FDA Briefing Materials
EGRIFTA (tesamorelin acetate for injection)

NDA 22-505

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

BACKGROUND INTRODUCTORY MEMORANDUM

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Forum: Endocrinologic and Metabolic Drugs Advisory Committee meeting

Topic: Egrifta (tesamorelin acetate) – NDA 22-505

INTRODUCTION

At the end of 2006, HIV prevalence was estimated to be around 1.1 million cases in the United States. The introduction of highly active anti-retroviral (HAART) therapies in the mid 1990s resulted in a dramatical decline in HIV- related mortality and morbidity but it was also associated with changes in body composition such as subcutaneous adipose tissue (SAT) loss and central fat accumulation that often coexisted with dyslipidemia and insulin resistance. These findings are collectively referred to as fat redistribution syndrome or HIV lipodystrophy. Although the exact prevalence of HIV-associated lipodystrophy is not known, it has been estimated that 18% - 83% of all HIV patients may have this condition depending on the case definition used in individual studies[1]. According to these observations, between 200,000 and 800,000 HIV-infected patients may exhibit the clinical manifestation of HIV lipodystrophy and represent a potential target for therapeutic interventions aimed at ameliorating or correcting the manifestations of this condition.

[1] Miller J et al. HIV lipodystrophy: prevalence, severity and correlates risk in Australia. HIV Medicine, 4, 293-301 (2003).
Grinspoon S and Carr A. Cardiovascular risk and body fat abnormalities in HIV-infected adults. NEJM, 352:48-62 (2005).

While protease inhibitors were initially seen as the agents likely responsible for the genesis of fat redistribution, clinical and biological evidence that accumulated in subsequent years indicate that the pathogenesis of HIV-associated lipodystrophy is more complex and likely multifactorial in nature, involving, among others, more than a single class of HIV medications, aspects of HIV disease itself, as well as patient-specific factors. The initial concept of redistribution of adipose tissue has also come under scrutiny and has evolved into a view according to which lipoatrophy and lipohypertrophy are two distinct processes that, although coincidental in temporal development, are not necessarily interdependent and are likely to have distinct etiologies.

In the presence of subcutaneous tissue atrophy, the excess of visceral adipose tissue (VAT) is viewed as the main component of abdominal lipohypertrophy. Evidence in non-HIV obese patients suggests that VAT may be contributing to the development or progression of both insulin resistance and dyslipidemia (two well known cardiovascular risk factors). As such, VAT reduction has been targeted therapeutically in HIV-infected patients with lipodystrophy. Another reason for treating VAT has been the negative psychological impact that excess VAT and severe abdominal dysmorphism have on HIV-infected patients, in particular when associated with the loss of subcutaneous tissue in the extremities. There have been reports that in such extreme situations patients have considered discontinuing life-saving anti-retroviral regimens, and a minority of patients actually did so.

Given its known lipolytic functions, recombinant human growth hormone (rhGH), as well as GH secretagogues such as GH-releasing factor and analogs thereof, have been evaluated as pharmacologic candidates for the reduction of excessive visceral adipose tissue. The main rationale for choosing these interventions and targeting VAT reduction has already been alluded to and is based on the observation that visceral fat accumulation is associated with insulin resistance, dyslipidemia and increased risk of cardiovascular disease in obese patients. In addition, HIV-infected patients that exhibit changes in body composition have reduced GH pulse amplitudes and findings of reduced GH secretion have been seen in more than 1/3 of HIV male patients with abdominal fat accumulation (as is the case for females, although to a lesser degree). It should be emphasized though that, despite the above mentioned rationale, it is not known if VAT reduction with therapies that target the GH axis is associated with any improvements in clinical endpoints such as reduction in number or severity of cardiovascular events or cardiovascular death. Regardless of their mechanism of action, to date, there are no therapeutic agents approved by the FDA for the reduction of excess visceral adipose fat in patients with HIV lipodystrophy, or in any other conditions for that matter. Nor does the Agency have any evidence, or has made any determination, that visceral fat reduction is a validated surrogate endpoint for cardiovascular benefit.

Recombinant human GH, recombinant human GH- releasing hormone (rhGHRH), GHRH analogs and VAT reduction – general considerations

Several clinical trials have been conducted and published to date in patients with HIV lipodystrophy describing the effect of rhGH, rhGHRH and a GHRH analog (Egrifta) on VAT reduction and on multiple other metabolic endpoints (triglycerides, cholesterol, fat mass, lean

body mass)[2]. Most of these clinical trials had similar objectives, and assessed either identical or highly related safety and efficacy measures. It is important to recognize that all the above-mentioned pharmacological interventions share a common mechanism of action in that they all increase blood GH concentrations, be it from an exogenous source (as in the case of rhGH) or endogenously (as is the case for GHRH or its analogs). Consequently, the actions of all these interventions are mediated by GH-GH receptor coupling followed by the post receptor activation events which are responsible for the lipolytic effects, as well as the other known GH effects (IGF-1 elevation, changes in insulin sensitivity, water retention, etc).

Of the classes of drugs listed above, recombinant human GH has been the therapeutic agent most extensively studied in patients with HIV-associated lipodystrophy. Several single- and multi-center, placebo-controlled clinical trials of durations extending between 12 weeks to 18 months, some enrolling as many as a few hundreds of patients, have been conducted across a range of rhGH doses. The dose regimens investigated to date cover a spectrum that includes, at one end, doses similar to those that provide physiological replacement for patients with adult GHD (0.33 mg/day and 1mg/day) and at the other end supraphysiological doses identical to those approved for the treatment of conditions associated with GH resistance such as AIDS wasting/cachexia (4-6 mg/day). The temporal sequence of published clinical trials suggests that higher rhGH doses were investigated initially but adverse events associated with such pharmacologic doses (exceedingly high serum IGF-1 levels, dysglycemia - including diabetes) were observed, resulting in subsequent clinical investigations evaluating lower doses of rhGH in an attempt to find a better balance between efficacy and safety.

The information accumulated in the above-listed studies seems to indicate that supraphysiological rhGH doses have an effect on VAT reduction but unfortunately an unacceptable safety profile and, overall, an unfavorable risk-to-benefit analysis, while low doses tend to loose some efficacy but in the process are not devoid of unfavorable effect on glucose metabolism. It should also be noted that regardless of the rhGH doses evaluated, there is no maintenance effect of treatment upon discontinuation. Patients have reaccumulation of VAT to near baseline values upon withdrawal of rhGH therapy.

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[2] Wanke C et al. Recombinant human growth hormone improves the fat redistribution syndrome (lipodystrophy) in patients with HIV. AIDS, 12:2099-2103 (1999).
Lo JC at al. The effects of recombinant human growth hormone on body composition and glucose metabolism in HIV-accumulated patients with fat accumulation. J. clin. Endocrinol. Metab 86:3480-3487 (2001).
Engelson ES et al. Effect of recombinant human growth hormone in the treatment of visceral fat accumulation in HIV infection. JAIDS 30:379-391 (2002).
Kotler DP et al. Effects of growth hormone on abnormal visceral adipose tissue accumulation and dyslipidemia in HIV-infected patients. J Acquir Immune Defic Syndr, 35, 3: 239-252 (2004).
Koutkia P et al. Growth hormone-releasing hormone in HIV-infected men with lipodystrophy. A randomized controlled trial. JAMA, 297: 210-218 (2004).
Faluz J et al. Metabolic effects of growth-hormone releasing factor in patients with HIV. NEJM. 357: 2359-70 (2007).
Grunfeld C et al. Recombinant human growth hormone to treat HIV-associated redistribution syndrome. 12-week induction and 24-week maintenance therapy. J Acquir Immune Defic Syndr; 45:286-297 (2007).
Lo J et al. Low-dose physiological growth hormone in patients with HIV and abdominal fat accumulation. A rendomized controlled trial. JAMA, 300: 509518 (2008).

Although it has been suggested that natural secretagogues such as GHRH and its analogs may be able to restore a more physiologic pattern of GH secretion because they may preserve both GH secretory pulsatility and IGF-1 feedback inhibition, the observations made in some clinical trials do not clearly support this assumption, as patients treated with these agents do not appear to be free of the adverse events seen with rhGH in general.

Egrifta, VAT reduction and Cardiovascular risk

In this context, this advisory committee panel is considering the efficacy and safety of Egrifta (tesamorelin acetate), a GHRH analog. This drug is chemically GHRH with a minor modification (an addition of a hexenoyl moiety to the N-terminal part of the sequence) aimed at prolonging its half-life while maintaining the same binding affinity as GHRH *in vitro*. When injected at a daily dose of 2 mg subcutaneously it demonstrated a statistically significant reduction in VAT at 6 months of 19.6% and 11.7%, respectively, relative to placebo in two independent Phase 3 clinical trials (VAT was measured as the cross-sectional area of a single slice CT scan at the L4-5 level). Egrifta was also associated with other metabolic benefits relative to placebo, such as a reduction in total fat mass of approximately 1.4 kg (almost all of it being due to trunk fat reduction) and an almost identical increase in lean body mass. Other desirable effects, such as triglyceride or cholesterol reduction, improvement in patient related outcomes, and reduction in waist circumference were seen either inconsistently during the trials or were of small magnitude.

Similar to the rhGH trials, the effect of Egrifta on VAT is not sustained with discontinuation of therapy. Patients in the Phase 3 trials who were switched from Egrifta to placebo after 24 weeks demonstrated a reaccumulation of VAT to near baseline levels. This is an important observation in the risk-benefit evaluation as it appears chronic therapy is necessary to maintain reductions in VAT that will also be accompanied by long-term effects of GH and IGF-1 stimulation.

Importantly, the Phase 3 program was not designed to evaluate the effect of Egrifta on CV risk reduction. As stated earlier, one of the rationale for treating HIV-associated lipodystrophy and the metabolic derangements of this condition is to reduce cardiovascular risk. This program has no evidence directly linking the change observed on a single slice CT scan measurement of VAT at L4-5 level or with other endpoints to a reduction of the risk of cardiovascular events such as myocardial infarctions or strokes. Given that the putative link between VAT reduction and cardiovascular benefit has not been validated to date in drug intervention trials (and thus cannot be extrapolated to the Egrifta program) and that no clinical endpoints have been evaluated in the Phase III trials, Egrifta's treatment effect on secondary endpoints such as triglycerides, cholesterol, patient-reported outcomes, and abdominal circumference have been planned as supportive evidence of efficacy beyond VAT reduction. With only modest and inconsistent results in these secondary endpoints, we are left to consider almost exclusively the benefit of VAT reduction and rely on an unvalidated biomarker for a yet-to-be demonstrated cardiovascular benefit.

In the final analysis, even if the degree of VAT reduction and other favorable metabolic changes promoted by Egrifta were to be considered valid surrogates of clinical benefit, one needs to make a determination as to what is the benefit-to-risk ratio for Egrifta in the face of 1) a statistically significant increase in the number of patients with diabetes in the tesamorelin group relative to placebo (a finding that may affect unfavorably the potential cardiovascular benefit of this therapy), and 2) an increase in the serum IGF-1 values above the upper range of normal in a considerable number of Egrifta-treated patients, especially since this treatment is anticipated to be given long-term and acknowledging the fact that HIV patients are at risk of non-AIDS defining malignancies.

This FDA Briefing Package will provide the following background information:

- the FDA clinical review, which will focus on comparisons of the efficacy and safety of Egrifta relative to placebo in the context of the Phase 3 pivotal clinical trials
- the statistical review, which presents the FDA's results of efficacy upon re-analysis of applicant's data, as well as several additional analyses
- the review of patient reported outcomes (PROs) by the Study Endpoints and Label Development (SEALD) team, which specializes in the development and analysis of PROs
- the immunology review, which will address the question of immunogenicity in case of inappropriate use of Egrifta for unapproved indications.

Following the review of this material and applicant's briefing package, the Agency has the following questions for the Advisory Committee:

1) Please comment on the clinical relevance of VAT reduction with Egrifta in the HIV population with respect to:

- cardiovascular risk reduction
- patient-perceived benefits.

2) Please comment on the findings of glucose intolerance and development of diabetes associated with Egrifta therapy and its impact on longterm cardiovascular risk.

3) Please comment on the increase in IGF-1 levels associated with Egrifta therapy and concerns associated with chronic use of Egrifta.

4) Is the risk-benefit of a fixed regimen of 2 mg/day of Egrifta in patients with HIV lipodystrophy and excess abdominal fat favorable and should Egrifta be approved on the basis of information provided in this NDA? (Yes/No vote requested).

If voting yes:

- please discuss basis for this recommendation
- please discuss whether any additional studies should be conducted post-approval.

If voting no:

- please discuss basis for this recommendation
- please discuss what additional studies would be necessary to address deficiency/deficiencies.

CLINICAL REVIEW
EGRIFTA (tesamorelin acetate for injection)

NDA 22-505

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1. INTRODUCTION

1.1 Drug substance and drug product

The drug substance in Egrifta is tesamorelin, a synthetic analog of human growth hormone-releasing hormone (GHRH) that contains the entire 44 amino acid sequence of human GHRH to which an additional hexenoyl moiety (a C6 hydrophobic side chain with a double bond at position 3) was attached to the tyrosine residue at the N-terminal part of the sequence. This chemical modification was created with the goal of making a GHRH-like molecule that is more resistant to enzymatic degradation once absorbed in the bloodstream. While this addition prolonged the half-life of the analog relative to native GHRH, in an *in vitro* assay it did not change the binding affinity of tesamorelin, which remains comparable to that of endogenous GHRH.

The Egrifta drug product is manufactured as a lyophilized powder containing tesamorelin free base and mannitol as the only excipient. The to-be-marketed Egrifta vial contains 1 mg of tesamorelin and 55 mg of mannitol to be reconstituted in Sterile Water for Injection at 1 mg/ml. It is meant to be injected once-a-day subcutaneously at a dose of 2 mg. Since the product is manufactured for immediate use, the vial contains no preservatives.

1.2 Indication

Thera Technologies is proposing the following indication for Egrifta:

> EGRIFTA (tesamorelin acetate for injection) is indicated to induce and maintain a reduction of excess abdominal fat in HIV-infected patients with lipodystrophy.

1.3 Clinical program

The clinical development program for Egrifta was extensive and consisted of, among others, 10 clinical pharmacology studies, several clinical efficacy studies in a variety of patient populations (including a Phase 2 dose-searching study in HIV patients with lipodystrophy), and three Phase 3 “pivotal trials”.

While the full review of the Egrifta application is still ongoing, this briefing summary will focus primarily on the pivotal trials. Reference to other studies will be made only when such information has direct implications for the interpretation of the pivotal trial results.

1.3.1 Pivotal trials (design, endpoints, planned analyses)

In support of the proposed indication Thera Technologies has submitted the results of three phase III "pivotal trials." They are Studies TH9507/III/LIPO/010, TH9507-CTR-1011, and TH9507-CTR-1012.

Study TH9507/III/LIPO/010 was a randomized, double-blind, placebo-controlled, multicenter[1], Phase 3 study that evaluated the efficacy and safety of a daily tesamorelin dose of 2 mg in patients with HIV lipodystrophy. It included a 6-month Main Phase followed by a 6-month Extension Phase. Patients were initially randomized 2:1 drug to placebo. At the end of the Main Phase patients who completed the tesamorelin group were re-randomized 3:1 to either tesamorelin or placebo; in this document they are referred to as the tesamorelin-tesamorelin group (or T-T group) and tesamorelin-placebo (T-P) group. Patients who were in the placebo arm during the Main Phase were switched without further randomization to 2 mg of tesamorelin daily during the Extension Phase (P-T group).

Study TH9507-CTR-1011 was also a randomized, double-blind, placebo-controlled, multicenter[2], Phase 3 study, which evaluated the same 2 mg dose of tesamorelin in patients with HIV-lipodystrophy. It lasted 6 months and randomized patients 2:1 drug to placebo. It has an identical design with that described above for the Main Phase of Study TH9507/III/LIPO/010.

Study TH9507-CTR-1012 was a 6-month extension of Study TH9507-CTR-1011 and was virtually identical to the Extension Phase of Study TH9507/III/LIPO/010, except that the drug-to-placebo randomization ratio for patients who completed the tesamorelin group was 1:1 (instead of 3:1). As in Study TH9507/III/LIPO/010, all patients who completed the placebo arm were switched to a daily tesamorelin dose of 2 mg after completing 6 months of treatment.

For the sake of clarity, this review will simplify the nomenclature of the clinical trials and refer to these studies as follows:

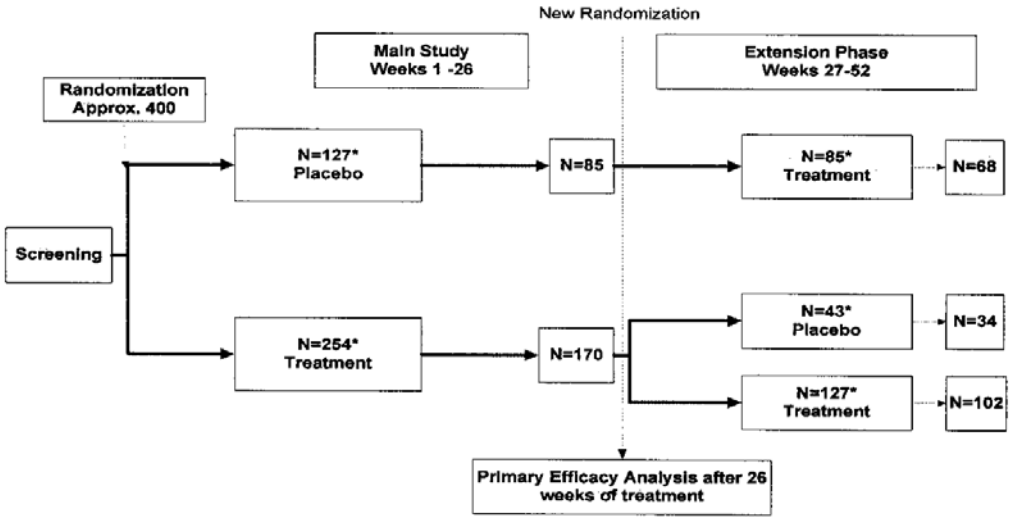
- Study TH9507/III/LIPO/010 will be referred to as "**Study 10**" and its extension as "**Study 10-extension**."
- Study TH9507-CTR-1011 will be referred to as "**Study 11**."
- Study TH9507-CTR-1012 will be referred to as "**Study 12**."

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**).

[1] 43 sites: 37 in US and 6 in Canada.
[2] 48 sites: 26 in US, 9 in Canada, and 13 in Europe.

A schematic representation of the pivotal trials can be found in applicant's Figure 1, 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 1. Study Schematic



Not only did Studies 10 and 11 have similar designs, but they also shared virtually identical inclusion criteria, as well as efficacy and safety assessments. Patients were included in the trials if they were adult (18 to 65 years), were HIV positive with a CD4 cell count > 100 cells/mm^3 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/m^2), 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 malignancy[3], 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. To enter the extension phase patients had to have had completed the first 26 weeks of the trial and to have a fasting blood glucose ≤150 mg at end of the Main Phase.

[3] 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.

Patients were stratified according to testosterone use and glucose status in Study 10[4] 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 cm^2 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:

- 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).

[4] 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).

2. Review of Efficacy

2.1 Main Phase

2.1.1 Baseline characteristics and demographics

The patient baseline characteristics for the individual studies and for both studies combined are shown in Table 1. 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/m^2; 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 1: 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 n (%)	**Male**	237 (86.8)	115 (83.9)	228 (84.4)	105 (83.3)	465 (85.6)	220 (83.7)
	Female	26 (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)	419 (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)	44 (8.1)	25 (9.5)

	Hispanic	21 (7.7)	13 (9.5)	23 (8.5)	12 (9.5)	71 (13.1)	34 (12.9)
	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/m^2)	**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 2). 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 regimen[5].

[5] 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

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

Table 2: 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)
	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 n (%)	**NRTI and NNRTI**	111 (40.7)	37 (27.0)	79 (29.3)	39 (31.0)	190 (35.0)	76 (28.9)

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.

	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 n (%)	**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)

Source: ISE Table 4

2.1.2 Subject Disposition

For a detailed summary of patient disposition of individual studies refer to the Appendix. 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 3, 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 3: 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
[a]Percentages based on the number of randomized subjects.
[b]Percentages based on the number of subjects in ITT population.
[c]Percentages based on number of subjects who discontinued prior to end of study.

2.1.3 Primary efficacy analysis

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 4 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 4: 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) Change (SE)		-17.8% (1.6) -27.4 (2.2)		+2.2% (2.2) +4.4 (3.2)	-19.6% (2.7) [-23.7, -15.3] p<0.001 -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) Change (SE)		-13.8% (1.5) -21.0 (2.4)		-2.4% (2.2) -0.4 (3.5)	-11.7% (2.7) [-16.2, -7.1] p<0.001 -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 5). 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).

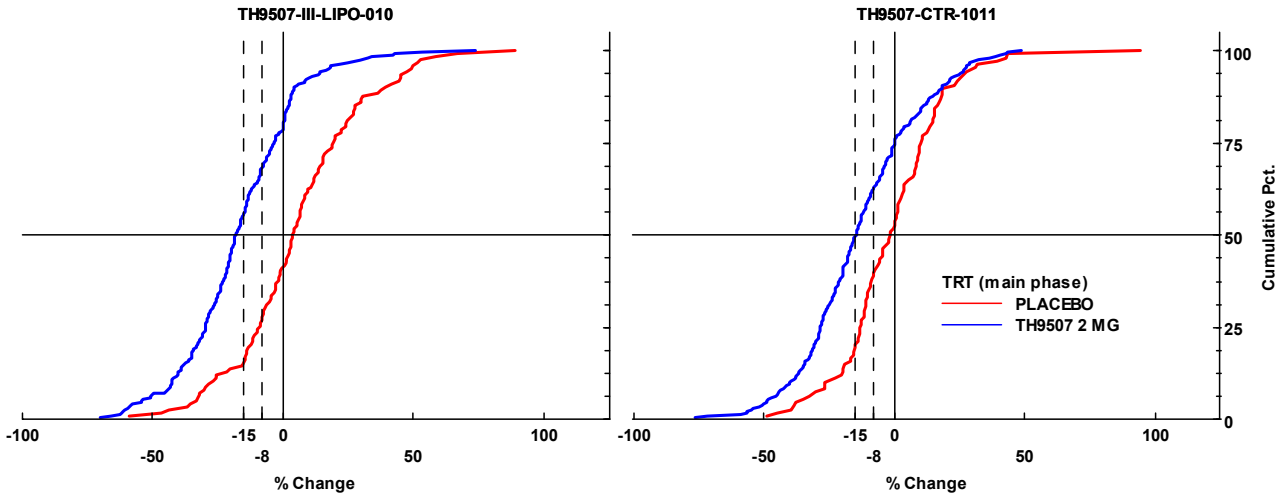
Table 5: ANCOVA* results for VAT % change from Baseline– Main Phase of Pivotal Trials (Individual Studies, Completers Only)

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 1: 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 6 (next page). The mean VAT at baseline was 182.36 cm^2 for the tesamorelin group and 182.49 cm^2 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 6: Change in VAT (cm^2) 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
[1]One tesamorelin patient and one placebo pateint were excluded from the analysis because their baseline VAT was missing.

Subgroup analyses by gender

Tables 7 and 8 (next page) 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 7: 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 (cm^2)		272	178 (76.9)	---	136	171 (76.9)	---	---
Week 13	**Actual value (cm^2)**	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 (cm^2)**	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 8: 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 (cm^2)		268	186 (86.6)	---	126	195 (95.5)	---	---
Week 13	**Actual value (cm^2)**	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 (cm^2)**	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.

2.1.4 Secondary efficacy endpoints

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 9, 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 9: 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 (hange 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 applicant's Table 3, 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 3: Overview of Ranked Secondary Variables for Study TH9507/III/LIPO/010 and Study TH9507-CTR-1011

	Ranking of Endpoint		
		Study TH9507-CTR-1011	
Secondary Endpoint	Study TH9507/III/LIPO/010	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.

