and 1.5% placebo) and pruritis (2.4% tesamorelin and 1.1% placebo); these events are analyzed separately in Section 3.5.4 of this review. Of the remaining adverse events, several fall largely under the category of infectious conditions (influenza, folliculitis, herpes zoster, onychomycosis, lower respiratory tract infection), while others do not fit into a collective class of adverse events (e.g. depression, vomiting, dyspepsia, palpitations, chest pain). Increased CPK (clinically insignificant) and hypertriglyceridemia were the only laboratory abnormalities that were

reported as adverse events. With respect with temporal occurrence, in general, adverse events appeared to be almost evenly distributed when comparing the first and the last three months of the Main Phase.

Table 77 Treatment Emergent Adverse Events - Main Phase of Pivotal Studies (Both Pivotal Studies Combined)*

Adverse event	Tesamorelin N=543 n (%)	Placebo N=263 n (%)
Arthralgia	72 (13.3)	29 (11.0)
Injection site erythema	46 (8.5)	7 (2.7)
Injection site pruritis	41 (7.6)	2 (0.8)
Extremity pain	33 (6.1)	12 (4.6)
Peripheral edema	33 (6.1)	6 (2.3)
Myalgia	30 (5.5)	5 (1.9)
Parasthesia	26 (4.8)	6 (2.3)
Nausea	24 (4.4)	10 (3.8)
Hypoesthesia	23 (4.2)	4 (1.5)
Injection site pain	22 (4.1)	8 (3.0)
Rash	20 (3.7)	4 (1.5)
Injection site irritation	16 (2.9)	3 (1.1)
Vomiting	14 (2.6)	0
Pruritis	13 (2.4)	3 (1.1)
Influenza	11 (2.0)	3 (1.1)
Depression	11 (2.0)	4 (1.5)
Musculoskeletal pain	10 (1.8)	2 (0.8)
Folliculitis	9 (1.7)	2 (0.8)
Dyspepsia	9 (1.7)	2 (0.8)
Pain	9 (1.7)	3 (1.1)
Musculoskeletal stiffness	9 (1.7)	1 (0.4)
Injection site hemorrhage	9 (1.7)	1 (0.4)
Injection site urticaria	9 (1.7)	1 (0.4)
Pharyngolaryngeal pain	9 (1.7)	2 (0.8)
Sinus congestion	9 (1.7)	0
Carpal tunnel syndrome	8 (1.5)	0
Joint stiffness	8 (1.5)	2 (0.8)
Injection site swelling	8 (1.5)	1 (0.4)
Herpes zoster	8 (1.5)	2 (0.8)
Increased blood CPK	8 (1.5)	1 (0.4)
Onychomycosis	7 (1.3)	2 (0.8)
Injection site reaction	7 (1.3)	2 (0.8)
Hypertension	7 (1.3)	2 (0.8)
Muscle spasms	6 (1.1)	2 (0.8)
Joint swelling	6 (1.1)	0
Rhinorrhea	6 (1.1)	1 (0.4)
Allergic Rhinitis	6 (1.1)	0
Palpitations	6 (1.1)	1 (0.4)
Abdominal pain, upper	6 (1.1)	2 (0.8)
Chest pain	6 (1.1)	2 (0.8)
Night sweats	6 (1.1)	1 (0.4)
Injection site rash	6 (1.1)	1 (0.4)
Lower respiratory tract infection	6 (1.1)	2 (0.8)
Muscle strain	6 (1.1)	0

Hypertriglyceridemia	6 (1.1)	1 (0.4)
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*Included are adverse events occurring in $\geq 1\%$ that had a higher frequency in the tesamorelin combined group relative to placebo
Source: ISS Table 1.4.1.1.

Table 78 presents the AEs considered “related” to treatment in the investigator’s assessment; it includes only AEs that occurred in more than 1% of patients and more frequently in the tesamorelin than in the placebo group. Overall, there was an imbalance in TEAEs classified as treatment-related, with 53.2% of such events reported with tesamorelin and 36.5% with placebo. Most of the AEs observed were either injection site reactions (i.e., erythema, pruritis, pain, irritation, urticaria, hemorrhage, swelling, etc.) or events known to be related to the effects of GH (i.e., arthralgia, headache, peripheral edema, myalgia, etc.). Nausea was an additional AE.