IGF-1 Levels

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 10. 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 10: IGF-1 Change from Baseline to Week 26* -- Main Phase of Pivotal Trials

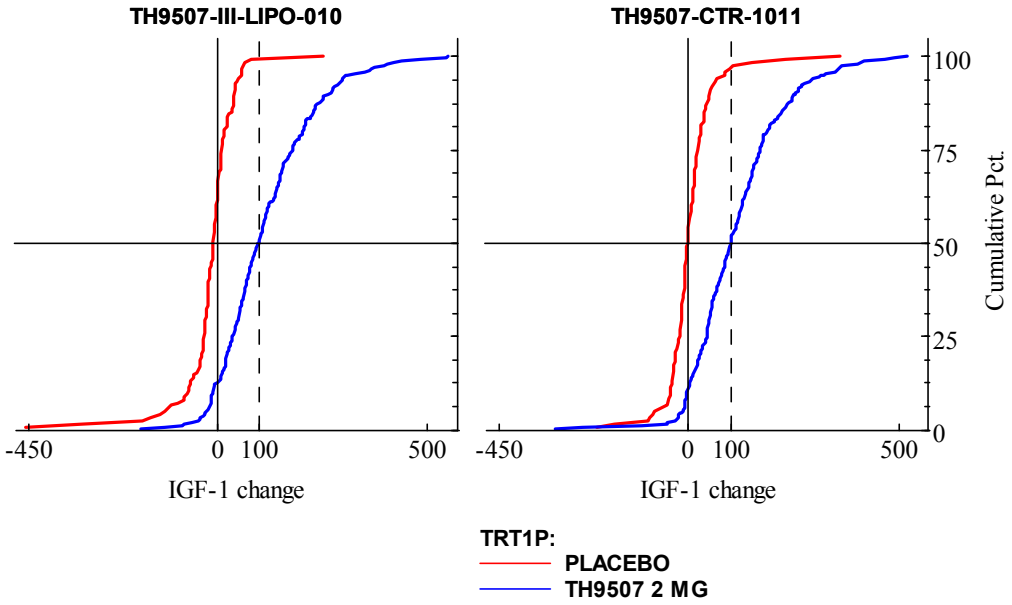
	Study 010				Study 011				Combined Results			
	Tesamorelin N=273		Placebo N=137		Tesamorelin N=270		Placebo N=126		Tesamorelin N=543		Placebo N=263	
Visit	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**n**	**Mean (SD)**
Baseline (ng/mL)	269	161.1 (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 2: Cumulative Distribution of IGF-1 from Baseline to Week 26 – Main Phase (Individual Pivotal Studies)



Source: FDA Statistical Review

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.

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 3:

Figure 3: PRO Scoring for Perceived Belly Size

Compared to my "healthy look," my current amount or size is…

Score	Patient's Answer	
-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 11 shows the descriptive statistics for BSE.

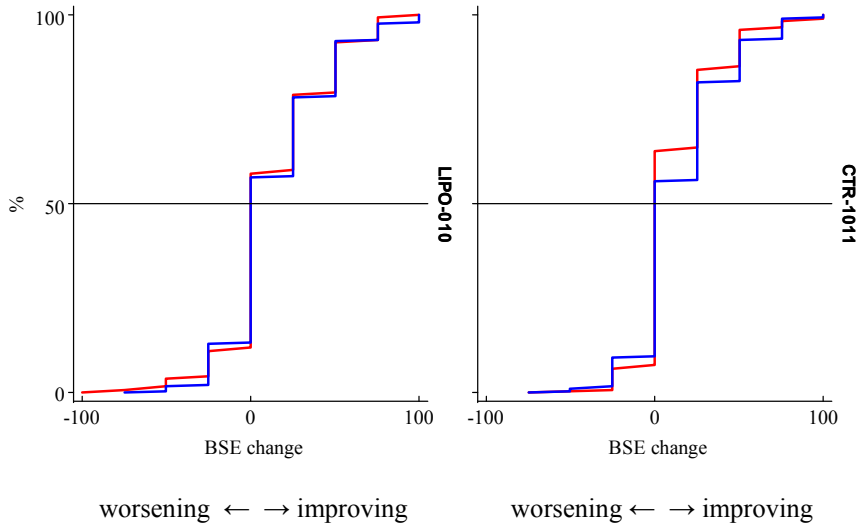
Table 11: Descriptive Statistics of Belly Size Evaluation[+] – Main Phase (Individual Pivotal Studies)

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 4 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 4: 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 Appearance Distress (BAD)

Subjects scored the distress related to their belly appearance using a body appearance distress scale (Figure 5). 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 5: 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 12.

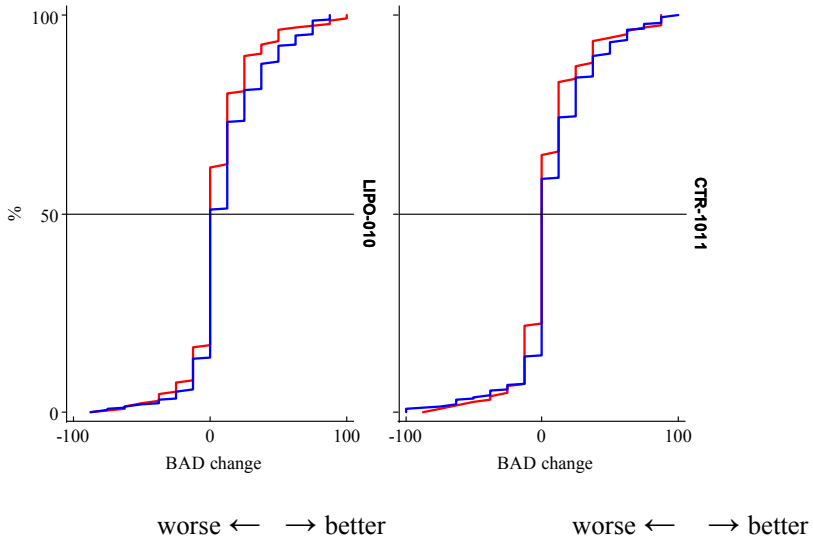
Table 12: Descriptive Statistics of Belly Appearance Distress* – Main Phase (Individual Pivotal Studies)

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
	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
	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 6 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 6: 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 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 13 displays the descriptive statistics from the FDA statistical review for responses to Belly Profile Question 1 in Studies 10 and 11.

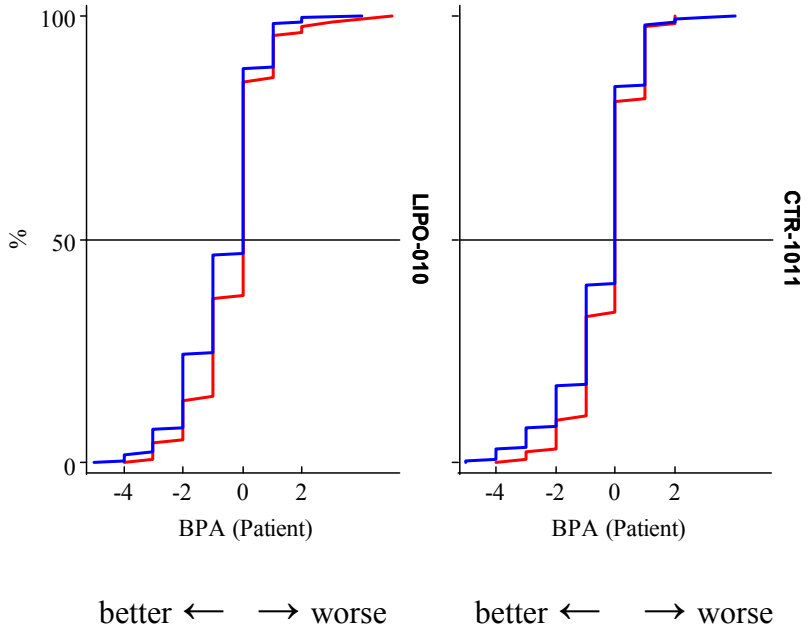
Table 13: Descriptive Statistics of Belly Profile (Question 1)* – Main Phase (Individual Pivotal Studies)

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

Figure 7: 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

Triglycerides

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 14).

Table 14 Triglyceride (mg/dL) Change from Baseline to Week 26 – Main Phase (Individual Studies)

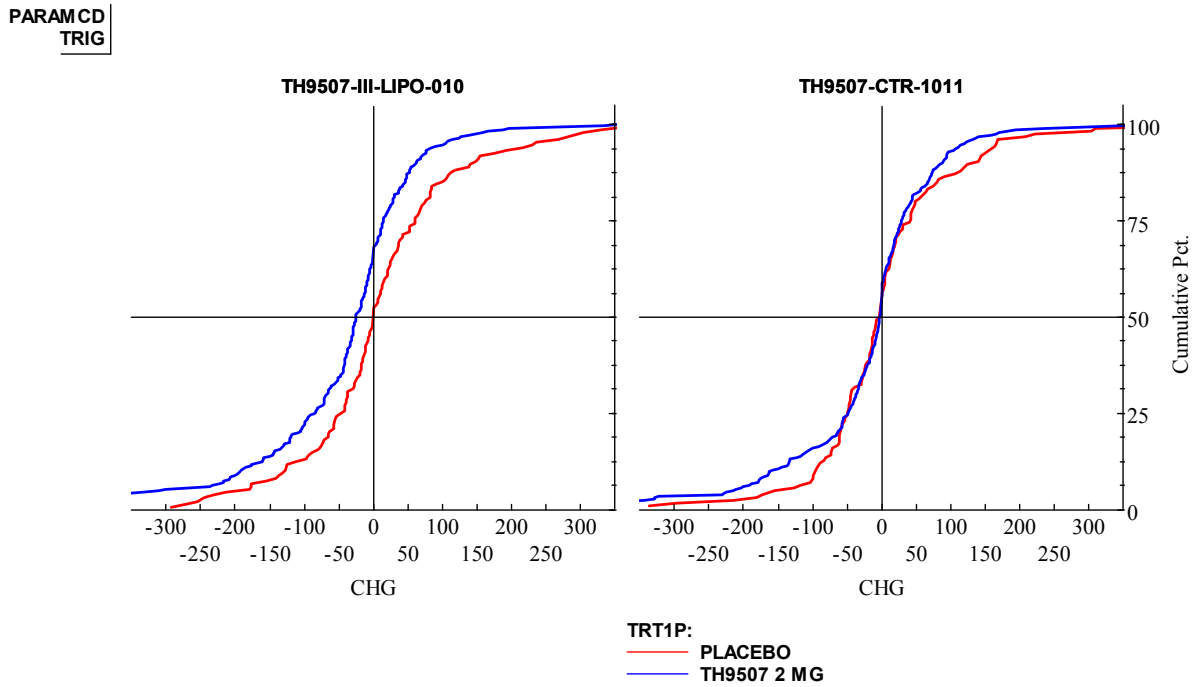
	Study 10			Study 11		
	Treatment		Difference from placebo*	Treatment		Difference from placebo*
	Tesamorelin N=273	Placebo n=137		Tesamorelin N=270	Placebo n=126	
Baseline mean (SD)	251.9 (188.1)	233.5 (145.0)		238.7 (261.3)	222.6 (143.9)	
LSM Change	-48.0	4.8	-52.8 (11.4)	-18.5 (6.9)	1.3	-19.9 (12.1)

from baseline (SE)	(6.6)	(9.3)	[-75.3, -30.4] p<0.001		(10.0)	[-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 8) indicate clear separation between drug and placebo in Study 10 but not in Study 11.

Figure 8: 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

Total Cholesterol: High-density Lipoprotein Cholesterol Ratio

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 15 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 15: Total Cholesterol: 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)	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.

Non HDL-Cholesterol

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 16).

Table 16: 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
[+]ITT population

2.1.5 Other Endpoints

Table 17 describes the changes from baseline to Week 26 in various parameters of body composition.

Table 17: Body Composition (Change from Baseline to Week 26) – Main Phase of Both Pivotal Studies

	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)	
Visit	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 (cm^2)												
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.

Source: ISE Table 10

The main findings from Table 17 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 18: Anthropometric Measurements (Change from Baseline to Week 26) – Main Phase of Both Pivotal Studies

	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)	
Visit	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

2.2 Extension Phase - Summary

This is a brief summary of the efficacy information provided in the extension trials (Study 10-extension and Study 12). The efficacy data are presented in detail in the Appendix.

Key findings for the Extension Phase studies are as follows:

- For the primary efficacy endpoint among patients who completed 52 weeks of tesamorelin (T-T group): sustained decrease from baseline in VAT, with a mean percent decrease of 17.50% for pooled data at the end of both studies.
- For patients who discontinued tesamorelin at Week 26 (T-P group): VAT re-accumulation, with a mean percent increase from baseline of 0.28% for pooled data at the end of both studies (after having showed a decrease of 14.50% at the time of tesamorelin discontinuation at Week 26).
- For additional efficacy endpoints among patients in the T-T group: sustained increases from baseline in LBM, IGF-1; improvement in belly appearance distress; decreases from baseline in trunk fat, total cholesterol, and non-HDL-C.

Percent change in VAT

Percent change in VAT was measured during the Extension Phase to evaluate the durability of tesamorelin's effect and determine whether a reversal of clinical effect occurs with discontinuation. At the start of the Extension Phase, mean VAT had decreased by 17.11% in the T-T group and by 14.50% in the T-P group. 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 ($p<0.001$). In the T-T group, there was a relatively small percent change from Week 26 to Week 52 (+4.5% for Study 10-extension and -1.4% for Study 12), whereas patients in the T-P groups experienced a significant increase in VAT % during the Extension Phase (+24.9% for Study 10-extension and +24.5% for Study 12).

IGF-1

At the start of the Extension Phase (after 26 Weeks of treatment with tesamorelin), mean IGF-1 had increased by 93.94% in the T-T group and by 100.52% in the T-P group. 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 (+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 change from Week 0 of -2.40%) This pattern held through Week 52, with a mean IGF-1 increase of 63.07% and a decrease of 9.07% for T-T and T-P groups respectively ($p<0.001$).

Patient Related Outcomes related to body image

For belly size image, belly appearance distress, and belly profile, the data indicates that the modest improvement in both tesamorelin and placebo groups at Week 26 was sustained 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-extension and a modest improvement in Study 12. For BAD and BP, T-P patients again experienced a modest decline for Study 10-extension and no significant change for Study 12. These results suggest that similar to the Main Phase, the effect of tesamorelin on various PRO measures is mixed.

Triglycerides, Total Cholesterol: HDL-C ratio, Non-HDL-C
In the Extension Phase Studies 10-extension and 12, the change from baseline (Week 0) to Week 52 for triglycerides and total cholesterol: HDL-C ratio was not statistically significant between the T-T and T-P groups. However, the change from baseline (Week 0) to Week 52 for non-HDL-C was considered statistically significant (p=0.034) with a mean decrease observed in the T-T group and a mean increase in the T-P group.

VAT/SAT Ratio
Tesamorelin maintained its reduction of the VAT/SAT ratio during the Extension Phase. The mean change from baseline (Week 0) in VAT/SAT ratio was significantly different between the T-T and T-P groups during both individual Extension Phase Studies. 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.

Total Body Fat, Total Limb Fat, Trunk Fat, Lean Body Mass
For both individual Extension Phase studies, patients in the T-T group had a statistically significant decrease from baseline (Week 0) to Week 52 in total body fat and trunk fat compared with T-P, along with a statistically significant increase in LBM. However, the change in total limb fat was not considered statistically significant.

Anthropometric Measurements
For both individual Extension Phase studies, patients in the T-T group had a statistically significant decrease from baseline (Week 0) to Week 52 in waist circumference compared with T-P. Compared to baseline, patients in the T-T group had a decrease in waist circumference of 3.43 cm, compared with a decrease of 1.78 cm for the T-P group (treatment effect of about 1.6 cm). There was not a statistically significant difference for hip circumference for the T-T and T-P groups.

2.3 Efficacy Conclusions

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.

3. REVIEW OF SAFETY

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 19). 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 19: 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.

3.2 Nonfatal Serious Adverse Events (SAEs)

3.2.1 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)[6]: 3.7% in tesamorelin-treated groups and 4.2% in the placebo groups. Largely, there were similar

[6] 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.

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 ≥ 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 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.

3.2.2 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, diarrhea, stomach discomfort, hypersensitivity, nasopharyngitis, abscess, anogenital warts, bone tuberculosis, pneumonia, urinary tract infection, ancillary mass, peripheral neuropathy, spinal cord disorder, dysphonia, pharyngolaryngeal pain, acne, and night sweats. 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.

3.3 Trial discontinuations due to adverse events

3.3.1 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 ≥ two patients and with greater frequency in the tesamorelin group relative to the placebo group are presented in Table 20. 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 20: 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.

3.3.2 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 ≥ 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 21. 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 21: 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.

3.4 Treatment-emergent adverse events (TEAEs)

3.4.1 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 22 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, parasthesia/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 tesamoralin 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 22: 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
Hypertrigyceridemia	6 (1.1)	1 (0.4)

*Included are adverse events occurring in ≥1% that had a higher frequency in the tesamorelin combined group relative to placebo
Source: ISS Table 1.4.1.1.

Table 23 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 23: 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)
Hyopesthesia	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 ≥1% that had a higher frequency in the tesamorelin combined group relative to placebo.
Source: ISS Table 1.4.1.8.

3.4.2 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 24 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, parasthesias, 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 24: 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 25; included are only AEs that occurred in ≥ 1% of tesamorelin-treated subjects and were more frequently seen with the study drug than placebo. Unlike the Main Phase wherein the 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 25: 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 ≥1% that had a higher frequency in the tesamorelin combined group relative to placebo
Source: ISS Table 1.4.1.9.

3.5 Adverse Events and Other Safety Assessments of Interest

3.5.1 Cancer

As shown in Table 26, 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 26: 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. Two of these patients were in the tesamorelin group during the Main Phase (with one developing rectal cancer and the other basal cell carcinoma), and the third was in the P-T group during the Extension Phase (and developed a lung neoplasm).

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 27 shows the incidence of individual injection site reactions for the Main Phase of the Pivotal Trials.

Table 27: 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 ≥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.

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 28). 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 28: 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 ≥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 29).

Table 29: 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

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.

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 30). 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 30: 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 31. 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 31: 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 32.

Finally, the patients in the P-T group (not included in Table 32), 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 32: 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 33. 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 33: 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)

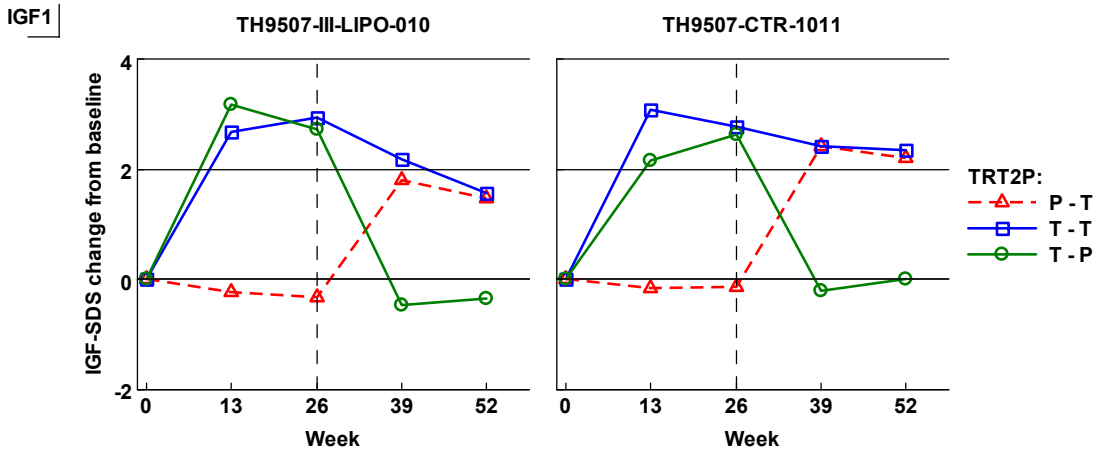
	Range	-2.7, 12.2	-2.9, 3.0	-1.5, 2.9	-1.9, -0.3
	SDS > +2 (%)	61 (36.3)	5 (6.3)	3 (13.6)	0
	SDS > +3 (%)	43 (25.6)	1 (1.3)	0	0

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 9, 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. It should be mentioned that these analyses do not account for the potential confounding effect of non-compliance. Non-compliance in Study 10-extension was 31.3% and it was even higher in Study 12 (50%). This suggests that, had patients been fully compliant, they could have conceivably had even higher mean IGF-1 SD scores (per protocol, a patient was deemed non-compliant if he received <80% of the planned study drug doses).

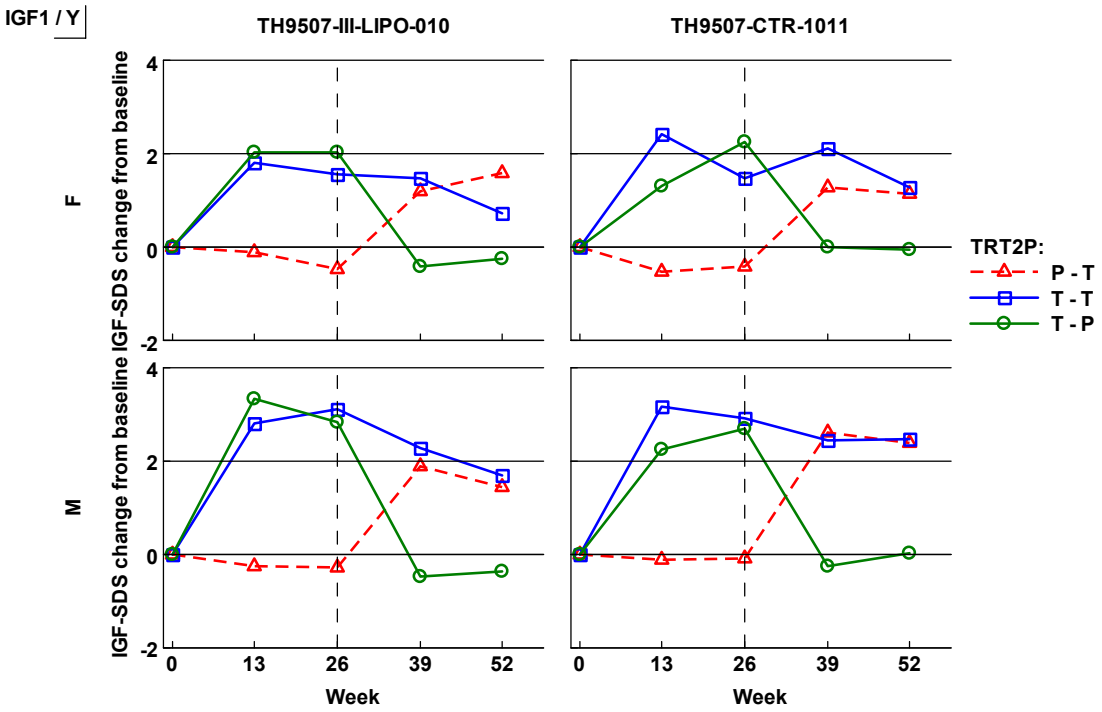
Figure 9: Mean IGF-1 Standard Deviation score (SDS) Over Time by Treatment Sequence – Extension Phase Completers



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 10. 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 10: 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 malignances.
- 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.

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 ≥ 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 34.

Table 34: 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)	2.65 (15.89)	0.70 (16.58)	
LSM	2.68	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)	0.03 (29.29	1.43 (21.93)	
LSM	0.84	-0.24	0.4992
HOMA-IR – baseline			
Mean (SD)	710.62 (1066.53)	603.30 (543.23)	
HOMA-IR – change from baseline			
Mean (SD)	-2.44 (1092.22)	56.33 (911.86)	
LSM	26.36	-2.59	0.6474
HbA1c %– baseline			
Mean (SD)	5.26 (0.50)	5.28 (0.48)	
HbA1c % – change from baseline			
Mean (SD)	0.14 (0.40)	0.02 (0.36)	
LSM	0.15	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 35).

Table 35: 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			0.6819
Mean (SD)	1.87 (14.48)	-2.02 (28.24)	
LSM	0.84	-0.13	
Insulin (µIU/mL) – baseline			
Mean (SD)	19.46 (20.22)	25.91 (31.38)	
Insulin (µIU/mL) – change from baseline			
Mean (SD)	-0.41 (19.52)	-6.88 (30.60)	
LSM	-2.04	-3.38	0.3588
HOMA-IR – baseline			
Mean (SD)	614.09 (737.73)	934.01 (1408.46)	
HOMA-IR – change from baseline			
Mean (SD)	-4.93 (718.09)	-315.65 (1430.24)	
LSM	-90.51	-126.43	0.5350
HbA1c %– baseline			
Mean (SD)	5.23 (0.50)	5.27 (0.47)	
HbA1c % – change from baseline			
Mean (SD)	0.07 (0.37)	0.08 (0.54)	0.6789
LSM	0.09	0.07	

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

Shifts in FBG

Main Phase

Table 36 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 36: 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 37 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 37: 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 38 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 38: 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 39 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 39: 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 40 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 40: 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 41 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 41: 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 ≥ 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 ≥ 6.5%.

Hemoglobin A1c: Extension Phase

Table 42 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 42: 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% ≤ A1c < 6.5%
DM = A1c ≥6.5%
Source: Table From Sponsor

Table 43 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 43: 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.

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 11. 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 Phase[7]). 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-assay[8]. Anti-tesamorelin neutralizing antibody testing was not performed in all

[7] Study 12 had an additional timepoint at Week 32.

[8] Neutralizing activity was tested via an in *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.

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.

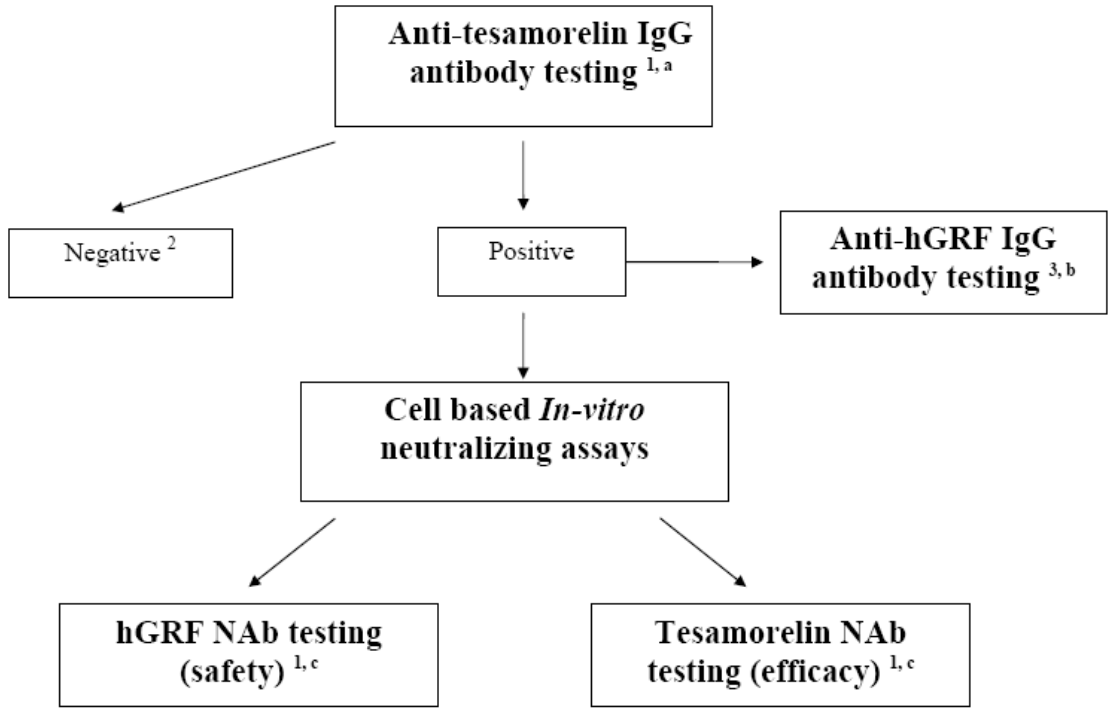
It appears that the applicant was concerned with performing the antibody testing at the time of the longest exposure to tesamorelin and that this is the unifying concept for the above-described testing plan; simpler said, all patients were tested at the last timepoint of tesamorelin treatment. In the 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.

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 11: General Immunogenicity Analysis Scheme for Pivotal Trials



Source: Sponsor's Figure

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 antibodies[9] (Table 44). 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, 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

[9] 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".

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 44: 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 45). The mean percent VAT change from baseline was similar for patients receiving tesamorelin regardless of antibody status and not statistically different.

Table 45: 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 (cm2)		
N	11	508
Mean	178.13	182.22
(SD)	(75.33)	(82.27)
Week 26 VAT (cm2)		
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

[a]P-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 ≥ 8% relative to their baseline value). These results are presented in Table 46. 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 46: 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 47 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 47: 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) LSM	(124.56) 123	(101.37) 126
P-Value[a]	0.85	

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
[a]P-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 48, 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 48: 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 (91.1ng/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.

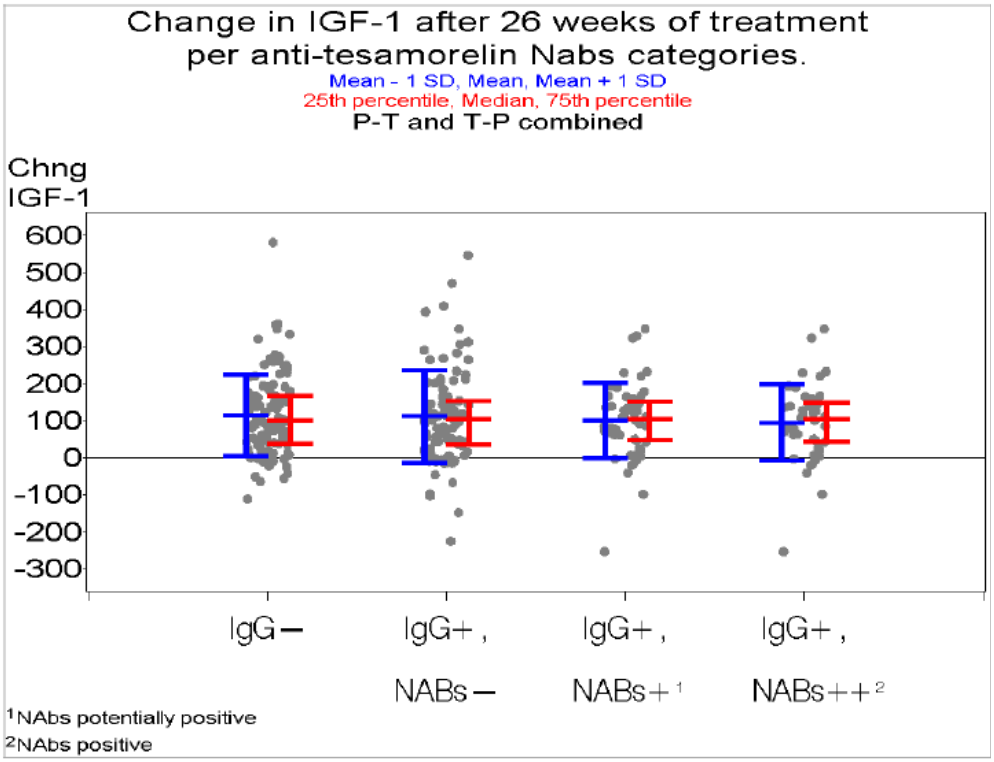
A description of the time-course of developing neutralizing antibodies cannot be made because (with the exception of a subset of patients in the T-P arm) the applicant has tested for neutralizing antibody activity only at a single timepoint in the trial (Week 52 for the T-T arm after 26 weeks of treatment 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).

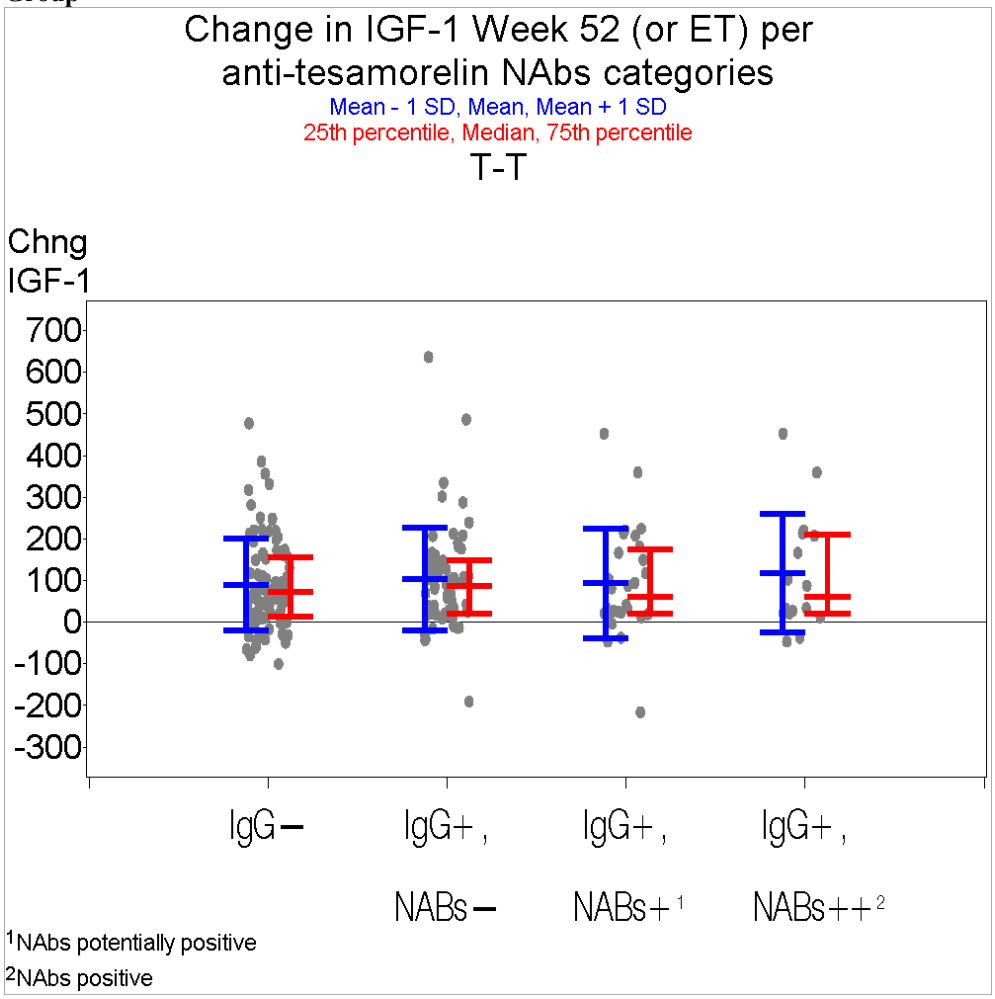
Figures 12 and 13 below show the effect of tesamorelin neutralizing antibodies on IGF-1. These figures illustrate the IGF-1 profiles for patients who did not develop anti-tesamorelin antibodies ("IgG-") along with patients who developed anti-tesamorelin antibodies but not neutralizing antibodies ("IgG+, NABs-") and patients who developed both anti-tesamorelin antibodies and neutralizing antibodies ("potentially positive" or "IgG+,NABs" and "positive" "IgG+,NABs++"). Figure 11 presents data collected for the P-T and T-P arms combined and Figure 12 for the T-T arm only. Qualitatively, these indicate similar IGF-1 profiles for patients with and without neutralizing antibodies.

Figure 12: Change in IGF-1 After 26 Weeks of Treatment Based on Tesamorelin NAb Status – T-P and P-T Groups



Source: Applicant's Immunogenicity Report

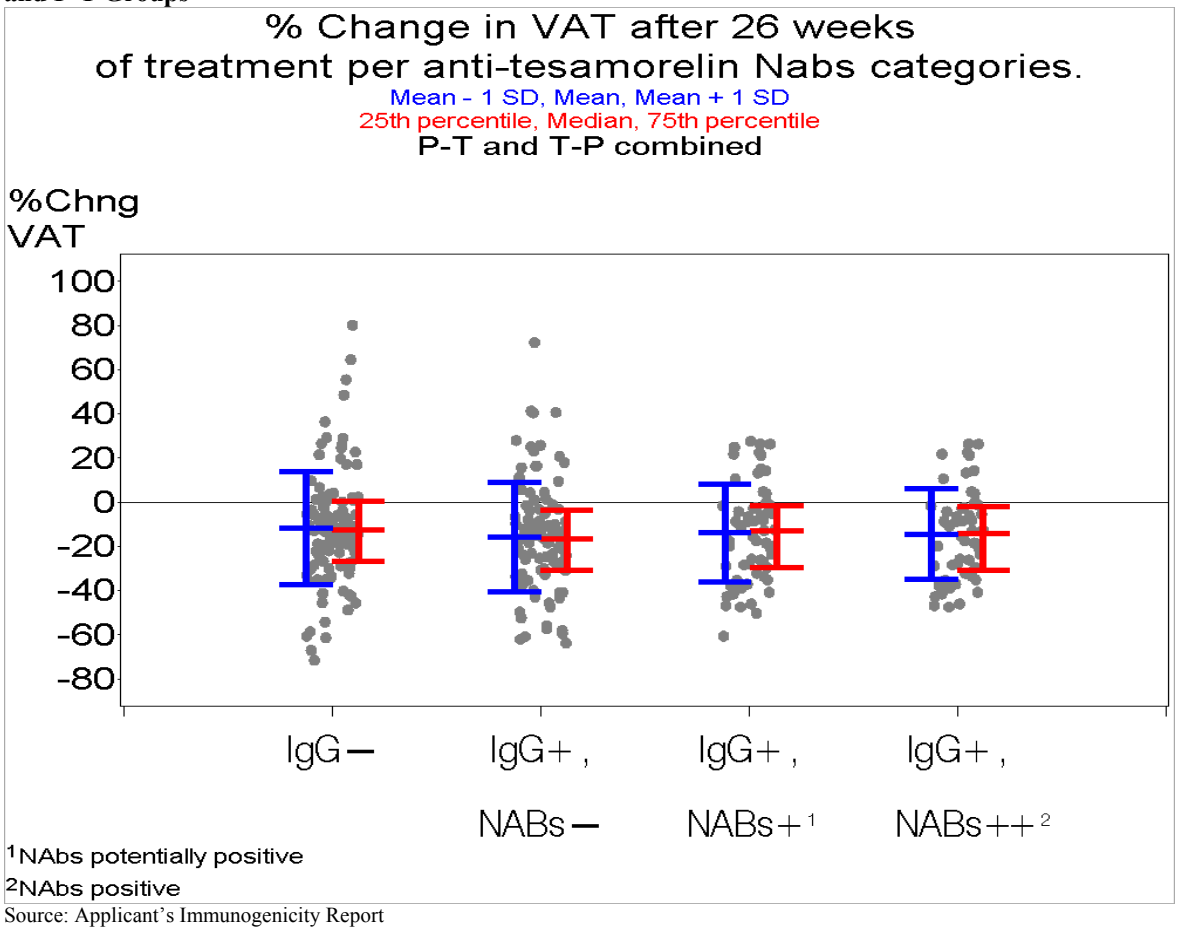
Figure 13: Change in IGF-1 After 52 Weeks of Treatment Based on Tesamorelin NAb Status – T-T Group



Source: Applicant's Figure

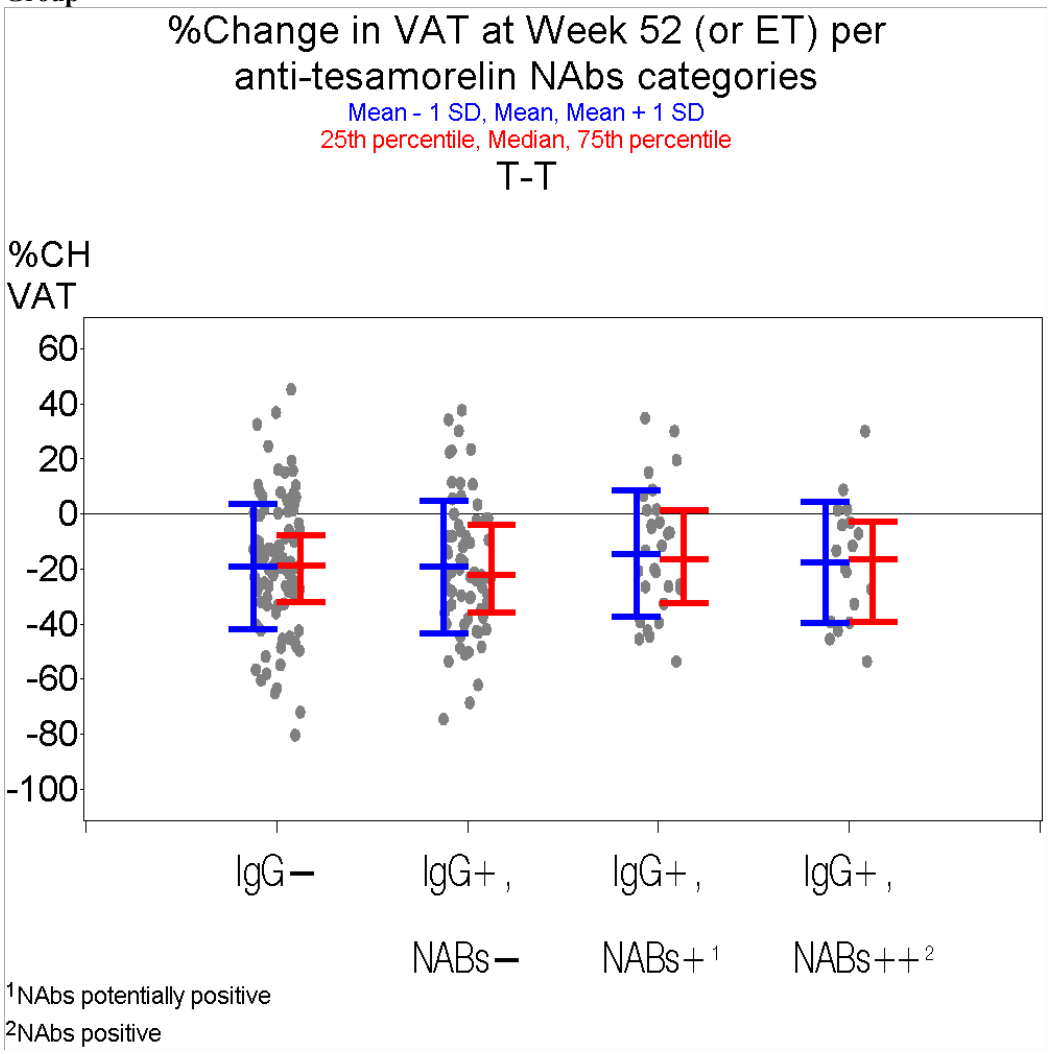
Similar to Figures 12 and 13 presented above, Figures 14 and 15 illustrate the VAT profiles for patients who did not develop anti-tesamorelin antibodies ("IgG-") along with patients who developed anti-tesamorelin antibodies but not neutralizing antibodies ("IgG+, NABs-") and patients who developed both anti-tesamorelin antibodies and neutralizing antibodies ("potentially positive" or "IgG+,NABs" and "positive" "IgG+,NABs++"). Figure 13 presents data collected for the P-T and T-P arms combined and Figure 14 for the T-T arm only. Qualitatively, the graphs indicate similar VAT profiles for patients with and without neutralizing antibodies.

Figure 14: Change in VAT After 26 Weeks of Treatment Based on Tesamorelin NAb Status – T-P and P-T Groups



Source: Applicant's Immunogenicity Report

Figure 15: Change in VAT After 52 Weeks of Treatment Based on Tesamorelin NAb Status – T-T Group



Source: Applicant's Figure

Anti-tesamorelin Antibodies – Cross Reactivity with human GHRH

Patients who developed anti-tesamorelin antibodies were tested for cross-reactivity with human GHRH[10]. 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 tested[11]. The results are presented in Table 49 by study. The cross reactivity was consistently seen at approximately 60% for each individual study.

[10] 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"

[11] 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 49: 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).

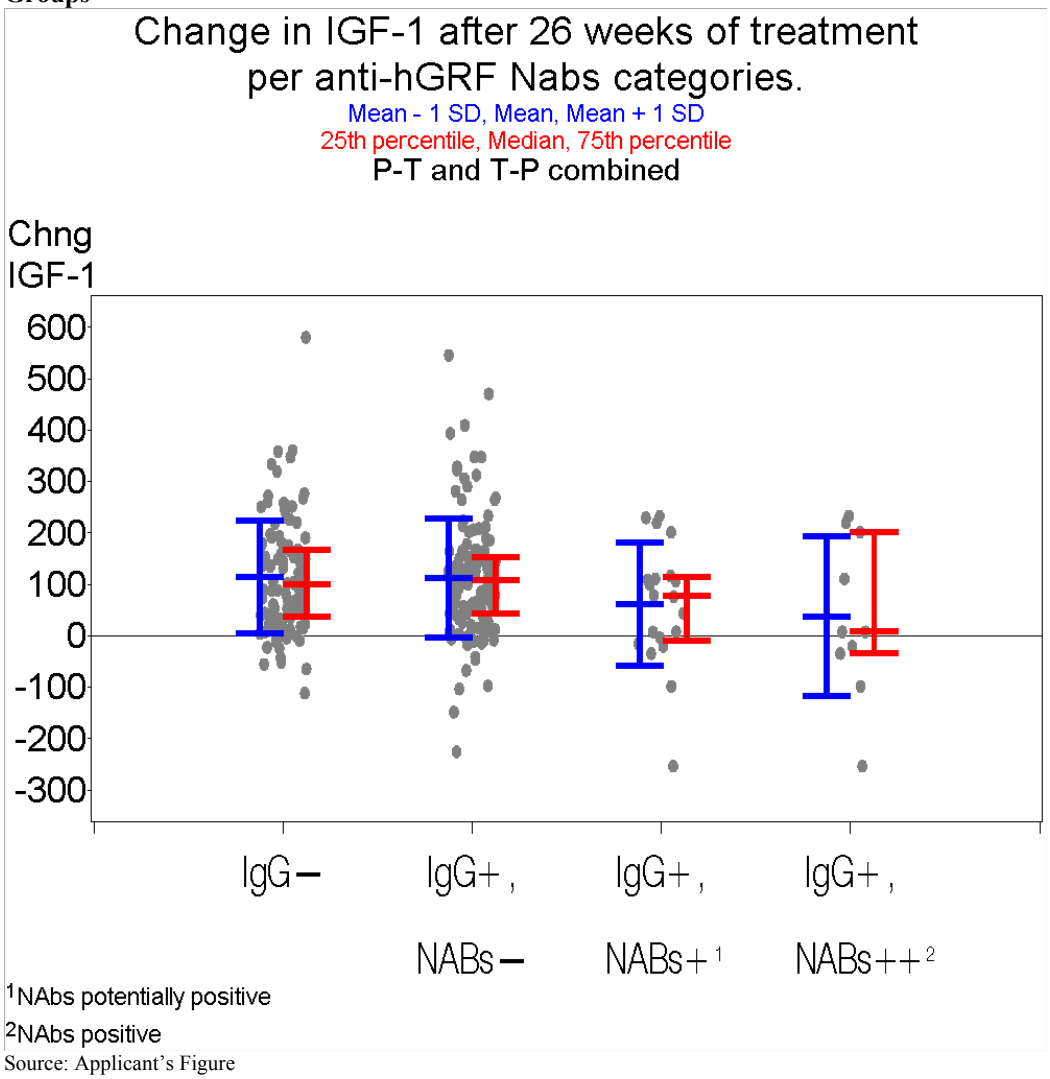
It should be mentioned that the only instance where neutralizing antibody testing was done at two successive timepoints was in the group just described (T-P group, at Week 26 and Week 52 in a subgroup of patients who were anti-tesamorelin positive at Week 52). The number of patients with positive samples 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)

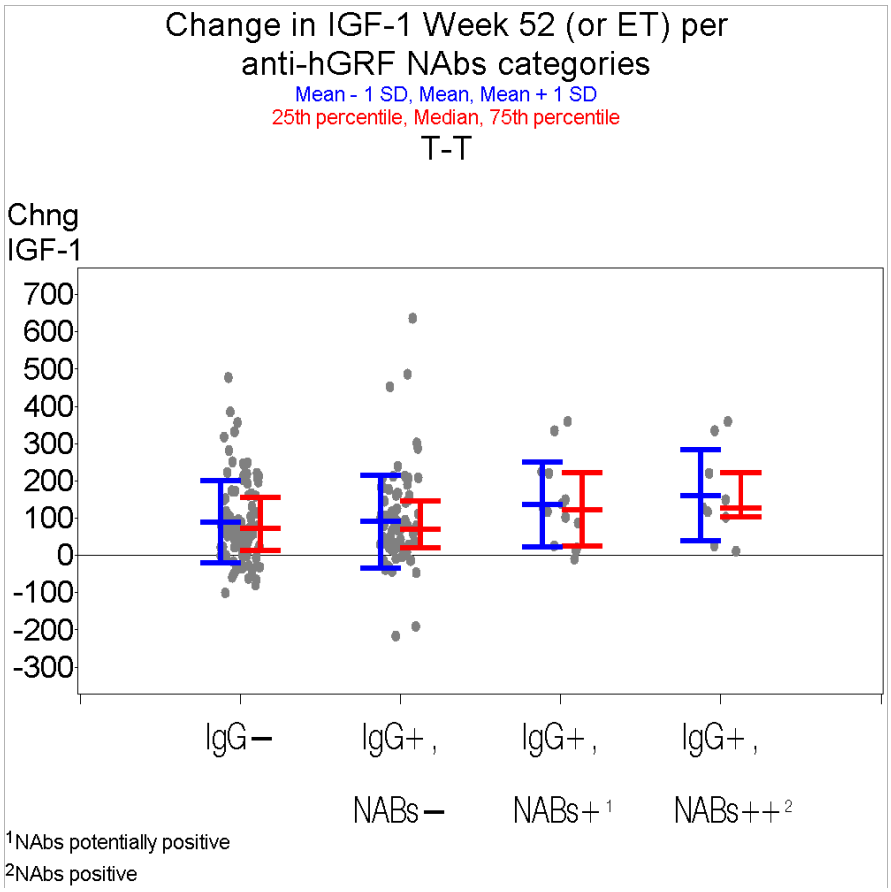
regarding IGF-1 changes at Weeks 26 and 52. These graphs (Figures 16 and 17) illustrate IGF-1 profiles for the antibody-negative and antibody-positive patients (including patients with neutralizing anti-GHRH antibodies). Figure 15 depicts the change in IGF-1 after 26 weeks of treatment (P-T and T-P groups), while Figure 16 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 16: Change in IGF-1 After 26 Weeks of Treatment Based on hGRF NAb Status – T-P and P-T Groups



Source: Applicant's Figure

Figure 17: Change in IGF-1 After 26 Weeks of Treatment Based on hGRF NAb Status – T-P and P-T Groups



[1]NAbs potentially positive
[2]NAbs positive
Source: Applicant's Figure

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.