Table 78 Treatment-Related Adverse Events – Main Phase of Pivotal Studies (Both Studies Combined)*

Adverse event	Tesamorelin N=543 n (%)	Placebo N=263 n (%)
Any related event	289 (53.2)	96 (36.5)
Arthralgia	57 (10.5)	20 (7.6)
Injection site erythema	45 (8.3)	7 (2.7)
Injection site pruritis	39 (7.2)	2 (0.8)
Headache	32 (5.9)	12 (4.6)
Peripheral edema	27 (5.0)	3 (1.1)
Myalgia	21 (3.9)	3 (1.1)
Injection site pain	20 (3.7)	8 (3.0)
Hypoesthesia	19 (3.5)	3 (1.1)
Extremity pain	16 (2.9)	5 (1.9)
Injection site irritation	14 (2.6)	3 (1.1)
Nausea	11 (2.0)	2 (0.8)
Rash	10 (1.8)	1 (0.4)
Injection site urticaria	9 (1.7)	1 (0.4)
Joint stiffness	8 (1.5)	1 (0.4)
Injection site hemorrhage	8 (1.5)	1 (0.4)
Injection site swelling	8 (1.5)	1 (0.4)
Injection site reaction	7 (1.3)	2 (0.8)
Musculoskeletal stiffness	7 (1.3)	1 (0.4)

*Included are adverse events occurring in $\geq 1\%$ that had a higher frequency in the tesamorelin combined group relative to placebo.
Source: ISS Table 1.4.1.8.

Extension Phase

As observed during the Main Phase, adverse events were seen with similar frequency in the tesamorelin and placebo groups (62.6% T-T and 60.0% T-P group). Similarly, most AEs were considered mild or moderate in severity and the proportions of patients with severe AEs were comparable between the two groups (6.1% T-T group and 5.2% among T-P). In contrast to observations made during the Main Phase of the trial, there was no discrepancy in frequency of treatment-related AEs during the extension period (21.5% T-T patients, and 20.7% T-P patients).

Table 79 lists the common adverse events encountered with greater frequency in the T-T group relative to the T-P group observed in ≥ 1 patient. The pattern of AEs is similar and

consistent with that observed during the Main Phase. Specifically, adverse events that are to be expected during rhGH treatment (i.e. peripheral edema, extremity pain, paresthesias, myalgias, carpal tunnel syndrome) have been observed more frequently with tesamorelin treatment, as were injection site reactions (pruritis, erythema, hemorrhage, irritation, rash). As noted before, there appeared to be an imbalance of adverse events in the infection SOC such as upper respiratory tract infection, nasopharyngitis, sinusitis, bronchitis, cellulitis, herpes zoster, onychomycosis, and lower respiratory tract infection. Generalized pruritis (1.2%) and urticaria (1.2%) were seen more commonly in the T-T group compared with T-P, although relatively infrequently. Increased CPK (clinically insignificant) was the only abnormality in a laboratory finding that was reported as an adverse event.

Table 79 Treatment-Emergent Adverse Events - Extension Phase (Both pivotal Studies Combined)*

Adverse event	Tesamorelin (T-T) N=246 n (%)	Placebo (T-P) N=135 n (%)
Upper respiratory tract infection	18 (7.3)	5 (3.7)
Sinusitis	12 (4.9)	0
Nasopharyngitis	10 (4.1)	3 (2.2)
Extremity pain	8 (3.3)	1 (0.7)
Bronchitis	6 (2.4)	3 (2.2)
Vomiting	5 (2.0)	1 (0.7)
Injection site pruritis	5 (2.0)	0
Peripheral edema	5 (2.0)	0
Lower respiratory tract infection	4 (1.6)	0
Cellulitis	4 (1.6)	0
Paresthesia	4 (1.6)	2 (1.5)
Hypoesthesia	4 (1.6)	1 (0.7)
Dizziness	4 (1.6)	2 (1.5)
Peripheral neuropathy	4 (1.6)	2 (1.5)
Pharyngolaryngeal pain	4 (1.6)	0
Hypertension	4 (1.6)	2 (1.5)
Depression	4 (1.6)	1 (0.7)
Myalgia	3 (1.2)	0
Joint sprain	3 (1.2)	1 (0.7)
Injection site erythema	3 (1.2)	0
Pruritis	3 (1.2)	1 (0.7)
Night sweats	3 (1.2)	0
Urticaria	3 (1.2)	0
Rhinorrhea	3 (1.2)	1 (0.7)
Hot flush	3 (1.2)	1 (0.7)
Insomnia	3 (1.2)	0
Musculoskeletal pain	2 (0.8)	0
Joint stiffness	2 (0.8)	0
Musculoskeletal stiffness	2 (0.8)	0
Injection site irritation	2 (0.8)	0
Injection site hemorrhage	2 (0.8)	0
Injection site reaction	2 (0.8)	0
Muscle strain	2 (0.8)	0
Onychomycosis	2 (0.8)	0
Chest pain	2 (0.8)	1 (0.7)

Carpal tunnel syndrome	2 (0.8)	0
Injection site swelling	1 (0.4)	0
Injection site rash	1 (0.4)	0
Herpes zoster	1 (0.4)	0
Increased blood CPK	1 (0.4)	0

Source: ISS Table 1.4.1.1e

* Included are adverse events with a higher frequency in the tesamorelin group relative to placebo.