3.6 Safety Conclusions

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 (1/2 over 2 SD and 1/3 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 malignances 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.

Appendix

Main Phase

Schedule of Assessments

Figure A1 describes the schedule of assessments in the Main Phase (Weeks 0-26).

Figure A1: Schedule of Assessments – Main Phase of Pivotal Studies

	Screening	Randomization	Treatment Period (Visit window ±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
Assessment/Procedure	**-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 Section 2.1

Patient Disposition

Study 10

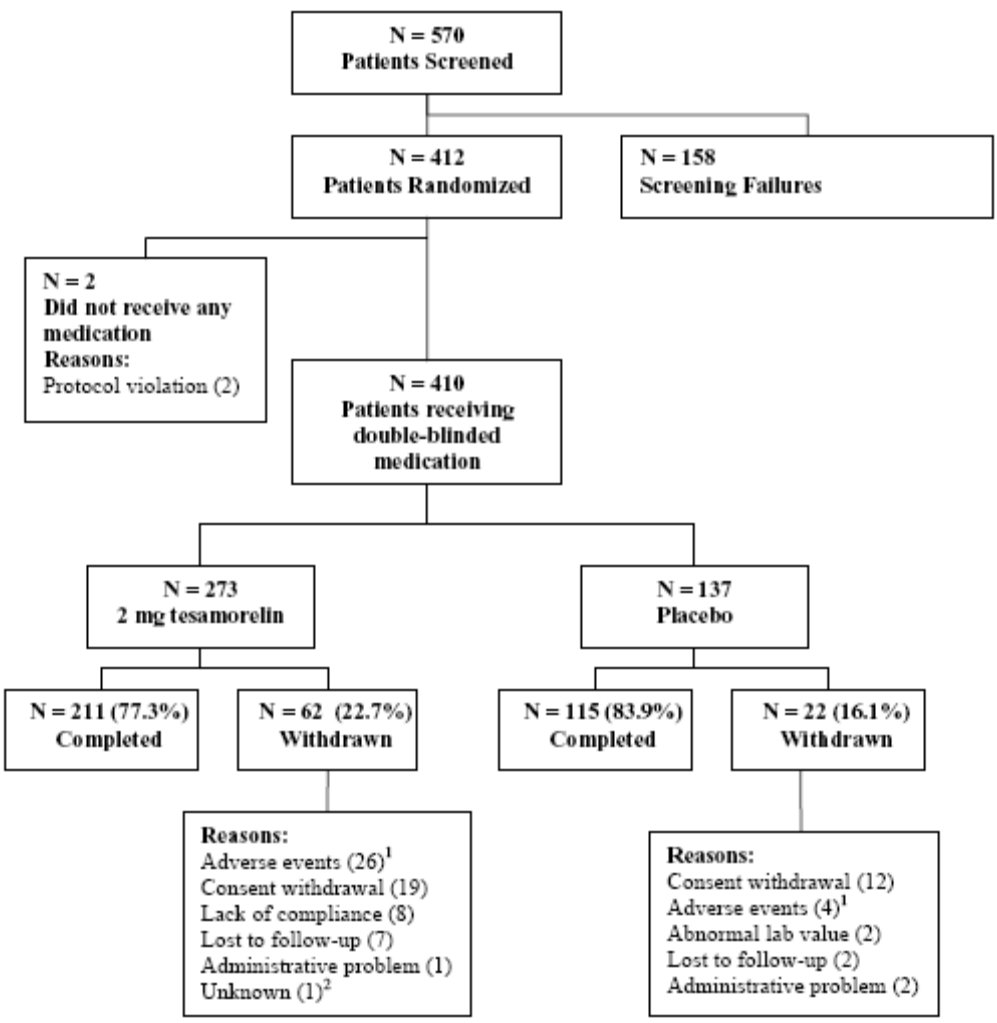
In total, 570 individuals were screened and 412 were randomized to receive tesamorelin or placebo. Two patients who were randomized to the tesamorelin arm did not receive any study drug when it was revealed that their testosterone regimen had changed in violation of an exclusion criterion. Thus, in total, 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 (≥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 A2 depicts patient disposition during the Main Phase of Study 10.

Figure A2: Patient Disposition – Study 10



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

Study 11

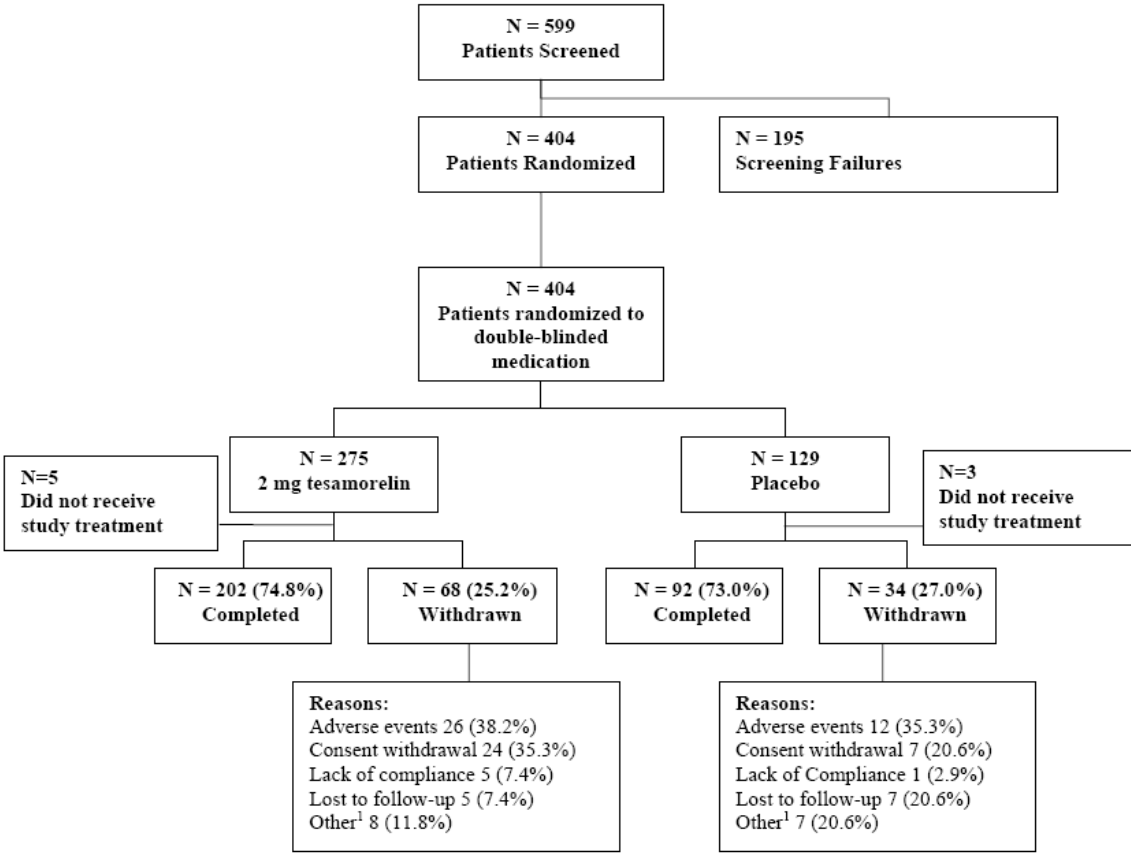
In total, 599 individuals were screened; 195 failed screening procedures and thus, 404 were randomized into the study. Reasons for screen failure were: failure to meet inclusion criteria (137 patients, 70.3%), withdrawal of consent (25 patients,12.8%), and other (32 patients,16.4%). The reason for screen 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 A3 depicts patient disposition during the Main Phase of Study 11.

Figure A3: Patient Disposition – Study 11



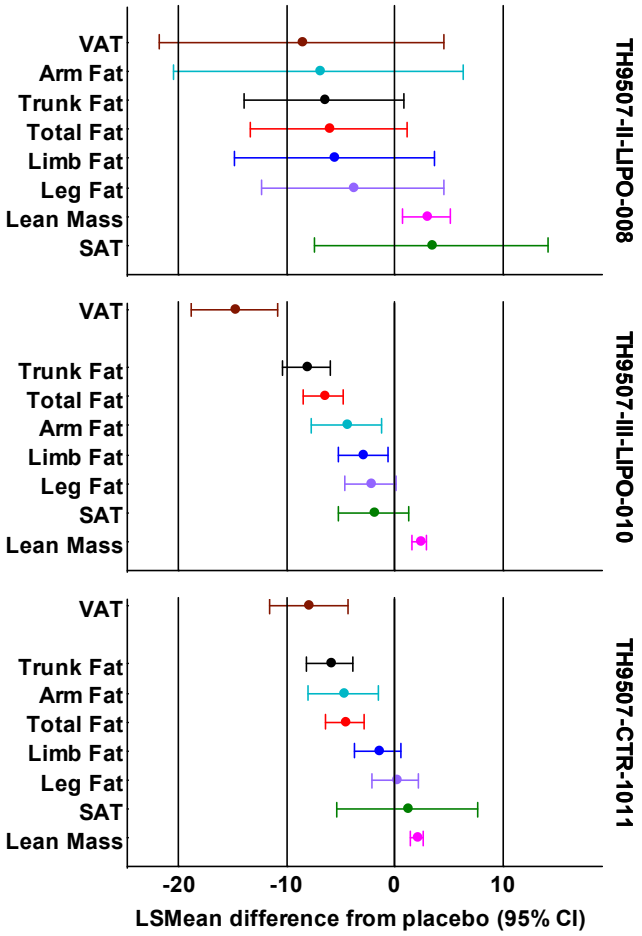
Source: TH9507-CTR-1011 CSR – Figure 2

Additional Secondary/"Other" Endpoint Analyses

Figure A4 illustrates the mean treatment difference and 95% confidence intervals between tesamorelin and placebo for the percent change in a number of

secondary/"other" efficacy endpoints. The analysis, performed by FDA statistical reviewer Lee-Ping Pian, includes the ITT populations from Studies 10 and 11 as well as the 12-week Phase 2 Study 008 (therefore the timeperiod covered is Baseline to Week 12 for the pivotal studies and the entirety of Study 008). Using a LOCF analysis, the figure indicates that the only endpoint in which there was a statistically significant change across all three studies was lean body mass, which increased over the 12-week time course. For Study 008, this was the only endpoint that demonstrated a statistically significant change. VAT, trunk fat, total fat, and arm fat showed statistically significant decreases in both pivotal studies. While limb fat showed a statistically significant decrease in Study 10, it did not in Study 11. Changes in leg fat and subcutaneous abdominal fat did not reach statistical significance in either pivotal trial.

Figure A4: Mean Treatment Difference Between Tesamorelin and Placebo – Secondary/"Other" Efficacy Endpoints (Baseline to Week 12, Studies 10, 11, 008)



Source: Statistical Review

Extension Phase

Schedule of Assessments

Figure A5 describes the schedule of assessments in the Extension Phase.

Figure A5: Schedule of Assessments – Extension Phase of Pivotal Studies

	Randomization	Treatment Period (Visit window ±4 days)				Post-treatment
	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10 / ET	
	Week 26	Week 32	Week 39	Week 45	Week 52	
Assessment/Procedure	182 days	224 days	273 days	315 days	364 days	30-day Follow-up
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	✓				✓	

[5] IGF-1 levels were measured for the purposes of safety and efficacy assessment.
[6] LDL-C and Apolipoproteins A1 and B were not assessed.

Source: ISE Section 2.1

Baseline characteristics and demographics

As shown in Table A1, 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/m^2 and 100.9 cm, respectively) compared to the T-T group (28.6 kg/m^2 and 99.1 cm, respectively).

Table A1: 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 (18.1)
	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 A2, 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 A2: 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/m^2)	**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.

Patient Disposition

Table A3 describes patient disposition and reasons for patient withdrawal in the Extension Phase studies.

Table A3: Patient Disposition – Extension Phase (Individual Pivotal Studies)

	Study 10-extension			**Study 12**		
Completed Main study	**Tesamorelin N=211**		**Placebo N=115**	**Tesamorelin N=202**		**Placebo N=92**
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%)

	Study 10-extension			Study 12		
Completed Main study	**Tesamorelin N=211**		**Placebo N=115**	**Tesamorelin N=202**		**Placebo N=92**
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**
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

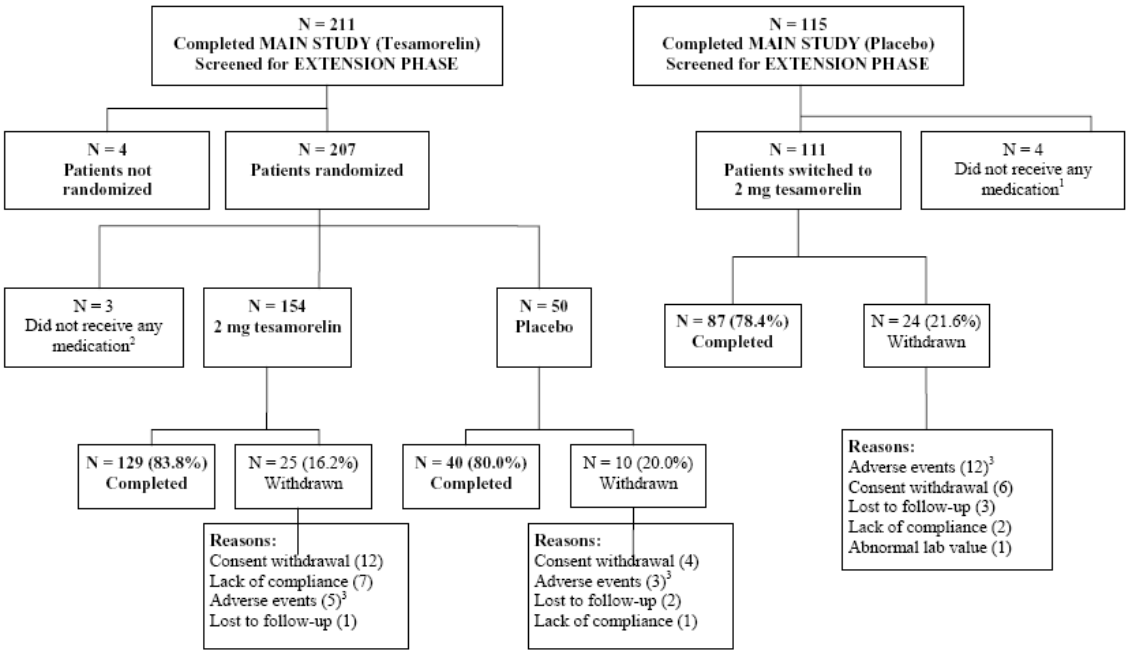
Study 10-extension

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 (≥78%) and similar among the three treatment groups.

Figure A6 outlines patient disposition during the Extension Phase of Study 10.

Figure A6: Patient Disposition – Study 10-extension



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

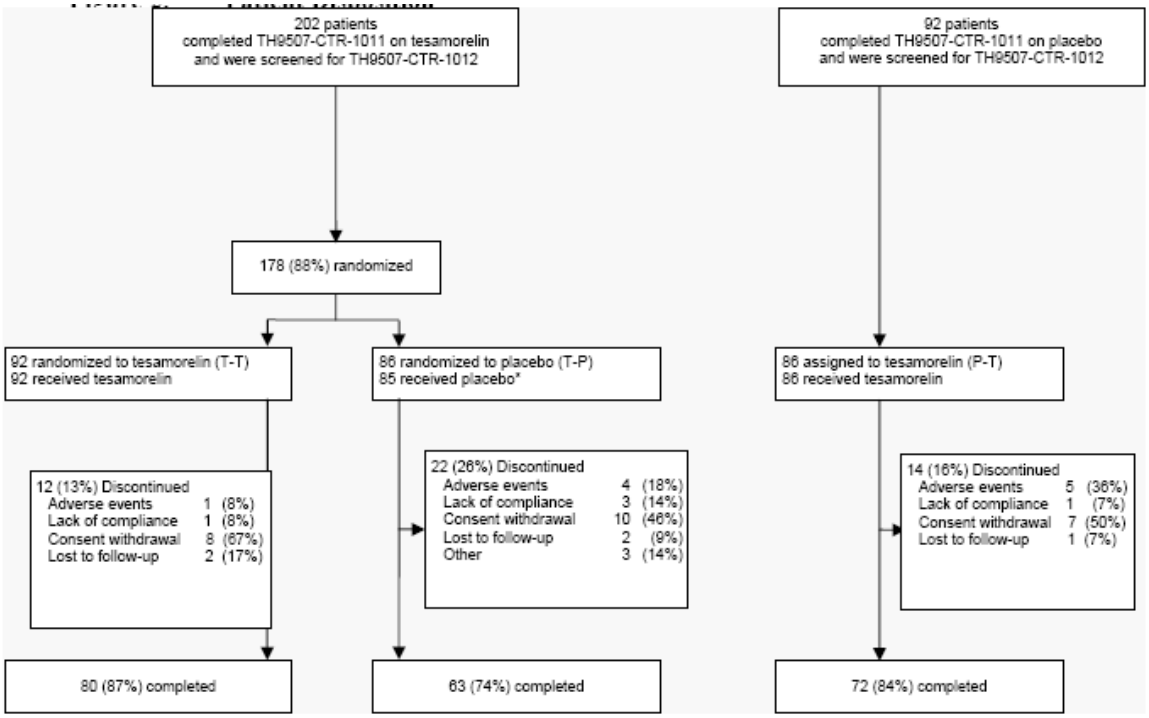
Study 12

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 A7 outlines patient disposition during Study 12.

Figure A7: Patient Disposition – Study 12



Source: TH9507-CTR-1012 CSR – Figure 2

Both Pivotal Studies Combined

As shown in Table A4, 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 A4: 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

Primary Efficacy Endpoint

Analyses of Visceral Adult Fat

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 A5), 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 A5: 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 (cm^2)/ (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 (cm^2)/ (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 (cm^2)/ (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 A6, 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 A6: 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 (cm^2)/ (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	**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 (cm^2)/ (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	**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	-31.62	-5.38	-24.36	-41.06	0.04	-26.13

	from Baseline (cm^2)/ (SD)	(45.46)	(39.96)	(41.87)	(57.42)	(52.61)	(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 A7 provides further ANCOVA analysis of the treatment difference from placebo in VAT for the indivdual 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 signficant 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.

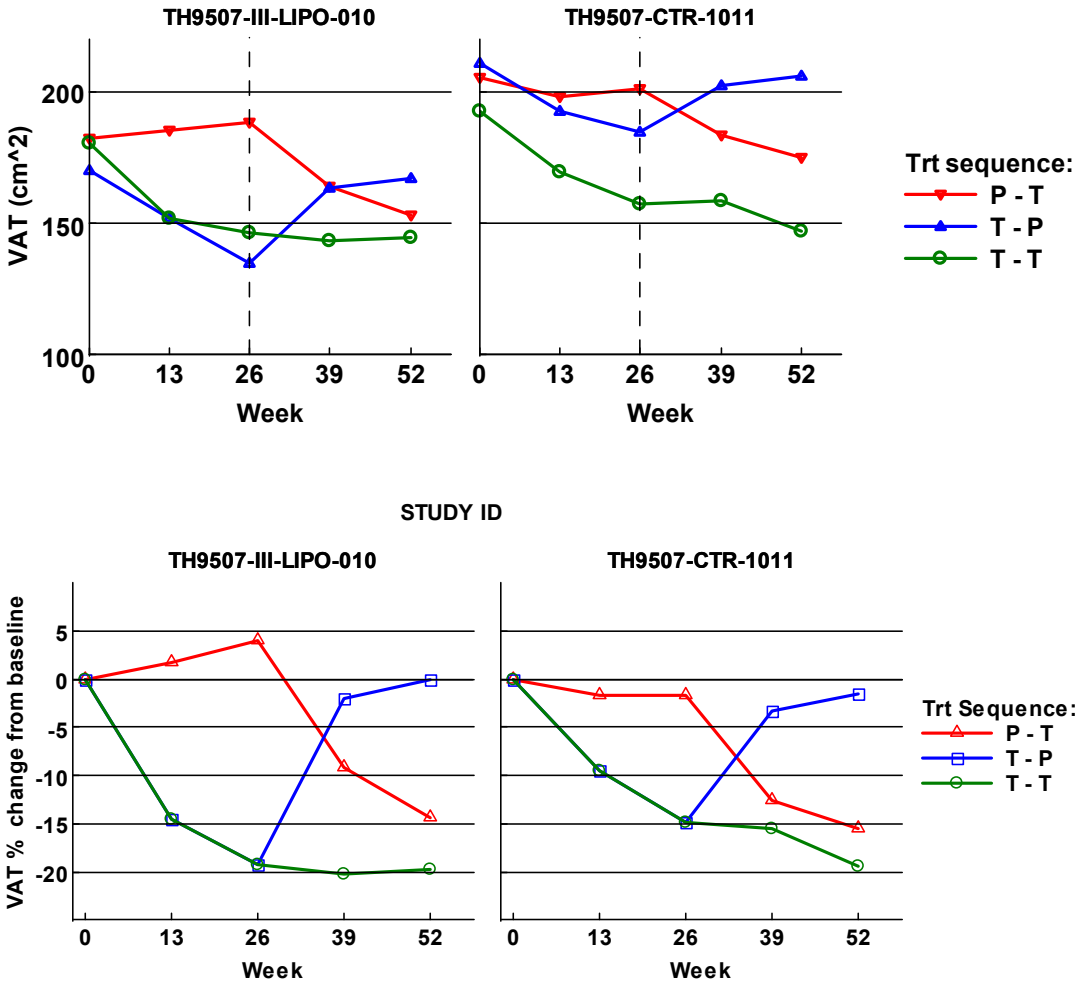
Table A7: ANCOVA* results for VAT % change from Week 26 to Week 52 – Extension Phase of Pivotal Trials (Individual Studies, ITT Analysis)

	T-T		**T-P**		**Treatment Difference from Placebo**
Study	**n**	**LSM**	**n**	**LSM**	**LSM, (SE) [95% CI] P-value**
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 A8 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. Futhermore, those patients in the T-P groups whose tesamorelin was discontinued exhibited a rapid and sustained return to baseline VAT values.

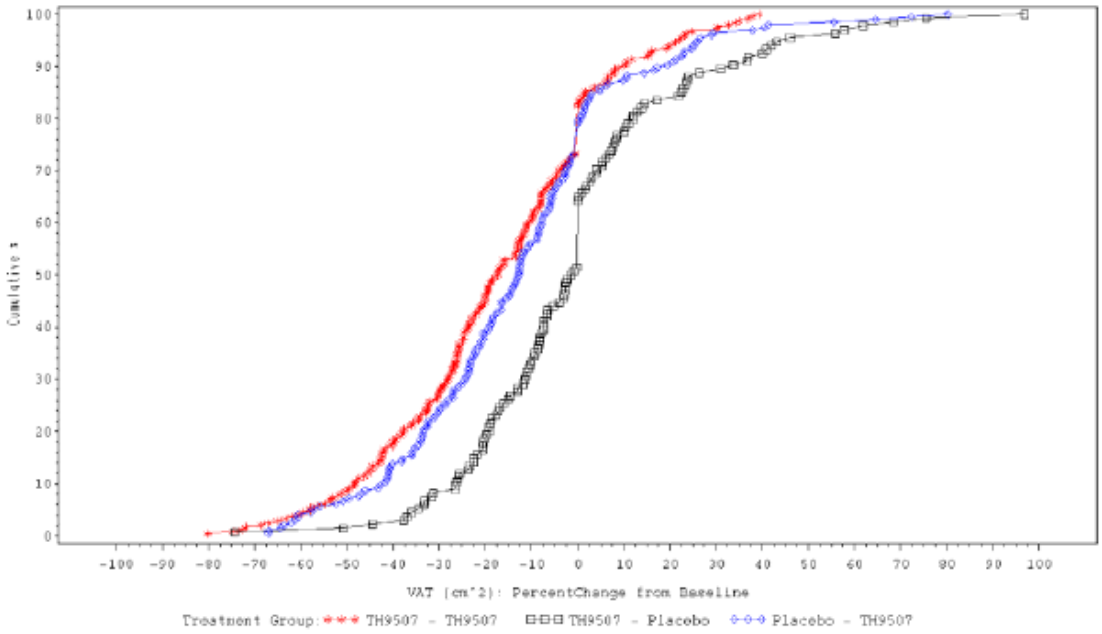
Figure A8: Mean % Changes in VAT from Week 0 to Week 52 –Pivotal Trials (Individual Trials 010 and 011)



Source: FDA Statistical Reviewer

Figure A9 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.

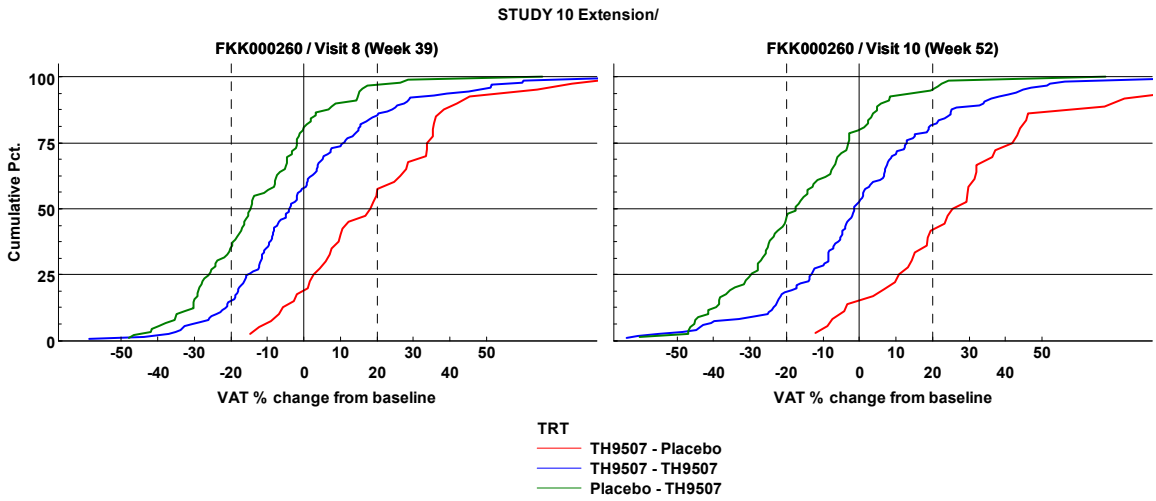
Figure A9: Cumulative Distribution Function of the Percent Change in VAT by Treatment Group at Week 52 – Extension Phase of Pivotal Trials (Both Trials Combined)



Source: ISE Figure 1

Figure A10 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).

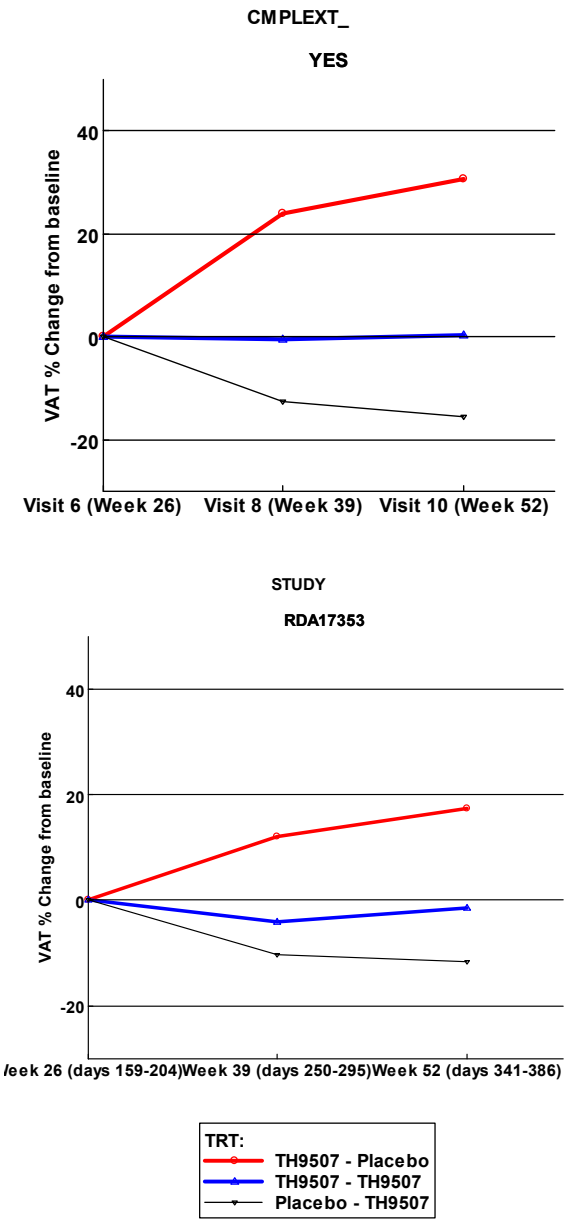
Figure A10: Cumulative Distribution Function of the Percent Change in VAT by Treatment Group from Week 26 to Week 52 –Extension Phase of Pivotal Trials (Individual Studies)



Source: Statistical Review

Figure A11 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 A11: VAT Mean and Median % Change from Re-Randomization – Extension Phase of Pivotal Trials (Individual Studies)



Source: FDA Statistical Review

Secondary efficacy endpoints

For the Main Phase Studies 10 and 11 and the Extension Phase Studies 10-extension and 12, secondary endpoints were the changes from baseline to Week 26 in the IGF-1 level, total cholesterol: HDL-C ratio, non-HDL-C, TG level, and PRO parameters (belly size, belly appearance distress, and belly profile).

IGF-1

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 A8), 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 9.07% 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 56.0%, 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 13.26% from baseline, comparable to those in the T-T group ($p<0.001$).

Table A8: 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	127.67	108.36	59.63
	Range	54.0; 746.0	87.0; 679.0	41.0; 428.0
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 (cm^2)/ (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 (cm^2)/ (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 (cm^2)/ (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 A9 (next page), 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.

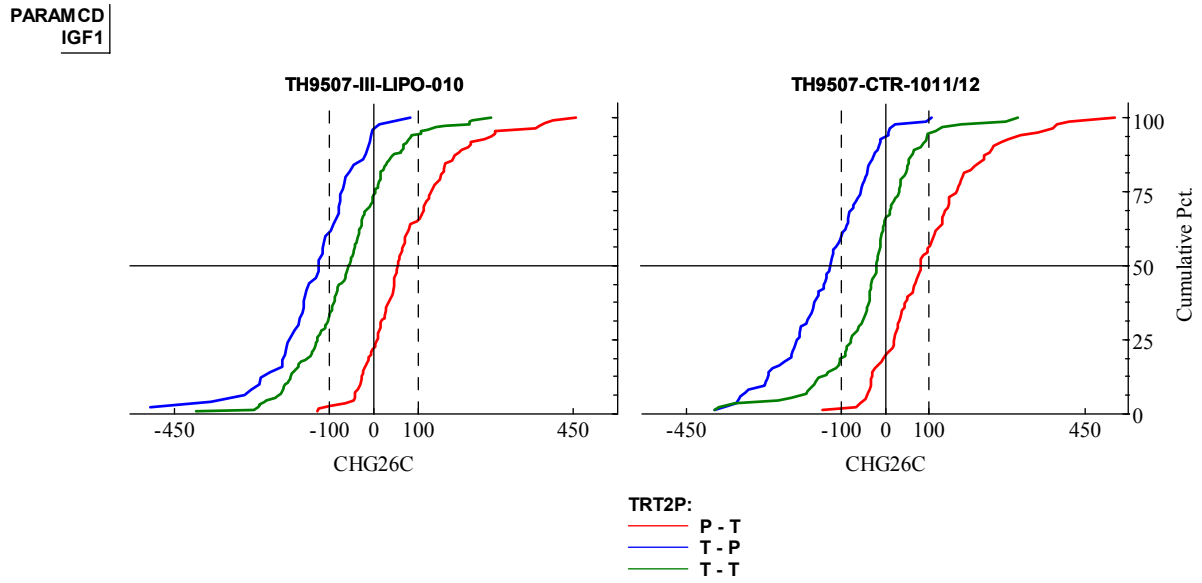
Table A9: Change in IGF-1 from Baseline – Extension Phase of Pivotal Trials (Individual Trials)

		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	428.0; 741.0	528.0; 356.0	47.0; 356.0	54.0; 746.0
	Change from Baseline (cm^2)/ (SD)	129.72 (111.67)	120.41 (100.15)	-19.94 (66.43)	121.15 (119.69)	125.01 (104.32)	-7.04 (53.65)
	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	**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 (cm^2)/ (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	**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 (cm^2)/ (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 A12 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 a increase in IGF-1 from 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).

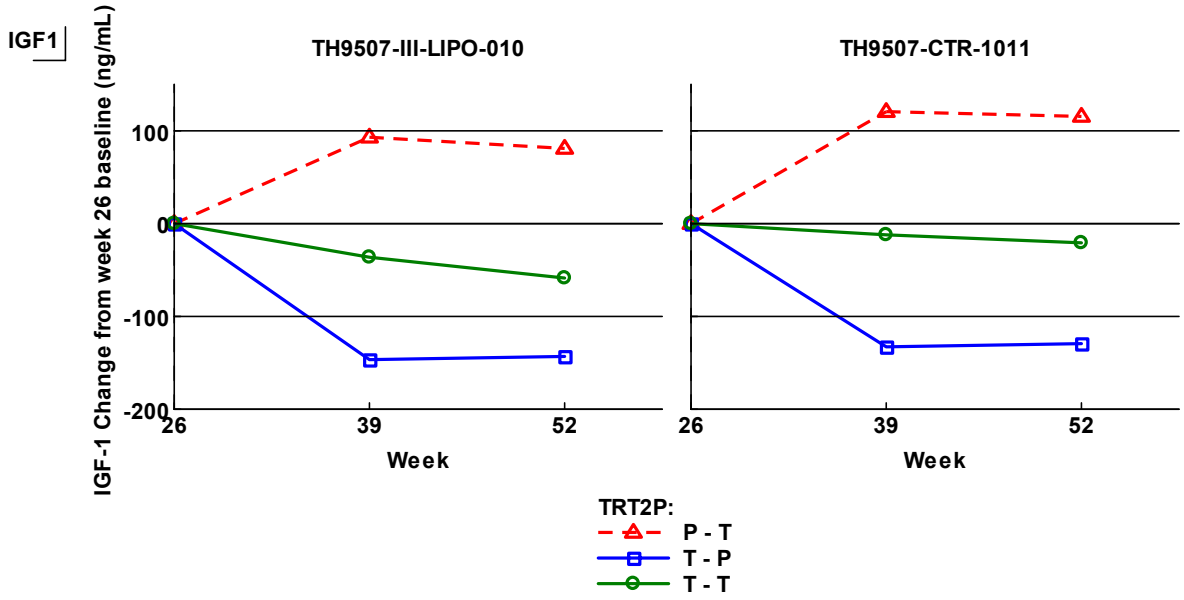
Figure A12: Cumulative Distribution of IGF-1 from Week 26 to Week 52 – Extension Phase (Individual Pivotal Studies)



Source: FDA Statistical Review

Figure A13 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).

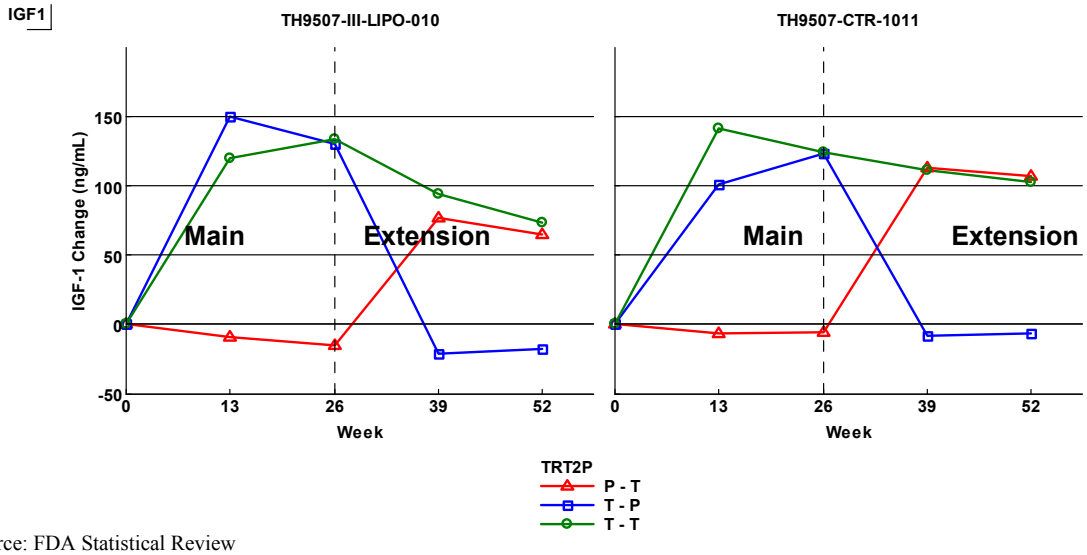
Figure A13: Mean IGF-1 Change from Week 26 to Week 52 – Extension Phase (Individual Pivotal Studies)



Source: FDA Statistical Review

Figure A14 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 A14: Mean IGF-1 Change from Week 0 to Week 52 – Individual Pivotal Studies



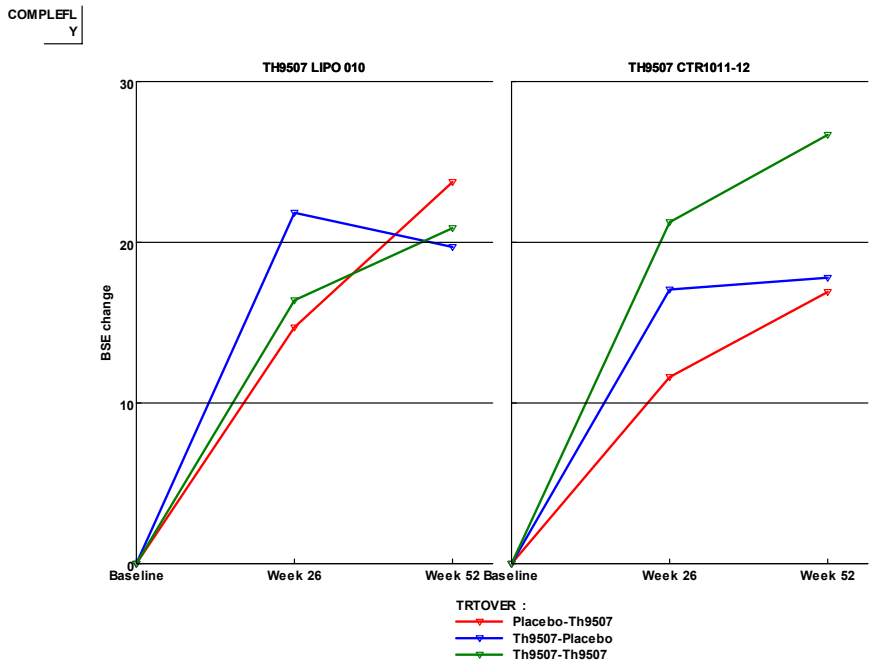
Source: FDA Statistical Review

Patient reported outcomes

Belly Size Evaluation

Figure A15 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 A15: Mean Change in BSE from Baseline at Weeks 26 and 52*



Source: FDA Statistical Review

Belly Appearance Distress

Table A10 displays the descriptive statistics for BAD and Figure A15 depicts these statistics graphically for Studies 101-extension and 12. The data in Table A10 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.

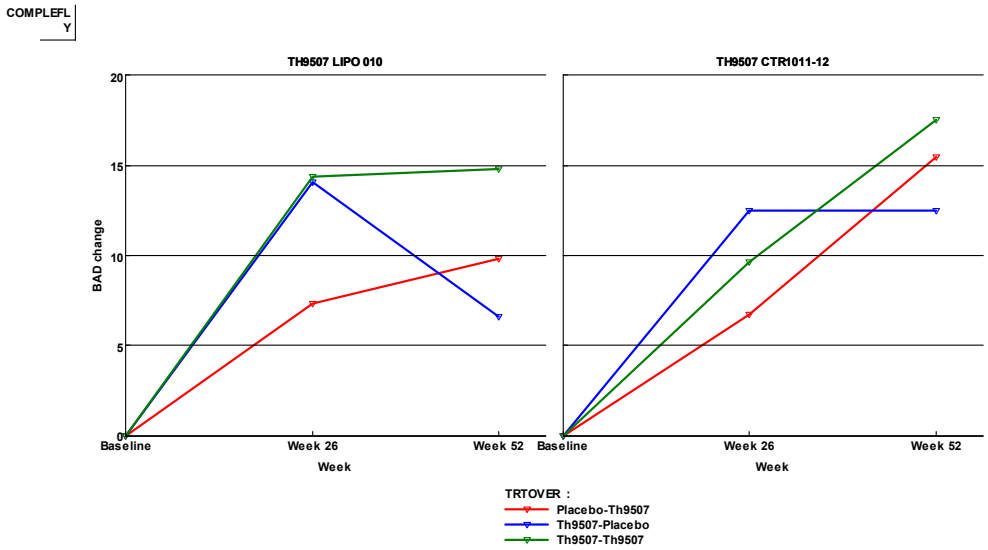
Table A10: Descriptive Statistics of Belly Appearance Distress* – Extension Phase (Individual Pivotal Studies)

		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 Baseline (SD)	12.17 (26.51)	5.00 (22.16)	7.66 (25.63)	13.20 (33.83)	9.90 (24.25)	12.50 (29.52)
	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 A16, 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 A16: Mean Change in BAD from Baseline at Weeks 26 and 52*

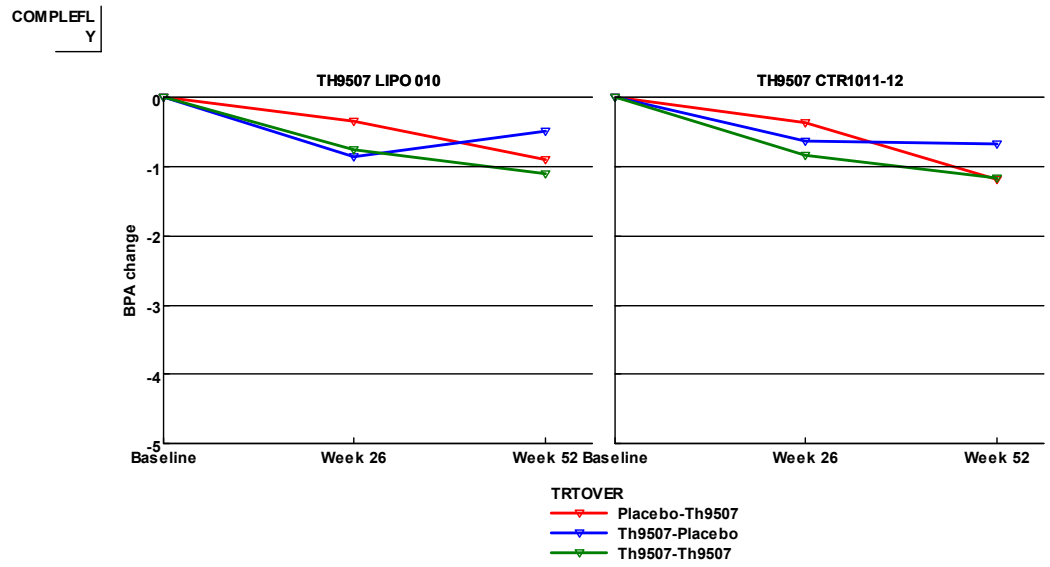


Source: FDA Statistical Review
*Completers only

Belly Profile

Figure A17 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 A17: Mean Change in BP from Baseline at Weeks 26 and 52*



Source: FDA Statistical Review
*Completers only

Triglycerides

Fasting triglycerides were measured at Weeks 32, 39, and 52 (or ET) (in addition to measurements at Weeks 0, 6, 13, and 26.