Adverse events considered “related” to the study drug by the investigator are presented in Table 80; included are only AEs that occurred in $\geq 1\%$ of tesamorelin-treated subjects and were more frequently seen with the study drug than placebo. Unlike the Main Phase wherein there was a higher incidence of treatment-related AEs in the tesamorelin group, during the Extension Phase similar proportions of subjects in the T-T and T-P groups reported at least one related AE (21.5% and 20.7%, respectively). Similar to observations made during the Main Phase, most of the related AEs observed were either injection site reactions (i.e, pruritis, erythema) or events known to be related to the effects of GH (e.g., arthralgia, headache, peripheral edema, etc.).

Table 80 Treatment-Related Adverse Events – Extension Phase of Pivotal Studies (Both Studies Combined)*

Adverse event	T-T N=246 n (%)	T-P N=135 n (%)
Any related event	53 (21.5)	28 (20.7)
Arthralgia	11 (4.5)	3 (2.2)
Extremity pain	5 (2.0)	1 (0.7)
Injection site pruritis	5 (2.0)	0
Peripheral edema	4 (1.6)	0
Injection site erythema	3 (1.2)	0
Peripheral neuropathy	3 (1.2)	1 (0.7)
Headache	3 (1.2)	0
Hypoesthesia	3 (1.2)	0

*Included are adverse events occurring in $\geq 1\%$ that had a higher frequency in the tesamorelin combined group relative to placebo
Source: ISS Table 1.4.1.9.

7.4.2 Laboratory Findings

Blood Chemistries

Blood chemistry laboratory results from the Main Phase and Extension Phase of the pivotal trials are presented in Tables 81 and 82. These are reported as mean changes from baseline to Weeks 13 and 26 during the Main Phase and Weeks 39 to 52 during the Extension Phase. Results include liver enzymes (alkaline phosphatase, ALT, AST and total bilirubin) and creatine kinase (CK), which was the only other parameter that showed a difference of $\geq 2.0\%$ between treatments.

No clinically meaningful changes from baseline in liver enzymes were observed during the Main Phase or Extension Phase. At the end of the Main Phase, the mean increase for CK values was greater in the placebo group than in the tesamorelin group (88.6 U/L vs. 20.1 U/L). At the end of the Extension Phase, subjects in the T-T group showed a larger mean increase in CK than subjects in the T-P group (60.2 U/L vs. 22.0 U/L).

Table 81 Liver Function and Creatine Kinase Values – Main Phase of Pivotal Trials (Both Studies Combined)

		Tesamorelin		Placebo	
Parameter (unit)		N	Mean (SD)	N	Mean (SD)
Alkaline Phosphatase (U/L)	Baseline	543	91.8 (29.92)	263	94.8 (31.78)
	Change to Week 13	466	0.6 (13.61)	221	0.11 (16.41)
	Change to Week 26	414	5.0 (17.38)	206	-2.6 (17.15)
ALT (U/L)	Baseline	543	40.6 (23.21)	263	39.8 (22.49)
	Change to Week 13	466	-2.2 (20.06)	221	-0.9 (27.09)
	Change to Week 26	413	-2.9 (22.80)	206	-2.2 (18.49)
AST (U/L)	Baseline	543	32.1 (14.14)	263	32.5 (14.48)
	Change to Week 13	466	0.34 (21.19)	221	-1.6 (13.99)
	Change to Week 26	413	-1.0 (13.95)	206	-0.6 (16.33)
Total Bilirubin (mg/dL)	Baseline	542	0.9 (1.14)	263	0.8 (0.83)
	Change to Week 13	465	-0.17 (0.69)	221	-0.06 (0.50)
	Change to Week 26	412	-0.18 (0.71)	206	-0.03 (0.58)
Creatine Kinase (U/L)	Baseline	435	199.4 (159.01)	212	193.3 (166.66)
	Change to Week 13	371	71.8 (658.97)	178	-8.7 (132.66)
	Change to Week 26	330	20.1 (166.92)	166	88.6 (771.89)

Source: ISS Table 1.5.1.1.1a

Table 82 Liver Function and Creatine Kinase Values – Extension Phase of Pivotal Trials (Both Studies Combined)