Table A11 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 A11: TG (mg/dL) Change from Baseline to Week 52 – Extension Phase (Individual Studies)

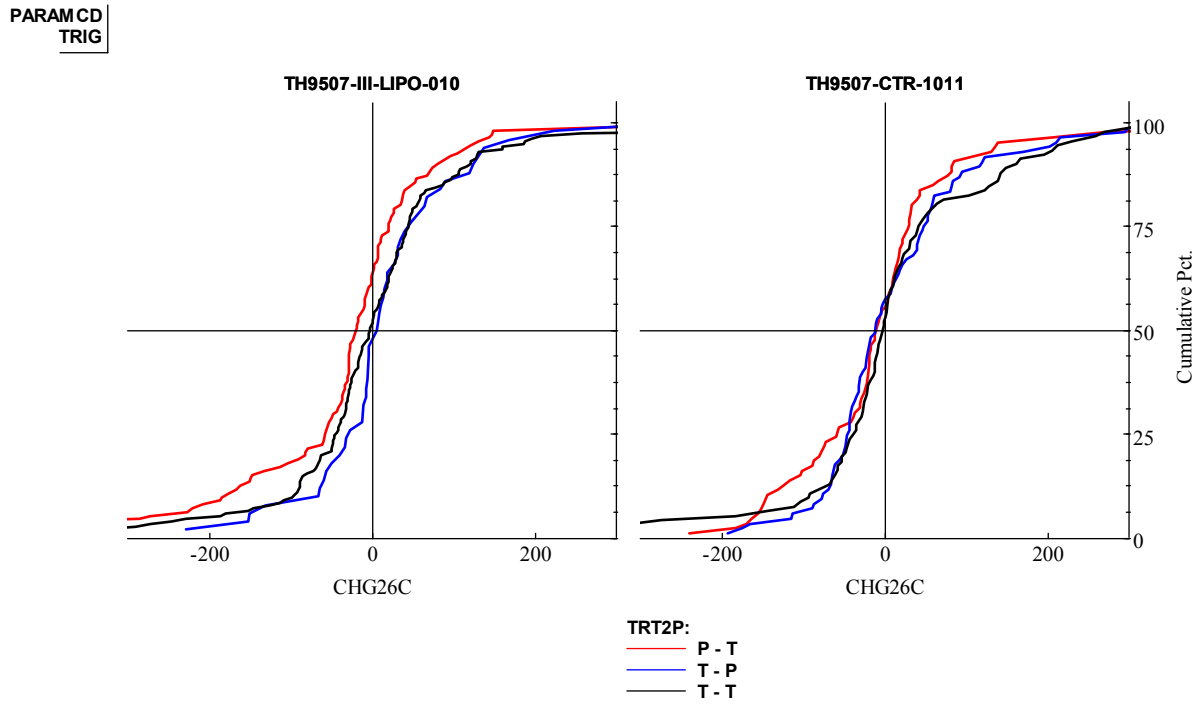
		Study 10-extension			Study 12		
		T-T N=154	T-P N=50	P-T N=111	T-T N=92	T-P N=85	P-T N=86
Baseline Week 0	**n**	151	49	110	89	84	85
	Mean	267.74	222.67	241.82	255.52	216.71	215.43
	SD	206.51	126.42	152.40	213.91	169.81	123.44
Week 26	**n**	151	49	110	89	84	85
	Mean	207.57	173.89	251.59	208.60	199.99	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

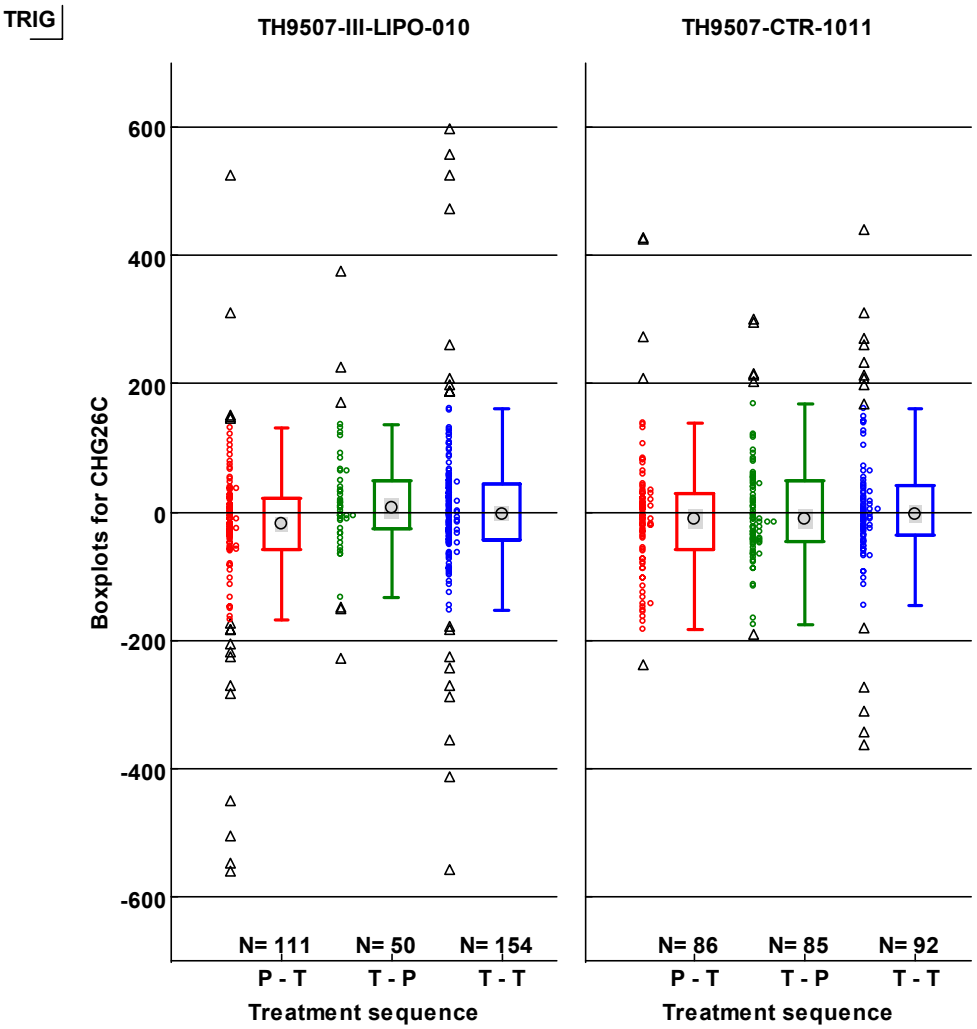
Figure A18 presents cumulative distribution for TG change and Figure A19 the boxplot for TG percent change from Weeks 26 to 52.

Figure A18: 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 A19: 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

Total Cholesterol: High-density Lipoprotein Cholesterol Ratio

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 A12, 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 A12: 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
[+]ITT population

Non HDL-Cholesterol

Fasting blood samples were collected at Weeks 32, 39, and 52 or ET (in addition to measurements at Weeks 0, 6, 13 and 26).

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 A13, 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 A13: 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
[+]ITT population

Other endpoints

VAT/SAT ratio

As shown in Table A14, 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 A14: 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	219.51	234.59	247.98	1.18	1.02	1.41
	SD	126.67	126.55	147.41	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		

As seen in Table A15, 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 cm^2) and those in the P-T group had a mean decrease of 2.97 cm^2 from baseline and a decrease of 12.82 cm^2 from Week 26. In Study 12, patients in the T-T group had a net increase of 4.58 cm^2 from baseline to Week 52, and patients in the P-T group had a mean increase of 0.818 cm^2 over the course of the Extension Phase (increase of 0.24 from cm^2 Weeks 26 to 52).

Table A15: Abdominal SAT (cm^2) 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 LSM[1])		-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-value[1]		0.009			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.

Total body fat

Table A16 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 A16: 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-value[1]		<0.001			<0.001		

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

Total limb fat

As shown in Table A17, 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 A17: 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

Trunk fat

Table A18 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 A18: 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 A19 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 (lthough 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 A19: 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-value[1]		<0.001			<0.001		

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

Anthropometric Measurements

Waist and hip circumferences were measured at Weeks -4 (screening), 13, 26, 39. and 52 (or end of trial). Table A20 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 A20: 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		

Additional analyses of glucose metabolism

Main Phase

Table A21 illustrates shifts in FBG over the 26 weeks of the Main Phase based on patients' baseline state of glycemic control (normal BG, IFG/IGT, or DM). Among patients who started with normal BG at baseline, tesamorelin-treated patients had a greater tendency to shift into a "more severe" category of glucose tolerance at Weeks 13 and 19. At Week 13, 66.9% of patients in the tesamorelin group who started in the normal category remained normal, as opposed to 80.0% of patients in the placebo group. At Week 19, the proportion of patients in the tesamorelin group who started and remained in the normal category had dropped to 60.8%, as opposed to 70.7% of patients in the placebo group. However, by Week 26, the proportions were similar in the tesamorelin (70.7%) and placebo groups (70.0%).

Among patients who were considered to have IFG/IGT at baseline, as a whole, patients in the placebo group tended to shift into a "better" category (i.e. toward normal BG) compared to those in the tesamorelin group. At Weeks 6, 13, 19, and 26, 36.4%, 44.6%,

27.5% and 34.2% of placebo patients who started with IFG/IGT had shifted into the normal group. In comparison, at these timepoints 24.0%, 28.9%, 20.1% and 19.5% of tesamorelin-treated patients had shifted from IFG/IGT to the normal group. At Weeks 13 and 19, a greater proportion of tesamorelin-treated patients who started with IFG/IGT had shifted into the DM group compared with placebo-treated patients (9.3% and 9.2% for tesamorelin patients compared with 3.6% and 2.7% for placebo patients). However, by Week 26 the proportions of patients who started with IFG/IGT and shifted into the DM group were similar between the tesamorelin (13.7%) and placebo groups (15.1%).

Although the data seems to indicate that a greater proportion of tesamorelin-treated patients compared with placebo-treated patients who started in the DM category stayed in the same category over the course of the Main Phase, the number of patients who started with DM in each treatment arm is too small to draw conclusions.

Table A21: Shifts in Glucose Tolerance – Main Phase of Pivotal Trials (Both Trials Combined)

		Tesamorelin N=543			Placebo N=263		
Baseline Evaluation		Post-Baseline Evaluation					
		Normal	IFG/IGT	DM	Normal	IFG/IGT	DM
Normal	**Week 6**	174 (69.3)	75 (29.9)	2 (0.8)	96 (70.1)	38 (27.7)	3 (2.2)
	Week 13	164 (66.9)	78 (31.8)	3 (1.3)	100 (80.0)	24 (19.2)	1 (0.8)
	Week 19	137 (60.8)	84 (36.8)	7 (2.4)	87 (70.7)	35 (28.5)	1 (0.8)
	Week 26	147 (70.7)	58 (27.8)	3 (1.5)	77 (70.0)	30 (27.3)	3 (2.7)
IFG/IGT	**Week 6**	46 (24.0)	128 (66.7)	18 (9.3)	31 (36.4)	46 (54.1)	8 (9.5)
	Week 13	56 (28.9)	120 (61.9)	18 (9.2)	37 (44.6)	43 (51.8)	3 (3.6)
	Week 19	37 (20.1)	126 (68.4)	21 (11.5)	22 (27.5)	55 (68.8)	3 (3.7)
	Week 26	42 (19.5)	127 (66.8)	21 (13.7)	25 (34.2)	37 (50.7)	11 (15.1)
DM	**Week 6**	3 (11.5)	9 (34.6)	14 (53.9)	1 (10.0)	7 (70.0)	2 (20.0)
	Week 13	4 (19.0)	8 (38.1)	9 (42.9)	3 (30.0)	6 (60.0)	1 (10.0)
	Week 19	5 (25.0)	7 (35.0)	8 (40.0)	1 (11.1)	4 (44.4)	4 (44.4)
	Week 26	2 (8.7)	9 (39.1)	12 (52.2)	2 (15.4)	8 (61.5)	3 (23.1)

Source: LIPO-010 Table 14.3.4.5.2c, LIPO-011 Table 14.3.4.5.2c
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 A22 lists all the individual patients who had at least one FBG value of ≥126 mg/dL (i.e. DM range) during the Main Phase of the Pivotal Studies. The table displays all the FBG values that these patients had in addition to the ≥126 mg/dL measurements, which

are marked with an asterisk. Its purpose is to give a visual display of what the patterns of FBG changes were for these patients. For instance, because patients with FBG in the DM range at baseline are presented at the beginning of the list for each treatment group, one can visually observe that for patients in the placebo group most post-baseline observations were within the normal range. For the tesamorelin group it appears that post-baseline values were about equally split between diabetic and non-diabetic categories. Visual inspection of FBG values ≥126 mg/dL observed for the first time in at post-baseline, indicates a larger number of individual patients with such values in the tesamorelin group. The patterns are quite variable with some patients developing FBG in the diabetes range which persist throughout the trial, while others return to non-diabetic values.

Table A22: FBG Trends: Patients with At Least One Value ≥ 126 mg/dL -- Main Phase of Pivotal Trials (Both Trials Combined)

		FBG (mg/dL)				
	Patient ID	Week 0	Week 6	Week 13	Week 19	Week 26
Tesamorelin (N=539)	TH9507-CTR-1011-110-0417	*156.0	*175.0	*165.0	*193.0	
	TH9507-CTR-1011-203-0001	*158.0	112.0			
	TH9507-CTR-1011-203-0004	*127.0	115.0	110.0	92.0	117.0
	TH9507-CTR-1011-203-0015	*128.0	100.0	80.0	102.0	108.0
	TH9507-CTR-1011-203-0023	*163.0	98.0			
	TH9507-CTR-1011-203-0024	*160.0	104.0	98.0	92.0	96.0
	TH9507-CTR-1011-204-0370	*148.0	*149.0	121.0	109.0	98.0
	TH9507-CTR-1011-209-0527	*154.0	*141.0	126.0	114.0	*136.0
	TH9507-CTR-1011-212-0538	*160.0				
	TH9507-CTR-1011-213-0315	*152.0	*161.0			
	TH9507-CTR-1011-216-0353	*147.0	*136.0	*175.0	*138.0	*136.0
	TH9507-CTR-1011-220-0054	*163.0	108.0	100.0	102.0	116.0
	TH9507-CTR-1011-220-0059	*171.0	101.0	109.0	100.0	93.0
	TH9507-CTR-1011-220-0060	*132.0	*136.0	*132.0	*128.0	*147.0
	TH9507-CTR-1011-222-0209	*137.0	*170.0	*267.0		
	TH9507-CTR-1011-224-0308	*151.0	100.0	85.0	96.0	97.0
	TH9507-CTR-1011-231-0464	*127.0	*131.0		*146.0	123.0
	TH9507-CTR-1011-804-0176	*132.0	*145.0	96.0		
	TH9507-III-LIPO-010-010-0020	*136.9				
	TH9507-III-LIPO-010-014-0004	*147.7	*182.0	*129.7		
	TH9507-III-LIPO-010-017-0004	*149.5		120.7	*154.9	*185.6
	TH9507-III-LIPO-010-019-0003	*149.5				
	TH9507-III-LIPO-010-025-0001	*176.6				
	TH9507-CTR-1011-101-0542	120.0	*130.0			
	TH9507-CTR-1011-102-0544	120.0	110.0	*135.0	118.0	118.0
	TH9507-CTR-1011-109-0349	121.0	*162.0	*167.0	*176.0	*158.0
	TH9507-CTR-1011-203-0010	110.0	102.0	105.0	*130.0	
	TH9507-CTR-1011-203-0312	106.0	100.0	114.0	*154.0	106.0
	TH9507-CTR-1011-209-0269	121.0	*131.0	113.0	117.0	125.0
	TH9507-CTR-1011-211-0536	126.0	*132.0	117.0	*159.0	*133.0
	TH9507-CTR-1011-213-0292	102.0	*185.0			
	TH9507-CTR-1011-214-0430	113.0	116.0	126.0	121.0	*128.0
	TH9507-CTR-1011-216-0414	119.0	97.0	*145.0	83.0	100.0
	TH9507-CTR-1011-220-0114	126.0	110.0	*134.0	109.0	121.0
	TH9507-CTR-1011-221-0049	115.0	108.0	102.0	*132.0	99.0
	TH9507-CTR-1011-221-0295	104.0	125.0	*145.0	*134.0	117.0

	TH9507-CTR-1011-224-0080	100.0	111.0	*130.0	106.0	125.0
	TH9507-CTR-1011-224-0083	88.0	110.0	107.0	118.0	*132.0
	TH9507-CTR-1011-224-0109	106.0	106.0	*133.0	116.0	101.0
	TH9507-CTR-1011-224-0113	100.0	105.0	98.0	*128.0	*129.0
	TH9507-CTR-1011-224-0122	101.0	102.0	99.0	*131.0	107.0
	TH9507-CTR-1011-224-0218	113.0	*149.0	*192.0	*131.0	126.0
	TH9507-CTR-1011-224-0424	115.0	*152.0	108.0	115.0	95.0
	TH9507-CTR-1011-224-0526	100.0	103.0	*129.0	109.0	109.0
	TH9507-CTR-1011-224-0596	100.0	91.0	79.0	*134.0	103.0
	TH9507-CTR-1011-226-0239	114.0	117.0	117.0	114.0	*132.0
	TH9507-CTR-1011-230-0048	81.0	83.0	100.0	100.0	*133.0
	TH9507-CTR-1011-230-0223	124.0	113.0	101.0	*130.0	103.0
	TH9507-CTR-1011-231-0419	114.0	120.0	111.0	115.0	*132.0
	TH9507-CTR-1011-701-0492	105.0	*127.0	122.0	*135.0	125.0
	TH9507-CTR-1011-701-0493	105.0	112.0	*130.0	104.0	101.0
	TH9507-CTR-1011-801-0342	90.0	93.0	101.0	*136.0	
	TH9507-CTR-1011-801-0457	76.0	100.0	*136.0	*147.0	*184.0
	TH9507-CTR-1011-805-0515	102.0	*151.0	102.0		
	TH9507-III-LIPO-010-004-0002	108.1	124.3	117.1	*127.9	102.7
	TH9507-III-LIPO-010-004-0006	118.9	86.5	104.5	106.3	*140.5
	TH9507-III-LIPO-010-005-0002	86.5		120.7	109.9	*151.3
	TH9507-III-LIPO-010-005-0016	122.5		108.1	*129.7	*172.9
	TH9507-III-LIPO-010-010-0004	122.5	*127.9	118.9	*140.5	118.9
	TH9507-III-LIPO-010-010-0011	109.9	*127.9	*131.5	117.1	*127.9
	TH9507-III-LIPO-010-011-0009	108.1	*135.1	*167.5	*144.1	113.5
	TH9507-III-LIPO-010-011-0024	109.9	*126.1	*133.3	*138.7	*142.3
	TH9507-III-LIPO-010-014-0016	104.5	91.9	100.9	*133.3	111.7
	TH9507-III-LIPO-010-014-0021	81.1	99.1	*144.1	*127.9	
	TH9507-III-LIPO-010-015-0003	111.7	*149.5	*131.5	99.1	108.1
	TH9507-III-LIPO-010-016-0008	66.7	111.7	99.1	*131.5	117.1
	TH9507-III-LIPO-010-016-0011	77.5	*145.9	120.7	95.5	
	TH9507-III-LIPO-010-017-0016	99.1	117.1	104.5	120.7	*140.5
	TH9507-III-LIPO-010-017-0023	88.3	109.9	*135.1	99.1	90.1
	TH9507-III-LIPO-010-017-0030	109.9	124.3	111.7	117.1	*127.9
	TH9507-III-LIPO-010-017-0041	97.3	88.3	84.7	99.1	*126.1
	TH9507-III-LIPO-010-017-0047	97.3	*129.7			
	TH9507-III-LIPO-010-018-0006	117.1	*133.3	*151.3	115.3	104.5
	TH9507-III-LIPO-010-019-0004	120.7	*142.3	117.1	*127.9	
	TH9507-III-LIPO-010-019-0015	108.1	111.7	*129.7	109.9	104.5
	TH9507-III-LIPO-010-019-0018	90.1	81.1	99.1	*133.3	86.5
	TH9507-III-LIPO-010-020-0007	120.7	*135.1	120.7	115.3	102.7
	TH9507-III-LIPO-010-021-0002	122.5	*165.7	106.3	120.7	
	TH9507-III-LIPO-010-024-0009	102.7	117.1	100.9	*126.1	108.1
	TH9507-III-LIPO-010-027-0005	111.7	*136.9	*153.1		
	TH9507-III-LIPO-010-029-0028	95.5	100.9	97.3	91.9	*129.7
	TH9507-III-LIPO-010-031-0005	104.5	113.5	*163.9	*127.9	*171.1
	TH9507-III-LIPO-010-040-0001	122.5	117.1	*135.1	*136.9	115.3
	TH9507-III-LIPO-010-042-0016	118.9	*135.1	122.5	*147.7	*135.1
	TH9507-III-LIPO-010-042-0019	86.5	118.9	106.3	*129.7	104.5

	TH9507-III-LIPO-010-045-0002	90.1	122.5	115.3	*127.9	106.3
	TH9507-III-LIPO-010-047-0009	97.3	*126.1	*138.7		
Placebo (N=259)	TH9507-CTR-1011-108-0529	*129.0	102.0	113.0	114.0	109.0
	TH9507-CTR-1011-203-0007	*140.0	92.0			
	TH9507-CTR-1011-203-0051	*181.0	109.0	110.0	123.0	111.0
	TH9507-CTR-1011-220-0041	*144.0	109.0	114.0	106.0	109.0
	TH9507-CTR-1011-804-0428	*199.0	101.0	80.0	87.0	92.0
	TH9507-III-LIPO-010-005-0036	*135.1	*129.7	117.1	124.3	102.7
	TH9507-III-LIPO-010-006-0002	*151.3				
	TH9507-III-LIPO-010-011-0004	*126.1		*138.7	*142.3	115.3
	TH9507-III-LIPO-010-020-0004	*129.7	102.7	111.7	109.9	106.3
	TH9507-III-LIPO-010-032-0001	*127.9				
	TH9507-III-LIPO-010-034-0001	*145.9		124.3	*151.3	*138.7
	TH9507-III-LIPO-010-039-0005	*133.3	109.9	95.5	99.1	102.7
	TH9507-III-LIPO-010-042-0013	*147.7	97.3	93.7	111.7	100.9
	TH9507-CTR-1011-105-0203	109.0	115.0	112.0	115.0	*140.0
	TH9507-CTR-1011-214-0479	111.0	113.0	113.0	119.0	*154.0
	TH9507-CTR-1011-216-0439	125.0	*132.0	102.0	103.0	116.0
	TH9507-CTR-1011-220-0518	94.0	*144.0	103.0	104.0	103.0
	TH9507-CTR-1011-701-0505	102.0	*155.0			
	TH9507-CTR-1011-801-0367	120.0	118.0	107.0	*152.0	*149.0
	TH9507-III-LIPO-010-001-0001	97.3	102.7	*129.7	91.9	97.3
	TH9507-III-LIPO-010-011-0013	90.1	104.5	122.5	*131.5	108.1
	TH9507-III-LIPO-010-013-0004	81.1	90.1	72.1	59.5	*126.1
	TH9507-III-LIPO-010-014-0017	117.1	*140.5	122.5		
	TH9507-III-LIPO-010-014-0022	106.3	*147.7	93.7	100.9	102.7
	TH9507-III-LIPO-010-017-0017	104.5	97.3	97.3	108.1	*126.1
	TH9507-III-LIPO-010-017-0042	97.3	108.1	97.3	95.5	*136.9
	TH9507-III-LIPO-010-017-0044	108.1	91.9	95.5	104.5	*133.3
	TH9507-III-LIPO-010-017-0051	118.9	124.3	*126.1	*126.1	120.7
	TH9507-III-LIPO-010-019-0016	122.5	*131.5	*126.1	106.3	109.9
	TH9507-III-LIPO-010-019-0026	99.1	117.1	111.7	*158.5	99.1
	TH9507-III-LIPO-010-021-0003	109.9	108.1	104.5	111.7	*127.9
	TH9507-III-LIPO-010-027-0004	97.3	*138.7			
	TH9507-III-LIPO-010-027-0010	90.1	*131.5	91.9	91.9	106.3
	TH9507-III-LIPO-010-039-0003	120.7	120.7	99.1	*147.7	*133.3
	TH9507-III-LIPO-010-040-0018	99.1	*127.9	*138.7	111.7	118.9

*>=126 mg/dL
Values = 126.0 mg/dL and not flagged ' * ', means they are < 126.0 mg/dL (i.e: 125.999 mg/dL)
Source: Sponsor's Figure

Table A23 looks at shifts in HbA1c over the 26 weeks of the Main Phase based on patients' baseline state of glycemic control (normal BG, pre-diabetes, or DM). Among patients who started with normal BG at baseline, tesamorelin-treated patients had a greater tendency to shift into a "more severe" category of glucose tolerance at Weeks 13 and 26. At Week 13, 84.5% of patients in the tesamorelin group who started in the normal category remained normal, as opposed to 91.7% of patients in the placebo group. At Week 26, the proportion of patients in the tesamorelin group who started and remained in the normal category had dropped to 82.2%, as opposed to 86.3% of patients in the placebo group.