		T-T		T-P	
Parameter (unit)		N	Mean (SD)	N	Mean (SD)
Alkaline Phosphatase (U/L)	Baseline	246	91.4 (31.76)	135	91.5 (26.76)
	Change to Week 39	213	4.1 (20.21)	110	5.7 (17.02)
	Change to Week 52	196	6.5 (22.86)	95	0.6 (19.61)
ALT (U/L)	Baseline	246	41.0 (21.81)	135	32.0 (14.05)
	Change to Week 39	214	-4.8 (23.06)	110	-1.7 (21.18)
	Change to Week 52	196	-4.9 (24.34)	95	-3.7 (15.78)

AST (U/L)	Baseline	246	32.7 (13.55)	135	32.0 (14.05)
	Change to Week 39	214	-1.6 (15.97)	110	-0.46 (15.07)
	Change to Week 52	196	-1.8 (15.13)	95	-2.5 (10.59)
Total Bilirubin (mg/dL)	Baseline	246	0.8 (1.14)	134	1.0 (1.27)
	Change to Week 39	212	-0.13 (0.65)	110	-0.24 (0.73)
	Change to Week 52	196	-0.18 (1.05)	95	-0.08 (0.49)
Creatine Kinase (U/L)	Baseline	188	196.6 (158.19)	115	205.5 (184.47)
	Change to Week 39	157	52.7 (323.33)	92	26.7 (238.75)
	Change to Week 52	144	60.2 (320.60)	79	22.0 (245.41)

Source: ISS Table 1.5.1.1.2a

Tables 83 and 84 depict the percentage of subjects with newly occurring or worsening blood chemistry abnormalities for the Main Phase and Extension Phase, respectively. No clinically significant differences among treatment groups and Phases were observed for the percentage of subjects with newly occurring or notable worsening liver enzyme values. During the Main Phase, the percentage of subjects with newly occurring or worsening creatine kinase values was greater among tesamorelin subjects than placebo subjects. A similar pattern was observed during the Extension Phase; a greater percentage of subjects in the T-T group had newly occurring or worsening creatine kinase values compared with subjects in the T-P group.

Table 83 Newly Occurring or Worsening Abnormalities in Liver Function and Creatine Kinase Values – Main Phase of Pivotal Trials (Both Studies Combined)

Parameter	Criteria for Notable Changes/Abnormalities	Visit	Group	
			Tesamorelin (N=543) n (%)	Placebo (N=263) n (%)
Alkaline Phosphatase (U/L)	>1.5x ULN	Week 13	1 (0.2)	4 (1.5)
		Week 26	5 (0.9)	4 (1.5)
ALT (U/L)	>3x ULN	Week 13	7 (1.3)	1 (0.4)
		Week 26	5 (0.9)	0
	>10x ULN	Week 13	0	0
		Week 26	0	0
AST (U/L)	>3x ULN	Week 13	5 (0.9)	1 (0.4)
		Week 26	1 (0.2)	2 (0.8)
	>10x ULN	Week 13	0	0

		Week 26	0	0
Total Bilirubin (mg/dL)	>1.2x ULN	Week 13	74 (13.6)	39 (14.8)
		Week 26	60 (11.0)	40 (15.2)
Creatine Kinase (U/L)	>200 U/L and >20%	Week 13	82 (15.1)	23 (8.7)
		Week 26	71 (13.1)	24 (9.1)

Source: ISS Table 1.5.1.3.1a

Table 84 Newly Occurring or Worsening Abnormalities in Liver Function and Creatine Kinase Values – Extension Phase of Pivotal Trials (Both Studies Combined)

Parameter	Criteria for Notable Changes/Abnormalities	Visit	Group	
			T-T (N=246) n (%)	T-P (N=135) n (%)
Alkaline Phosphatase (U/L)	>1.5xULN	Week 39	2 (0.8)	0
		Week 52	5 (2.0)	2 (1.5)
ALT (U/L)	>3xULN	Week 39	1 (0.4)	1 (0.7)
		Week 52	3 (1.2)	0
	>10x ULN	Week 39	0	0
		Week 52	0	0
AST (U/L)	>3x ULN	Week 39	1 (0.4)	1 (0.7)
		Week 52	2 (0.8)	0
	>10x ULN	Week 39	0	0
		Week 52	0	0
Total Bilirubin (mg/dL)	>1.2x ULN	Week 39	30 (12.2)	15 (11.1)
		Week 52	20 (8.1)	17 (12.6)
Creatine Kinase (U/L)	>200 U/L and >20%	Week 39	45 (18.3)	19 (14.1)
		Week 52	37 (15.0)	11 (8.1)

Source: ISS Table 1.5.1.3.1a

Hematology

Hematology laboratory results from the Main Phase and Extension Phase of the pivotal trials are presented in Tables 85 and 86. These are reported as mean changes from baseline to Weeks 13 and 26 during the Main Phase and Weeks 39 to 52 during the Extension Phase. Results include liver enzymes (alkaline phosphatase, ALT, AST and total bilirubin) and creatine kinase (CK), which was the only other parameter that showed a difference of $\geq 2.0\%$ between treatments.

No clinically meaningful changes from baseline in liver enzymes were observed during the Main Phase or Extension Phase. At the end of the Main Phase, the mean increase for CK values was greater in the placebo group than in the tesamorelin group (88.6 U/L vs. 20.1 U/L). At the end of the Extension Phase, subjects in the T-T group showed a larger mean increase in CK than subjects in the T-P group (60.2 U/L vs. 22.0 U/L).

Table 85 Hematology Values – Main Phase of Pivotal Trials (Both Studies Combined)

Parameter (unit)		Tesamorelin		Placebo	
		N	Mean (SD)	N	Mean (SD)
Erythrocytes (x10 ¹² /L)	Baseline	543	4.5 (0.62)	263	4.5 (0.57)
	Change to Week 13	460	0.02 (0.32)	216	-0.01 (0.31)
	Change to Week 26	405	0.01 (0.37)	203	-0.03 (0.34)
Eosinophils (x10 ⁹ /L)	Baseline	542	0.13 (0.10)	263	0.13 (0.12)
	Change to Week 13	457	0.06 (0.16)	216	0.00 (0.13)
	Change to Week 26	401	0.05 (0.15)	203	0.02 (0.12)

Source: ISS Table 1.5.1.1.3a

Table 86 Hematology Values – Extension Phase of Pivotal Trials (Both Studies Combined)

Parameter (unit)		T-T		T-P	
		N	Mean (SD)	N	Mean (SD)
Erythrocytes (x10 ¹² /L)	Baseline	246	4.5 (0.64)	135	4.5 (0.56)
	Change to Week 39	210	-0.01 (0.37)	109	0.03 (0.41)
	Change to Week 52	196	0.00 (0.39)	94	0.03 (0.44)
Eosinophils (x10 ⁹ /L)	Baseline	246	0.13 (0.09)	134	0.14 (0.11)
	Change to Week 39	210	0.04 (0.13)	108	0.01 (0.17)
	Change to Week 52	195	0.05 (0.15)	92	0.00 (0.14)

Source: ISS Table 1.5.1.1.4a

Tables 87 and 88 depict the percentage of subjects with newly occurring or notable worsening hematology abnormalities by treatment assignment for the Main Phase and Extension Phase, respectively, for the hematology parameters of interest. During the Main Phase, the percentage of subjects with newly occurring or notable worsening erythrocyte values was higher among tesamorelin-treated subjects compared with placebo subjects; the difference between groups for eosinophils was not as significant. During the Extension Phase, the percentage of subjects with newly occurring or notable worsening erythrocyte values was higher in the T-T group than in the T-P group.

Table 87 Newly Occurring or Worsening Abnormalities in Liver Hematology Values – Main Phase of Pivotal Trials (Both Studies Combined)

Parameter	Criteria for Notable Changes/Abnormalities	Visit	Group	
			Tesamorelin (N=543) n (%)	Placebo (N=263) n (%)
Erythrocytes (x10 ¹² /L)	≥10% change from Screening	Week 13	68 (12.5)	18 (6.8)
		Week 26	68 (12.5)	21 (8.0)
Eosinophils (x10 ⁹ /L)	> 1.1x ULN	Week 13	24 (4.4)	4 (1.5)
		Week 26	13 (2.4)	6 (2.3)

Source: ISS Table 1.5.1.3.3a

Table 88 Newly Occurring or Worsening Abnormalities in Liver Hematology Values – Extension Phase of Pivotal Trials (Both Studies Combined)

Parameter	Criteria for Notable Changes/Abnormalities	Visit	Group	
			T-T (N=246) n (%)	T-P (N=135) n (%)
Erythrocytes (x10 ¹² /L)	≥10% change from Screening	Week 13	43 (17.5)	18 (13.3)
		Week 26	44 (17.9)	16 (11.9)
Eosinophils (x10 ⁹ /L)	> 1.1x ULN	Week 13	7 (2.8)	2 (1.5)
		Week 26	12 (4.9)	3 (2.2)

Source: ISS Table 1.5.1.3.4a

Urinalysis

Tables 89 and 90 show mean changes in pH from baseline to Week 13 and Week 26 for the Main Phases and Extension Phases, respectively, of the Pivotal Studies. No clinically meaningful mean changes from baseline or differences between or among the treatment groups in mean changes from baseline were observed.