Among patients who were considered to have pre-diabetes at baseline, as a whole, patients in the placebo group tended to shift into a "better" category (i.e. toward normal HbA1c) compared to those in the tesamorelin group. At Weeks 13 and 26, 32.5 and 30.6% of placebo patients who started with pre-diabetes had shifted into the normal

group. In comparison, at these timepoints 21.5% and 19.4% of tesamorelin-treated patients had shifted from pre-diabetes to the normal group. Similarly, at Weeks 13 and 26, a greater proportion of tesamorelin-treated patients who started with pre-diabetes had shifted into the DM group compared with placebo-treated patients (19.0% and 25.4% for tesamorelin patients compared with 5.0% and 11.1% for placebo patients).

Although the data seems to indicate that a greater proportion of tesamorelin-treated patients compared with placebo-treated patients who started in the DM category stayed in the same category over the course of the Main Phase, the number of patients who started with DM in each treatment arm is too small to draw conclusions.

Table A23: Shifts in HbA1c – Main Phase of Pivotal Trials (Both Trials Combined)

Baseline Evaluation		Tesamorelin N=543			Placebo N=263		
		Post-Baseline Evaluation					
		Normal	Pre-Diabetes	DM	Normal	Pre-Diabetes	DM
Normal	Week 13	305 (84.5)	54 (15.0)	2 (0.6)	154 (91.7)	14 (8.3)	0 (0.0)
	Week 26	264 (82.2)	53 (16.5)	4 (1.2)	138 (86.3)	22 (13.8)	0 (0.0)
Pre-Diabetes	Week 13	17 (21.5)	47 (59.5)	15 (19.0)	13 (32.5)	25 (62.5)	2 (5.0)
	Week 26	13 (19.4)	37 (55.2)	17 (25.4)	11 (30.6)	21 (58.3)	4 (11.1)
DM	Week 13	0 (0.0)	1 (12.5)	7 (87.5)	0 (0.0)	1 (33.3)	2 (66.7)
	Week 26	0 (0.0)	2 (28.6)	5 (71.4)	0 (0.0)	2 (66.7)	1 (33.3)

Data are presented as n (%)
Normal = A1c < 5.7%
Pre-Diabetes = 5.7% ≤ A1c < 6.5%
DM = A1c ≥6.5%

Source: Sponsor's Figure

Table A24 evaluates each individual patient who had at least one HbA1c value of ≥6.5% (i.e. DM range) during the Main Phase of the Pivotal Studies and displays their HbA1c trends over time. It clearly indicates that there were more patients in the tesamorelin group who developed post-baseline HbA1c values >6.5% and overwhelmingly they tended to stay that way.

Table A24: HbA1c Trends: Patients with At Least One Value ≥ 6.5% -- Main Phase of Pivotal Trials (Both Trials Combined)

		HbA1c (%)		
	Patient ID	Week 0	Week 13	Week 26
Tesamorelin (N=524)	TH9507-CTR-1011-203-0001	*6.5		
	TH9507-CTR-1011-204-0370	*6.9	*6.9	6.1
	TH9507-CTR-1011-205-0433	*6.7		
	TH9507-CTR-1011-209-0527	*6.5	*6.6	*7.1
	TH9507-CTR-1011-216-0353	*6.5	*7.0	*7.3
	TH9507-III-LIPO-010-014-0004	*7.4	*8.0	
	TH9507-III-LIPO-010-025-0001	*6.7		
	TH9507-III-LIPO-010-027-0002	*7.2	*7.3	*7.4
	TH9507-III-LIPO-010-029-0026	*6.5	*6.9	6.3
	TH9507-III-LIPO-010-031-0005	*6.6	*7.2	*8.1
	TH9507-III-LIPO-010-042-0035	*6.5	6.4	*6.5
	TH9507-CTR-1011-109-0349	6.0	*8.8	*7.7
	TH9507-CTR-1011-110-0476	6.3	*6.6	*6.7
	TH9507-CTR-1011-110-0567	6.1	*6.5	*6.7
	TH9507-CTR-1011-211-0288	6.0	6.2	*6.5
	TH9507-CTR-1011-211-0536	6.2	*6.5	*6.6
	TH9507-CTR-1011-215-0279	6.1	6.2	*6.7
	TH9507-CTR-1011-222-0209	5.7	*7.6	
	TH9507-CTR-1011-223-0397	5.9	*6.5	6.4
	TH9507-CTR-1011-224-0083	5.3	6.4	*6.5
	TH9507-CTR-1011-224-0553	5.9	*6.5	*6.6
	TH9507-CTR-1011-224-0596	5.6	*6.5	6.0
	TH9507-CTR-1011-226-0239	6.2	*6.5	*6.5
	TH9507-CTR-1011-226-0358	5.7	*7.1	*6.9
	TH9507-CTR-1011-230-0048	6.1	5.7	*7.0
	TH9507-CTR-1011-230-0223	6.1	*6.5	*6.6
	TH9507-CTR-1011-230-0408	6.1	*6.5	6.3
	TH9507-CTR-1011-403-0585	5.8	6.4	*7.4
	TH9507-CTR-1011-701-0492	5.5	6.1	*6.5
	TH9507-III-LIPO-010-002-0024	6.1	*6.7	
	TH9507-III-LIPO-010-010-0004	6.0	6.1	*7.1
	TH9507-III-LIPO-010-010-0011	5.9	*6.7	*6.6
	TH9507-III-LIPO-010-011-0009	5.3	6.1	*6.5
	TH9507-III-LIPO-010-011-0011	5.8	6.3	*6.8
	TH9507-III-LIPO-010-011-0024	6.0	6.0	*6.6
	TH9507-III-LIPO-010-014-0021	5.6	*7.1	*6.6
	TH9507-III-LIPO-010-015-0003	6.1	*6.6	6.0
	TH9507-III-LIPO-010-017-0004	6.3	6.3	*6.8
	TH9507-III-LIPO-010-027-0005	5.7	*6.8	
Placebo (N=255)	TH9507-CTR-1011-203-0011	*6.5	5.7	5.7
	TH9507-III-LIPO-010-031-0001	*6.7	*6.8	6.2
	TH9507-III-LIPO-010-034-0001	*6.8	*6.5	*6.5
	TH9507-CTR-1011-204-0271	5.9	6.2	*6.5
	TH9507-CTR-1011-216-0439	5.9	6.0	*6.5
	TH9507-CTR-1011-220-0518	6.0	6.0	*6.5
	TH9507-CTR-1011-801-0367	5.9	6.4	*6.5
	TH9507-III-LIPO-010-021-0003	5.9	*6.6	6.2
	TH9507-III-LIPO-010-027-0009	6.2	*6.5	5.7

*>=6.5%
Source: Sponsor's Figure

Extension Phase

Table A25 looks at shifts in FBG over the 26 weeks of the Extension Phase (T-T and T-P groups) based on patients' baseline state of glycemic control (normal BG, IFG/IGT, or DM). Among patients who started with normal BG at baseline, T-T patients had a greater tendency to shift into a "more severe" category of glucose tolerance at Weeks 45 but were otherwise similar to T-P patients. At Week 45, 74.0% of patients in the T-T group who started in the normal category remained normal, as opposed to 87.3% of patients in the T-P group. However, at all other timepoints by Week 26, the proportions were similar in the T-T and T-P groups.

Among patients who were considered to have IFG/IGT at baseline, as a whole patients in the T-P group tended to shift into a "better" category (i.e. toward normal BG) midway through the Extension Phase compared to those in the T-T group, before equalizing by Week 52. Although proportions who had shifted into the normal category were similar at Week 32, at Weeks 39 and 45, 55.6% and 41.0% of T-P patients who started with IFG/IGT had shifted into the normal group. In comparison, at these timepoints 45.6%, and 24.5% of T-T patients had shifted from IFG/IGT to the normal group. However, by Week 52 the proportions of patients who started with IFG/IGT and shifted into the normal group were similar between the T-T (35.9%) and placebo groups (37.1%).

The number of patients who started with DM in each treatment arm is too small to draw conclusions for the FBG shift data.

Table A25: Shifts in Glucose Tolerance – Extension Phase of Pivotal Trials (Both Trials Combined)

		T-T N=246			T-P N=135		
Baseline Evaluation		**Post-Baseline Evaluation**					
		Normal	**IFG/IGT**	**DM**	**Normal**	**IFG/IGT**	**DM**
Normal	**Week 32**	118 (76.7)	33 (21.4)	3 (1.9)	51 (81.0)	12 (19.0)	0
	Week 39	127 (84.1)	20 (13.2)	4 (2.7)	48 (77.4)	13 (21.0)	1 (1.6)
	Week 45	108 (74.0)	36 (24.7)	2 (1.3)	48 (87.3)	6 (10.9)	1 (1.8)
	Week 52	100 (76.3)	28 (21.4)	3 (2.3)	39 (78.0)	11 (22.0)	0
IFG/IGT	**Week 32**	21 (34.4)	32 (52.5)	8 (13.1)	16 (35.6)	28 (62.2)	1 (2.2)
	Week 39	31 (45.6)	30 (44.1)	7 (10.3)	25 (55.6)	19 (42.2)	1 (2.2)
	Week 45	13 (24.5)	31 (58.5)	9 (17.0)	16 (41.0)	22 (56.4)	1 (2.6)
	Week 52	23 (35.9)	35 (54.7)	6 (9.4)	13 (37.1)	18 (51.4)	4 (11.5)
DM	**Week 32**	0	4 (100.0)	0	4 (44.4)	4 (44.4)	1 (11.1)

	Week 39	2 (50.0)	2 (50.0)	0	5 (50.0)	2 (20.0)	3 (30.0)
	Week 45	0	3 (75.0)	1 (25.0)	4 (40.0)	4 (40.0)	2 (20.0)
	Week 52	3 (37.5)	4 (50.0)	1 (13.5)	4 (36.4)	2 (18.2)	5 (45.4)

Source: LIPO-010 Table 14.3.4.5.2c, LIPO-011 Table 14.3.4.5.2c
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 A26 lists all the individual patients who had at least one FBG value of ≥126 mg/dL (i.e. DM range) during the Extension Phase of the Pivotal Studies and displays their FBG trends over time, in addition to the ≥126 mg/dL measurements, which are marked with an asterisk. Its purpose is to give a visual display of what the patterns of FBG changes were for these patients. There were more patients with FBG ≥126 mg/dL at the beginning of the extension phase in the T-T group. The overall pattern of changes was variable.

Table A26: FBG Trends: Patients with At Least One Value ≥ 126 mg/dL -- Extension Phase of Pivotal Trials (Both Trials Combined)

		FBG (mg/dL)				
	Patient ID	**Week 26**	**Week 32**	**Week 39**	**Week 45**	**Week 52**
T-T (N=246)	TH9507-CTR-1011-209-0527	*136.0	115.0	94.0	*137.0	116.0
	TH9507-CTR-1011-214-0430	*128.0		106.0	114.0	
	TH9507-CTR-1011-224-0113	*129.0		119.0	125.0	101.0
	TH9507-CTR-1011-230-0048	*133.0	*148.0	*145.0	123.0	101.0
	TH9507-CTR-1011-801-0457	*184.0	95.0	91.0	92.0	94.0
	TH9507-III-LIPO-010-004-0006	*140.5	113.5	111.7	108.1	84.7
	TH9507-III-LIPO-010-005-0002	*151.3	*156.7			
	TH9507-III-LIPO-010-010-0011	*127.9	118.9	118.9	111.7	*126.1
	TH9507-III-LIPO-010-011-0024	*142.3	*149.5	*158.5		
	TH9507-III-LIPO-010-014-0021	*127.9	120.7	*171.1	*145.9	90.1
	TH9507-III-LIPO-010-017-0016	*140.5	106.3	122.5	120.7	115.3
	TH9507-III-LIPO-010-017-0041	*126.1	102.7	91.9	115.3	
	TH9507-III-LIPO-010-019-0004	*127.9		*126.1	115.3	*127.9
	TH9507-CTR-1011-102-0544	118.0	123.0	124.0	*138.0	
	TH9507-CTR-1011-203-0281	88.0	108.0	*131.0	94.0	104.0
	TH9507-CTR-1011-216-0414	100.0	110.0	88.0	*128.0	88.0
	TH9507-CTR-1011-231-0190	114.0	*152.0	*127.0	106.0	112.0
	TH9507-III-LIPO-010-007-0004	90.1	*126.1	84.7	*126.1	*129.7
	TH9507-III-LIPO-010-010-0037	102.7	99.1	106.3	93.7	*129.7
	TH9507-III-LIPO-010-011-0009	113.5	*158.5	113.5	*131.5	93.7
	TH9507-III-LIPO-010-017-0033	99.1	118.9	*126.1	*127.9	95.5
	TH9507-III-LIPO-010-017-0038	97.3	*138.7	104.5	99.1	84.7
	TH9507-III-LIPO-010-018-0006	104.5	117.1	120.7	*145.9	*127.9
	TH9507-III-LIPO-010-019-0015	104.5	104.5	*140.5	120.7	
	TH9507-III-LIPO-010-019-0017	104.5	113.5	*126.1	117.1	*127.9
	TH9507-III-LIPO-010-020-0007	102.7	104.5	115.3	*129.7	*127.9
	TH9507-III-LIPO-010-020-0011	111.7	*133.3	104.5	102.7	122.5
	TH9507-III-LIPO-010-038-0002	99.1	117.1	*126.1	124.3	109.9
	TH9507-III-LIPO-010-040-0001	115.3	*140.5	113.5	*138.7	*201.8
	TH9507-III-LIPO-010-040-0011	106.3	111.7	102.7	*156.7	100.9
	TH9507-III-LIPO-010-043-0001	118.9	*126.1	109.9	124.3	106.3
	TH9507-III-LIPO-010-045-0002	106.3	*129.7	100.9	63.1	84.7

T-P (N=135)	TH9507-CTR-1011-216-0353	*136.0	*147.0	*162.0	*171.0	*167.0
	TH9507-CTR-1011-220-0060	*147.0	123.0	*129.0	*138.0	*138.0
	TH9507-CTR-1011-224-0083	*132.0		110.0	99.0	101.0
	TH9507-CTR-1011-226-0239	*132.0	99.0	105.0	102.0	
	TH9507-III-LIPO-010-005-0016	*172.9	109.9	113.5	104.5	
	TH9507-III-LIPO-010-017-0030	*127.9	120.7	118.9	113.5	
	TH9507-III-LIPO-010-029-0028	*129.7	108.1	79.3	102.7	95.5
	TH9507-III-LIPO-010-042-0016	*135.1	115.3	88.3		
	TH9507-CTR-1011-203-0015	108.0	116.0	117.0	122.0	*331.0
	TH9507-CTR-1011-203-0024	96.0	92.0	*151.0	88.0	95.0
	TH9507-CTR-1011-203-0031	110.0	102.0	*129.0		110.0
	TH9507-CTR-1011-203-0147	97.0		106.0	*129.0	82.0
	TH9507-CTR-1011-211-0288	108.0	103.0	107.0	104.0	*136.0
	TH9507-CTR-1011-221-0128	105.0	104.0	103.0	108.0	*128.0
	TH9507-CTR-1011-224-0218	126.0		*132.0	110.0	*134.0
	TH9507-III-LIPO-010-021-0002	120.7	*136.9	118.9		

Baseline extension: latest available value prior to re-randomization and up to Week 13
* >=126 mg/dL
Values = 126.0 mg/dL and not flagged ' * ', means they are < 126.0 mg/dL (i.e: 125.999 mg/dL)

Table A27 looks at shifts in HbA1c over the 26 weeks of the Extension Phase based on patients' baseline state of glycemic control (normal BG, pre-diabetes, or DM). Among patients who started with normal BG at baseline, results for both T-T and T-P patients were similar, with the vast majority remaining in the normal category at Weeks 39 and 52. Specifically, at Week 39, 96.0% of patients in the T-T group who started in the normal category remained normal, as did 92.8% of patients in the placebo group. At Week 52, the proportion of patients in the T-T group who started and remained in the normal category was 93.0%, as did 95.7% of patients in the placebo group.

Among patients who were considered to have pre-diabetes at baseline, patients in the T-P group tended to shift into a "better" category (i.e. toward normal HbA1c) compared to those in the T-T group. At Weeks 39 and 52, 57.1% and 35.0% of T-P patients who started with pre-diabetes had shifted into the normal group. In comparison, at these timepoints 42.0% and 29.5% of T-T patients had shifted from pre-diabetes to the normal group. There were too few patients who had shifted into the DM group to draw conclusions. Similarly, the number of patients who started with DM in each treatment arm is too small to draw conclusions.

Table A27: Shifts in HbA1c – Extension Phase of Pivotal Trials (Both Trials Combined)

Baseline Evaluation		T-T N=246			T-P N=135		
		Post-Baseline Evaluation					
		Normal	Pre-Diabetes	DM	Normal	Pre-Diabetes	DM
Normal	Week 39	145 (96.0)	6 (4.0)	0 (0.0)	77 (92.8)	6 (7.2)	0 (0.0)
	Week 52	132 (93.0)	10 (7.0)	0 (0.0)	67 (95.7)	2 (2.9)	1 (1.4)
Pre-Diabetes	Week 39	21 (42.0)	27 (54.0)	2 (4.0)	12 (57.1)	9 (42.9)	0 (0.0)
	Week 52	13 (29.5)	30 (68.2)	1 (2.3)	7 (35.0)	12 (60.0)	1 (5.0)
DM	Week 39	0 (0.0)	4 (36.4)	7 (63.6)	0 (0.0)	3 (50.0)	3 (50.0)
	Week 52	1 (10.0)	7 (70.0)	2 (20.0)	1 (25.0)	1 (25.0)	2 (50.0)

Baseline extension: latest available value prior to re-randomization and up to Week 13
Data are presented as n (%)
Normal = A1c < 5.7%
Pre-Diabetes = 5.7% ≤ A1c < 6.5%
DM = A1c ≥6.5%
Source: Table From Sponsor

Table A28 evaluates each individual patient who had at least one FBG value of ≥6.5% (i.e. DM range) during the Main Phase of the Pivotal Studies and displays their FBG trends over time.

Table A28: HbA1c Trends: Individual Patients with At Least One Value ≥ 6.5% -- Extension Phase of Pivotal Trials (Both Trials Combined)

		HbA1c (%)		
	Patient ID	Week 26	Week 39	Week 52
T-T (N=246)	TH9507-CTR-1011-110-0476	*6.7	*6.6	6.0
	TH9507-CTR-1011-110-0567	*6.7	6.2	*6.5
	TH9507-CTR-1011-209-0527	*7.1		6.4
	TH9507-CTR-1011-226-0358	*6.9	6.4	6.3
	TH9507-CTR-1011-230-0048	*7.0	*7.0	6.2
	TH9507-III-LIPO-010-010-0004	*7.1	5.8	5.7
	TH9507-III-LIPO-010-010-0011	*6.6	*6.5	6.2
	TH9507-III-LIPO-010-011-0009	*6.5	5.7	5.0
	TH9507-III-LIPO-010-011-0024	*6.6	*6.5	
	TH9507-III-LIPO-010-014-0021	*6.6	*7.5	6.3
	TH9507-III-LIPO-010-027-0002	*7.4	*7.2	*7.3
	TH9507-III-LIPO-010-042-0035	*6.5	*7.1	
	TH9507-CTR-1011-204-0370	6.1	*6.6	6.2
	TH9507-CTR-1011-216-0285	5.7	5.1	*6.7
	TH9507-CTR-1011-230-0408	6.3	*6.6	
T-P (N=135)	TH9507-CTR-1011-211-0288	*6.5	*7.0	*6.6
	TH9507-CTR-1011-215-0279	*6.7	5.7	6.3
	TH9507-CTR-1011-216-0353	*7.3	*6.8	*7.2
	TH9507-CTR-1011-224-0083	*6.5		
	TH9507-CTR-1011-224-0553	*6.6	*6.7	
	TH9507-CTR-1011-226-0239	*6.5	6.1	
	TH9507-III-LIPO-010-011-0011	*6.8	5.8	5.6
	TH9507-CTR-1011-203-0015	5.4	5.4	*8.4
	TH9507-CTR-1011-231-0464	6.3	6.1	*6.5

*>=6.5%

Source: Table from Sponsor

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number:	22-505 / N000
Drug Name:	Egrifta (tesamorelin acetate) 2 mg/day subcutaneous injection
Indication(s):	Treatment of excess abdominal fat in HIV-infected patients with lipodystrophy
Applicant:	Theratechnologies Inc.
Date(s):	May 29, 2009 submission
Review Priority:	Standard
Biometrics Division:	Division of Biometrics 2 (HFD-715)
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1 Summary

Based on results from studies 10 and 11, 2 mg subcutaneous tesamorelin (TH9507) was statistically significantly superior to placebo in reducing VAT, the primary efficacy endpoint, from baseline to week 26. Triglycerides and the patient reported outcome belly appearance distress were not consistently statistically different from placebo. IGF-1 was statistically significantly increased in the TH9507 group compared to placebo in both studies.

Results from the re-randomized extension withdrawal phase showed that VAT increased when TH9507 was discontinued. Continuation of TH9507 2 mg treatment to week 52 was necessary in order to maintain the effect of the drug beyond week 26.

2 Background

Tesamorelin (TH9507) is a synthetic analog of human growth hormone releasing factor developed for the treatment of excess abdominal fat in HIV patients with lipodystrophy.

The submission included one phase 2 study and two phase 3 studies to evaluate TH9507 vs. placebo in the treatment of excess abdominal fat in HIV-infected patients with lipodystrophy. The two phase 3 studies (referred to as Studies 10 & 11/12) were similarly designed with a 26-week main phase for efficacy assessment using VAT (Visceral Adipose Tissue) percent change from baseline to week 26 as the primary efficacy endpoint and a 26-week extension phase which re-randomized patients who completed the TH9507 treatment in the main phase to continue on TH9507 or placebo. The efficacy objective of the 26-week withdrawal extension phase was to explore the effect of TH9507 following discontinuation. The placebo-treated patients in the main phase were switched to TH9507 (2 mg) in the extension phase.

Study 11 was undertaken to confirm the findings of Study 10.

3 Results

VAT

The primary efficacy endpoint, VAT (visceral adipose tissue) percent change from baseline to Week 26, was statistically significantly different between TH9507 and placebo. Table 1 displays the analysis of covariance (ANCOVA) results for change and percent change for the 2 studies. The treatment differences, -19.6% [-23.7, -15.3] in study 10 and -11.7% [-16.2, -7.1%] in study 11, exceeded the clinical benchmark of an 8% reduction. The upper bound of the 2-sided 95% confidence interval (-15.3%) for Study 10 exceeded the 8% benchmark. The upper bound of the 2-sided 95% confidence interval for Study 11 (-7.1%) fell just short of an 8% reduction. Figure 1 displays between-treatment differences and confidence intervals by study for VAT percent change and VAT change from baseline to Week 26.

Secondary efficacy endpoints triglycerides and patient reported outcome (PRO) related to Body Image (belly size) were not consistently statistically significant. IGF-1 change from baseline was statistically significantly increased in the TH9507 group compared to placebo in both studies.

The extension phases of both studies showed reversals of treatment effects in patients who discontinued TH9507 and were re-randomized to placebo. There were no further improvements on VAT in TH9507 patients re-randomized to TH9507.