Table 89 Urinalysis Mean Changes – Main Phase of Pivotal Trials (Both Studies Combined)

Parameter (unit)		Tesamorelin		Placebo	
		N	Mean (SD)	N	Mean (SD)
pH	Baseline	158	5.6 (0.51)	85	5.6 (0.54)
	Change to Week 13	79	0.01 (0.53)	44	-0.01 (0.50)
	Change to Week 26	83	-0.18 (0.53)	37	-0.23 (0.60)

Source: ISS Table 1.5.1.1.5

Table 90 Urinalysis Mean Changes – Extension Phase of Pivotal Trials (Both Studies Combined)

Parameter (unit)		T-T		T-P	
		N	Mean (SD)	N	Mean (SD)
Erythrocytes (x10 ¹² /L)	Baseline	73	5.6 (0.46)	36	5.6 (0.59)
	Change to Week 39	45	-0.19 (0.53)	17	-0.09 (0.57)
	Change to Week 52	44	-0.07 (0.51)	20	-0.20 (0.64)

Source: ISS Table 1.5.1.1.6

7.4.3 Vital Signs

Vital signs were recorded in all studies and generally included respiration rate, pulse rate (after 5 minutes of rest) and sitting blood pressure (after 5 minutes of rest). There were no dose response changes with respect to mean or % change from the mean in blood pressure or heart rate. There were no dose response changes with respect to markedly abnormal increases or decreases in blood pressure or heart rate. Overall no clinically significant findings in vital signs or physical exams were identified in these studies.

7.4.4 Electrocardiograms (ECGs)

ECGs were performed at screening and at Week 6 through Week 26 in the Pivotal Trials. Following an episode of congestive heart failure in 1 tesamorelin-treated subject in Study 10, management and monitoring procedures were implemented for Studies 11 and 12. These included ECG at baseline and regularly at post-baseline visits, and close clinical follow-up at each visit for any subject who presented ECG signs of ventricular hypertrophy at baseline or who developed such signs during the study. In addition, for those individuals who presented ECG signs of ventricular hypertrophy at baseline or during treatment, echocardiography was performed. Suspected cases of ventricular hypertrophy at ECG were confirmed by a cardiologist who determined the need for ECHO. At the end of each study, all ECGs performed were transferred to a central reading center where the tracings were centrally reviewed and analyzed.

Results indicated that tesamorelin showed no signal or any effect on heart rate, atrioventricular conduction or cardiac depolarization as measured by the PR and QRS interval durations. The preponderance of data also demonstrated that tesamorelin had no effect on cardiac repolarization using the QTcF interval.

7.4.5 Special Safety Studies/Clinical Trials

No information regarding special safety studies was included in this submission.

7.4.6 Immunogenicity

Data related to the development of immunogenicity to Egrifta are analyzed at length in Section 7.3.5.7.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Not applicable, since the Pivotal Studies only evaluated the 2mg dose of EGRIFTA.

7.5.2 Time Dependency for Adverse Events

Analyses and discussion regarding time dependency for adverse events have been incorporated in this review. When presenting tables of adverse events, I reviewed the frequencies of AEs observed in both the Main Phase and Extension Phase to exclude any major discrepancies.

7.5.3 Drug-Demographic Interactions

Efficacy subgroup analyses have already been presented in Section 6.1.7. Safety subgroup analyses are presented here.

The Sponsor analyzed differences in the AE profile for the following subgroups: age, gender, race, ethnicity, BMI, duration of diabetes, and renal function. The analysis of adverse events in subjects with renal impairment is discussed separately in Section 6.1.7. This analysis is limited by small sample sizes of certain subgroups, including those over 75 years old, blacks, and Hispanic/Latinos. Overall, this analysis revealed few differences in the AE profile based on these subgroups.

7.5.4 Drug-Disease Interactions

Safety results were compared across the following subgroups: CD4 cell count, HIV viral load, hepatitis status, anti-tesamorelin IgG antibodies, IGF-1 standard deviation scores, and impaired glucose tolerance/diabetes condition.

CD4 Cell Count

Among the AEs with notable differences during the Main Phase, no differences $\geq 10.0\%$ were observed between subpopulations of CD4 cell count in the tesamorelin group. Among the AEs with notable differences during the Extension Phase, no differences $\geq 10.0\%$ were observed between subpopulations of CD4 cell count in the T-T group. No clinically significant differences between CD4 cell count groups were observed for the incidence rates of AEs.

HIV Viral Load

Among the AEs with notable differences during the Main Phase, no differences $\geq 10.0\%$ among HIV viral load subpopulations in the tesamorelin group were observed. Among the AEs with notable differences during the Extension Phase (27-52 weeks), differences $\geq 10.0\%$ among subpopulations of HIV viral load in the T-T group were observed for the following AEs:

- fungal infection: 10.0% high viral load versus 0% undetectable and 0% low viral load
- arthralgia: 15.0% high viral load versus 5.2% undetectable and 2.9% low viral load

The variability in incidence may be related to the small number of subjects with high viral load. No differences for the incidence rates of AEs among subpopulations of HIV viral load were clinically significant.

Hepatitis Status

AEs were analyzed by hepatitis status (hepatitis B, hepatitis C, hepatitis B and C, other hepatitis) within each treatment group; however, subjects without hepatitis were not presented for comparison. Therefore, overall AEs that occurred in $\geq 5\%$ of tesamorelin subjects in Study Group 1 during the Main Phase, including injection site erythema, injection site pruritus, peripheral edema, arthralgia, pain in extremity, and myalgia, were displayed for tesamorelin and placebo subjects who had hepatitis after combining subjects across the hepatitis subgroups. The numbers of subjects with hepatitis were then subtracted from the overall AE incidences to obtain the number of subjects with these events who did not have hepatitis. The procedure was also repeated for the Extension Phase, using the same events.

Among the AEs identified for evaluation by hepatitis status, no differences $\geq 10.0\%$ were observed among tesamorelin subjects with and without hepatitis during the Main Phase, or for subjects in the T-T group with and without hepatitis in the Extension Phase. No differences for the incidence rates of AEs among subpopulations of hepatitis status were clinically significant.

IGF-1 Standard Deviation Scores

Please see Section 7.3.5.5 for a complete description.

Impaired Glucose Tolerance/Diabetes Mellitus

Please see Section 7.3.5.6 for a complete description.

Anti-tesamorelin Antibodies

Please see Section 7.3.5.7 for a complete description.

7.5.5 Drug-Drug Interactions

See Dr. Ritesh Jain's Clinical Pharmacology review for details. As described in Section 4.4.4, in vivo drug-drug interaction studies showed that tesamorelin has no clinically significant impact on the metabolism of simvastatin and ritonavir.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

EGRIFTA did not appear to be carcinogenic in the nonclinical program. The clinical development program (6 month Main Phase with additional 6 month Extension Phase, for

a maximum duration of one year) is likely of insufficient duration to reliably assess the long-term risk of carcinogenicity. Nevertheless, I reviewed all PTs under the SOC Neoplasms Benign, Malignant, and Unspecified for the pooled studies. Within each of these populations, no individual neoplasm PT appeared more than once in an EGRIFTA-treated subject. In addition, no unusual neoplasms were reported.

7.6.2 Human Reproduction and Pregnancy Data

Within the EGRIFTA clinical development program, no cases of pregnancy were observed.

7.6.3 Pediatrics and Assessment of Effects on Growth

In the clinical development program, EGRIFTA was studied in subjects 18 years and older. There is no clear unmet medical need for EGRIFTA in children less than 18 years of age. In order to comply with the Pediatric Research and Equity Act (PREA), the Division has planned to grant a pediatric waiver for children <18 years old.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose

EGRIFTA doses above 2mg were not evaluated in the Pivotal Trials, and there were no reports of overdose among these patients. Given the known effects of GH, acute overdosage could lead to hyperglycemia. Long-term overdosage could result in signs and symptoms of acromegaly consistent with the known effects of excess GH.

Drug Abuse Potential

The potential for drug abuse was not specifically studied. However, given the effects of GH on the maintenance and improvement in muscle mass and strength, as well as its potential to decrease fat from multiple compartments, there is justified concern for off-label use for indications other than that studied in these trials.

Withdrawal and Rebound

These effects were not studied.

7.7 Additional Submissions / Safety Issues

Not applicable.

8 Postmarketing Experience

Tesamorelin is not currently marketed. Therefore, post-marketing data are not available.

9 Appendices

9.1 Literature Review/References

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- lipodystrophy. *J Clin Endocrinol Metab.* 2008;93:2937-2945.
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9.2 Labeling Recommendations

A summary and line-by-line labeling review will be added as an addendum to this Review.

9.3 Advisory Committee Meeting

A meeting of the Endocrinologic and Metabolic Drugs Advisory Committee was held on May 27, 2010 to evaluate the clinical merits and drawbacks of EGRIFTA. The following are the points for discussion and voting questions (both bolded) which were posed to the committee. Each question is followed by a brief overview of the panel's discussion and conclusions (italicized), as summarized by the committee Chairman. Official transcripts of the meeting are available at:

<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM224181.pdf>

Points for Discussion

- 1. Please comment on the findings of glucose intolerance in development of diabetes associated with Egrifta therapy and its impact on long-term cardiovascular risk.**

The committee agreed that cardiovascular disease is a risk factor; that HIV is a risk factor for cardiovascular disease; and, that increased visceral adiposity is a problem both with image and potentially with insulin resistance, although the link between visceral adiposity, insulin resistance, as well as growth hormone, and with cardiac hard endpoints is not exactly clear. Visceral adiposity is a distant surrogate for cardiac endpoints.

The data on glucose metabolism showed a statistically significant change in A1C that probably is not clinically significant, and the disease could be treated if it shows up. The committee did want post-marketing studies looking at the effect of drug on glucose metabolism and makes the point that diabetes and hemoglobin A1C is a continuum, and that an arbitrary cut-point of 6.5, for example, is just that, arbitrary. The population

studied is not representative and it is not known or not clear at all that the other populations would have the same responses.

The committee also wanted long-term studies with regard to carcinogenesis and a year-long study is not adequate for that.

There was also discussion about whether there can be a prospective study of cardiovascular outcomes, and there is a difference of opinion in the group, with some members thinking that it is possible, others thinking it is less likely. If not possible for a prospective five-year study with hard outcomes, then it would be reasonable, for a retrospective study, observational study, dividing the group into different quartiles or quintiles and seeing what the risk of cardiovascular disease is.

2. Please comment on the increase in IGF-1 levels 17 associated with Egrifta therapy and concerns 18 associated with chronic use of Egrifta with respect to 19 long-term cancer and cardiovascular risks.

The consensus of the committee is that the risk of cancer is low, but real, and the patients need to be monitored and have IGF-1 levels. The company proposes that patients who have an IGF-1 level greater than 3 standard deviations after one year will be removed from the study. Growth hormone should be measured, as well as IGF-1. I think there was a suggestion that there should be a time limit for this agent, even if the IGF-1 levels remain within the proper level, and that there has to be a registry for monitoring these 6 patients in a very meticulous fashion.

3. Please comment on the clinical relevance of Visceral Adipose Tissue (VAT) reduction with Egrifta (tesamorelin) in the HIV population with respect to cardiovascular risk reduction; patient-perceived benefits; and adherence to anti-retroviral therapies.

With regard to clinical relevance of VAT reduction in the HIV population with treatment with respect to cardiovascular reduction, decreasing VAT was the goal -- the primary objective of the study -- and this was accomplished. The unknown link is how this relates to cardiovascular outcomes, and that needs to be studied further. There was discussion whether there should be a trial and whether that trial should be a benefit trial or a no harm trial. As was brought up, there seemed to be some discussion regarding that, that the cardiac outcomes in relation to that are speculative at the present time and that everyone agrees, for this question, as well as that of adherence to anti-retroviral therapies, more data is required.

With respect to the clinical relevance of VAT reduction by treatment in HIV patients with respect to patient-perceived benefits, there seemed to be consensus and appreciation of the patient testimony presented to the committee, which was quite impressive. That perceived benefit seems to be important.

It is mainly on lipohypertrophy, not on lipotrophy, which needs to be studied, as well. The tools that study body perception were used and showed that there was a benefit and

this has a benefit on the potential daily living and psychiatric outlook of these patients. There was a discordance between the small quantitative changes in waist circumference and the perceived benefit that was obtained in the questionnaire, and that we need further information regarding other psychological aspects, such as body image, such as quality of daily life and psychological profile.

With regard to the clinical relevance of VAT reduction with Egrifta, with respect to adherence to antiretroviral therapies, compliance does not seem to have played a major part in the VAT impression and in the VAT changes. There was a suggestion that the potential effect of noncompliance on the IGF-1 data -- for example, in Study 10, the noncompliance was found in 26 percent of patients, while, in Study 11, it was 39 percent. This suggests that in compliant patients, IGF levels may be even higher, although that is not known. But there seemed to be consensus that compliance did not play a major role in the findings that were seen.

Voting Questions

Does the overall risk-benefit assessment of a fixed dose regimen of Egrifta, tesamorelin, 2 milligrams per day support its approval for the treatment of excess abdominal fat in HIV-1 infected patients with lipodystrophy?

(VOTE requested) YES: 16 NO: 0 ABSTAIN: 0

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

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