Table 1 ANCOVA* results for VAT % change and change from baseline to Week 26 – ITT, LOCF

Study		TH9507 (2 mg)		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)	272	-17.8% (1.6)	136	+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)	268	-13.8% (1.5)	126	-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**

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

Figure 1 LSMean difference from placebo at 26 Week

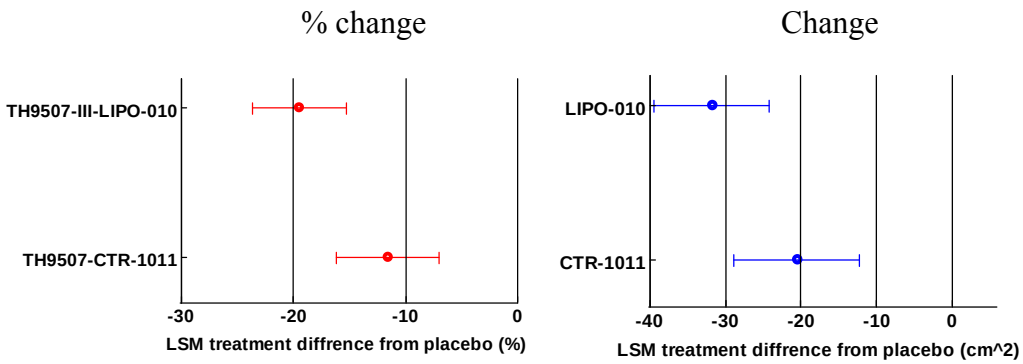


Figure 2 displays the cumulative percentage of patients (y-axis) having a VAT percent change that is equal to or less than that shown on the x-axis. Fig 3 shows boxplots for VAT percent change.

Figure 2 Cumulative distribution of VAT % change from baseline to Week 26 by main phase treatment
– ITT excluding patients with baseline carried forward

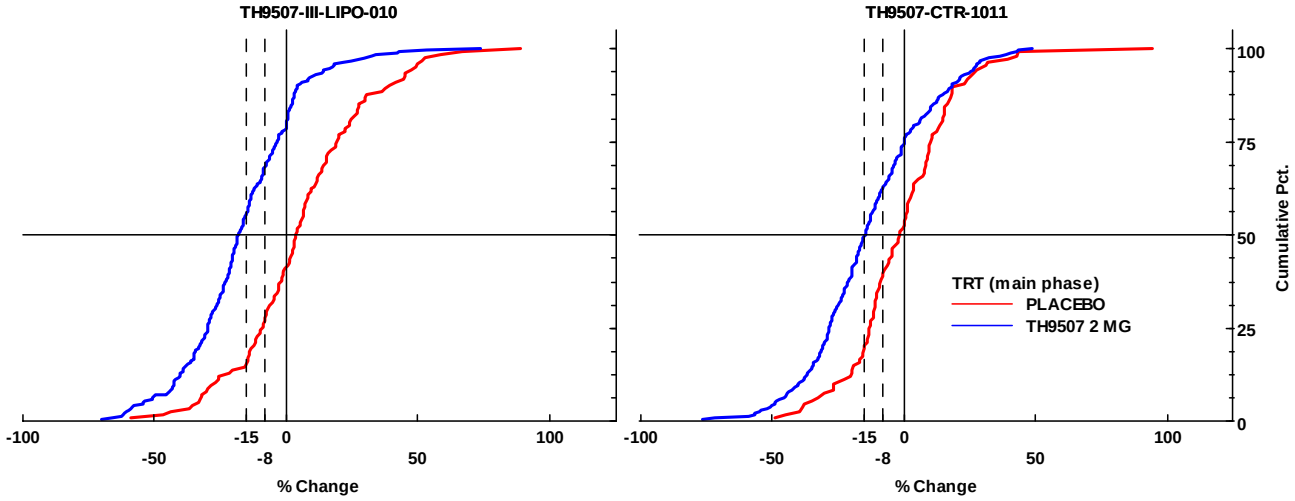
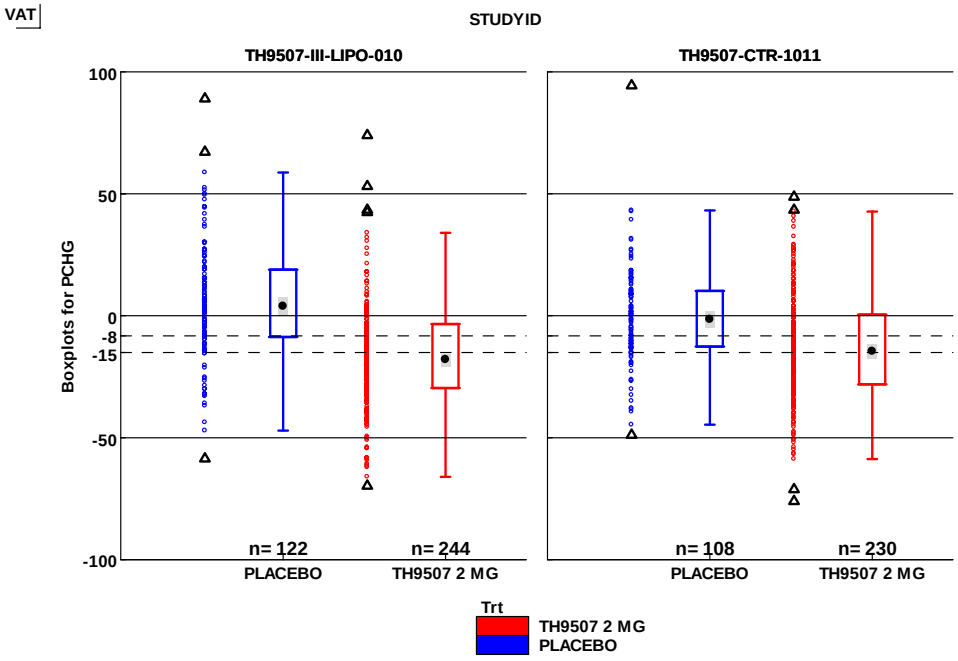


Figure 3 Boxplots of VAT % change from baseline to Week 26 –
ITT excluding patients with baseline carried forward



The box displays the interquartile range (IQR, the middle 50% of the distribution). The wiskers extend from the box to 1.5 times the IQR (75% value +1.5*IQR and 25% value-1.5*IQR). The triangles are outliers

Secondary efficacy variables were change from baseline in TG, IGF-1 and patient reported outcomes (PROs) related to body image (specifically, belly appearance distress (BAD), belly size evaluation (BSE) and patient's belly profile assessment (BPA)). There was a prespecified gatekeeper strategy to control the type 1 error. The testing order for Study 10 was: 1. VAT change from baseline to week 26, 2. BAD change score, 3. Total cholesterol:HDL-C ratio and 4. Triglycerides change from baseline to week 26. For Study 11, the testing order was 1. VAT change from baseline to week 26, 2. BAD change score and TG change from baseline to week 26 (using Hochberg's adjustment) 3. total cholesterol/HDL cholesterol ratio.

Triglycerides (TG)

Table 2 displays descriptive statistics for TG change and percent change from baseline to week 26. Both TG percent change from baseline and change from baseline were statistically different between TH9507 and placebo in Study 10 but not in Study 11 (Table 3). Fig 4 displays the cumulative distribution for TG percent change. Fig 5 shows boxplots for TG change and percent change with outliers.

In study 10, treatment-by-baseline interaction was significant for TG change from baseline ($p<0.0001$) but not for TG percent change ($p=0.96$) (Fig. 6). For this reason, the % change endpoint is more readily interpretable than change from baseline.

Forty-four percent of patients were on lipid lowering therapy at baseline. TG levels were significantly higher in patients on lipid-lowering therapy (median 220) than without therapy (median 177). The treatment-by-lipid lowering therapy interaction for TG percent change from baseline was not significant ($p=0.2$). Figure 7 displays boxplots of TG levels at baseline and week 26 by treatment for lipid-lowering therapy (yes or no).

Table 2 Descriptive statistics for triglyceride (TG) change from baseline to week 26 - ITT

	Study 10		Study 11	
	TH9507 N=273	Placebo N=137	TH9507 N=270	Placebo N=126
Baseline mean (SD)	252 (188)	234 (145)	239 (261)	223 (144)
Median	206	194	168	182
[min, max]	[43, 1009]	[56, 896]	[38, 3276]	[54, 795]
Mean change (SD)	-51 (145)	9 (118)	-22 (131)	3 (106)
Median change	**-25**	**0**	**-2**	**-2**
[min, max]	**[-855, 357]**	**[-293, 455]**	**[-1060, 435]**	**[-337, 540]**
Mean % change (SD)	-8% (40)	12%(57)	3% (45)	8%(46)
Median % change	**-13%**	**0%**	**-1.6%**	**-1.5%**
[min, max]	**[-85, 183]**	**[-71, 333]**	**[-81, 226]**	**[-62, 174]**

Table 3 Analysis results for triglyceride (TG) (mg/dL) change from baseline to week 26

	Study 10			Study 11		
	Treatment		Trt Difference from placebo*	Treatment		Trt Difference from placebo*
	TH9507 N=273	PLACEBO n=137	LSM (SE) [95% CI] p-value	TH9507 N=270	PLACEBO n=126	(SE) [95% CI] p-value
LSM % Change (SE)	-8% (3)	11% (4)	**-19% (5) [-29%, -10%] P<0.0001**	4% (3)	8% (4)	**-4% (5) [-14%, +6%] P=0.4**
LSM Change (SE)	-48.0 (6.6)	4.8 (9.3)	**-53 (11) [-75, -30] P<0.0001**	-18.5 (6.9)	1.3 (10.0)	**-20 (12) [-44, 4] P=0.10**

*ANCOVA model with treatment, lipid lowering treatment (Y/N) as fixed effects and baseline TG as covariate
LSM=Least-square mean

Figure 4 Cumulative distribution of TG % change from baseline to Week 26 – ITT excluding patients with baseline carried forward

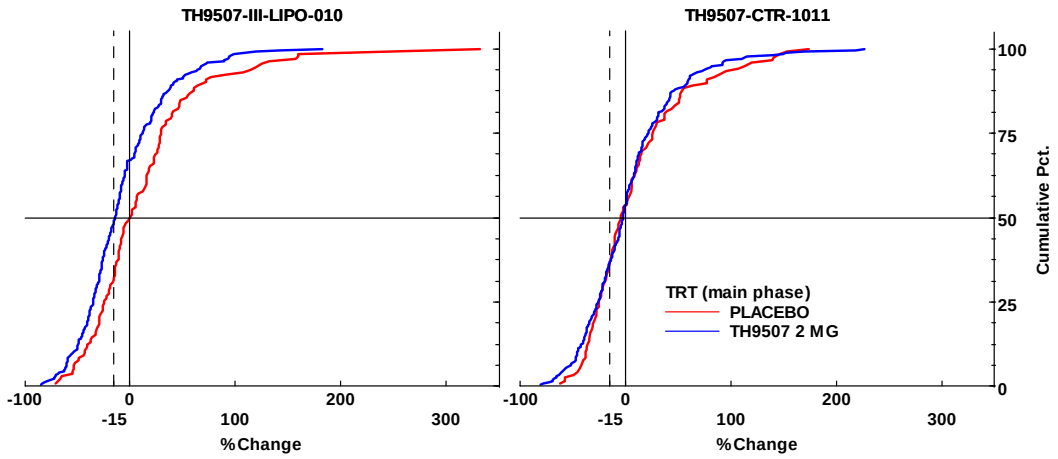
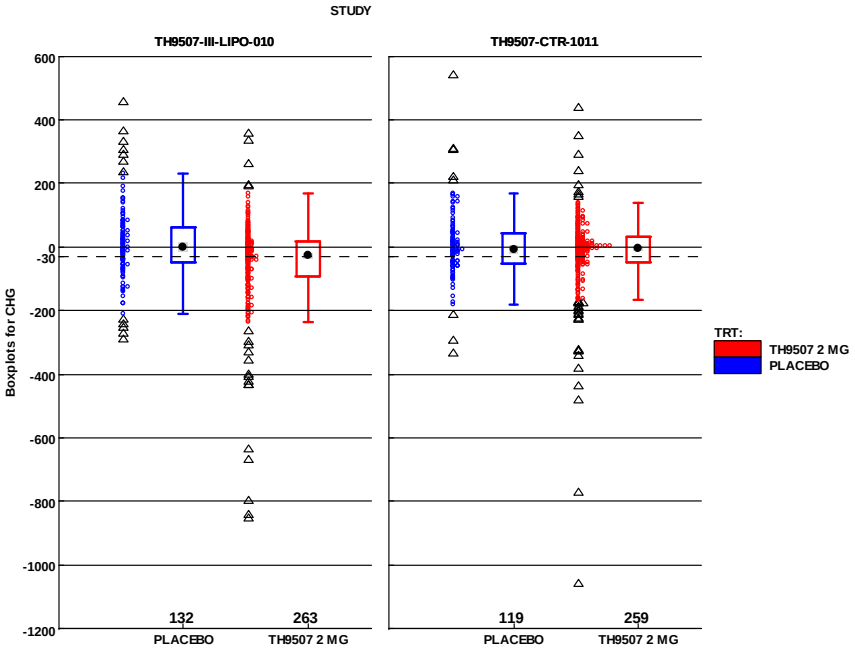


Figure 5 Boxplots for TG change from baseline and % change from baseline to Week 26 – ITT excluding patients with baseline carried forward

TG Change from baseline



TG % Change for baseline

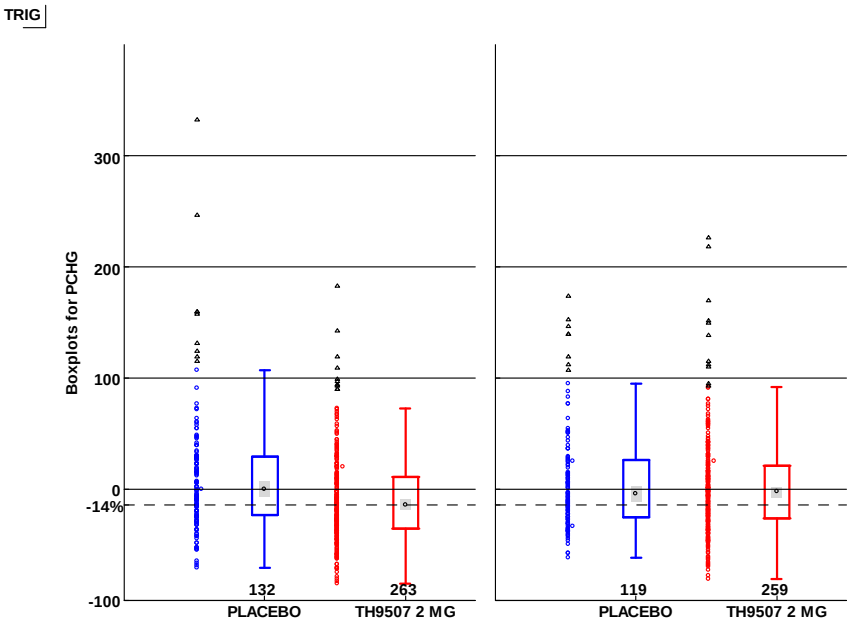
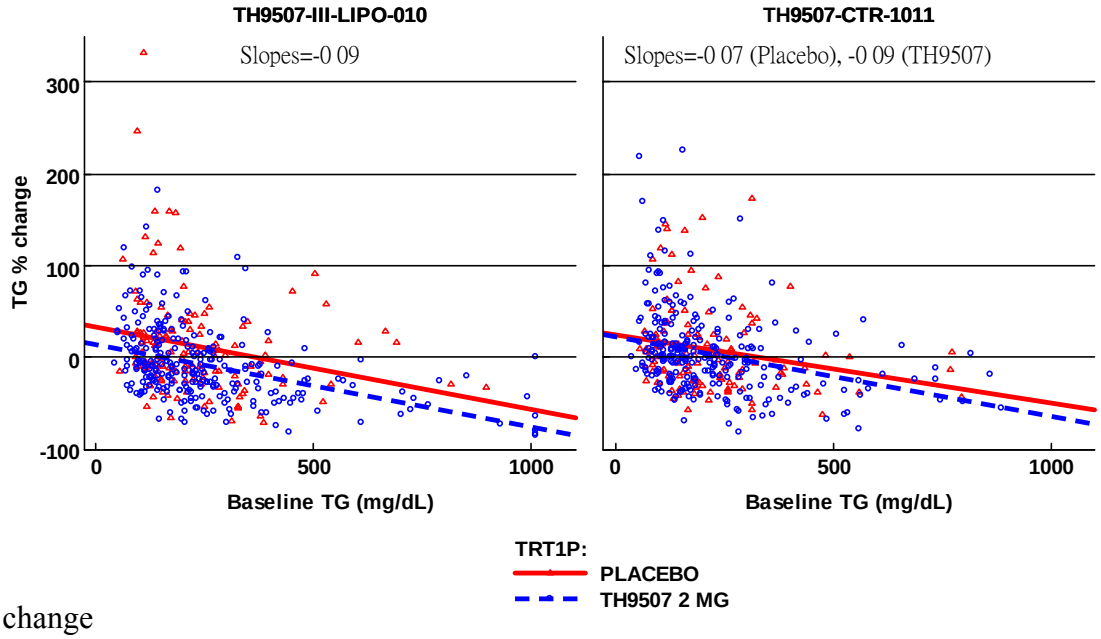


Figure 6 % change and change of TG from baseline to Week 26 by baseline TG – ITT excluding patients with baseline carried forward

TG % change



TG change

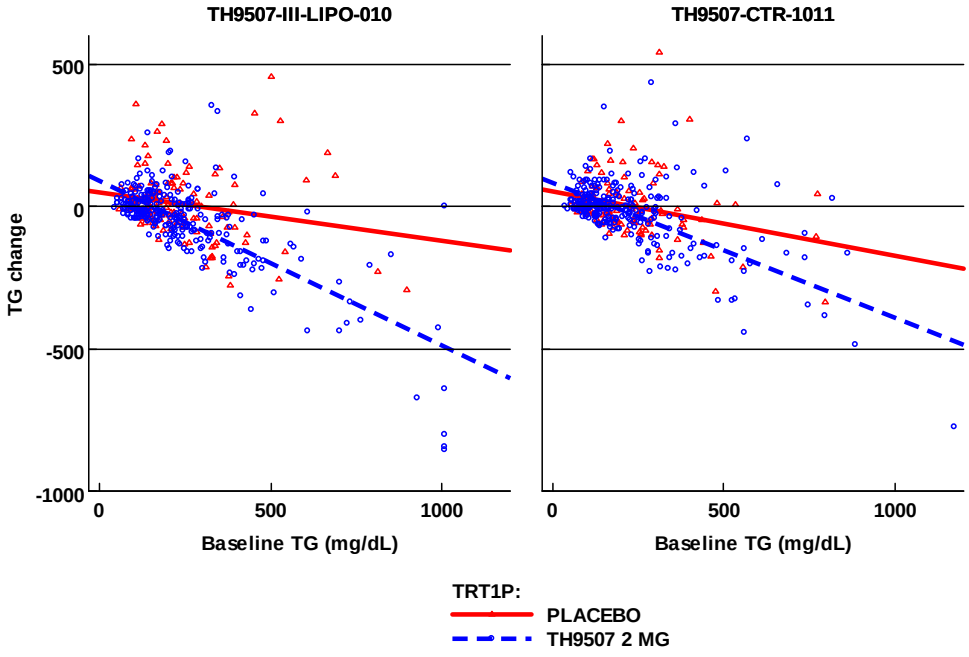
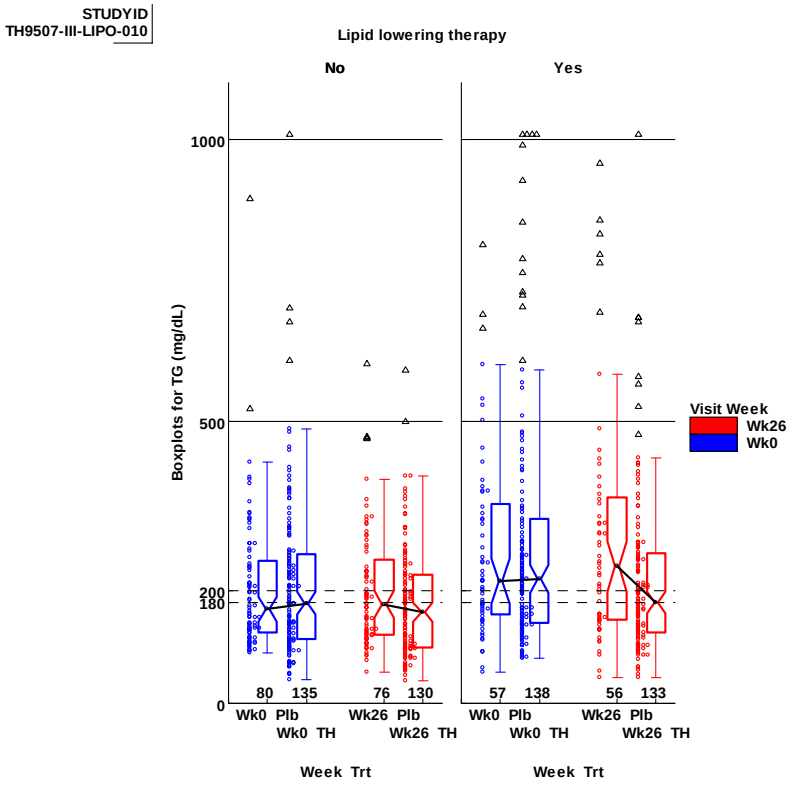


Figure 7 TG levels at baseline and Week 26 by lipid lowering therapy – ITT excluding patients with baseline carried forward



IGF-1

IGF-1 change from baseline to week 26 for TH9507 was statistically significantly different from placebo ($p<0.001$) (Table 4). Figures 8 and 9 show cumulative distributions and boxplots for IGF-1 change from baseline to week 26, respectively.

Table 4 ANCOVA* results for IGF-1 (mg/dL) change from baseline to week 26

	Study 10			Study 11		
	Treatment		Difference	Treatment		Difference
	TH9507 N=269	PLACEBO n=136	From placebo	TH9507 N=265	PLACEBO n=125	From placebo
	LSM (SE)	LSM (SE)	LSM (SE) [95% CI]	LSM (SE)	LSM (SE)	LSM (SE) [95% CI]
Baseline	146.2 (65.9)	149.1(59.4)		161.1 (59)	168.1 (75)	
Change from baseline	106.5 (5.9)	-14.7 (8.3)	**121.1 (10.2) [101.1, 141.3]**	108.4 (5.9)	2.6 (8.6)	**105.7(10.5) [85.1, 126.3]**

*ANCOVA included treatment as effect and baseline IGF-1 as covariate
LSM=least-square mean

Figure 8 Cumulative distributions for IGF-1 change from baseline to Week 26 – ITT excluding patients with baseline carried forward

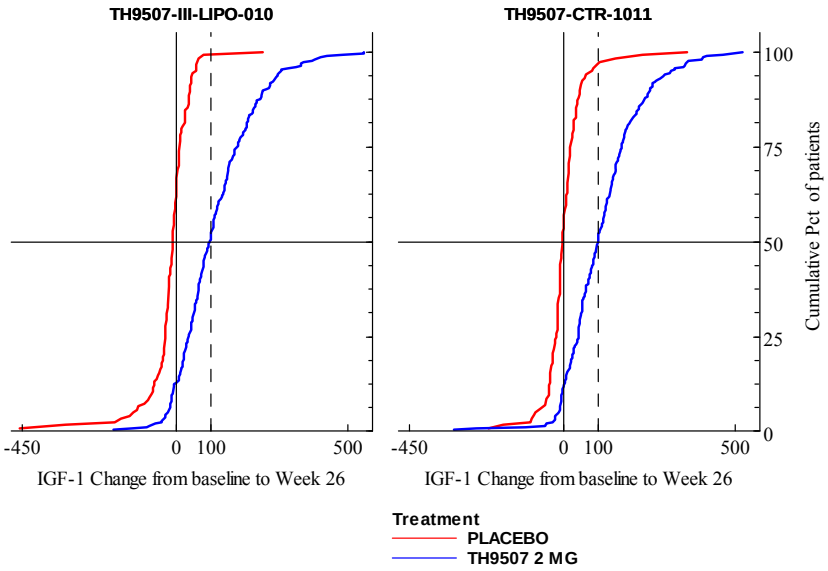
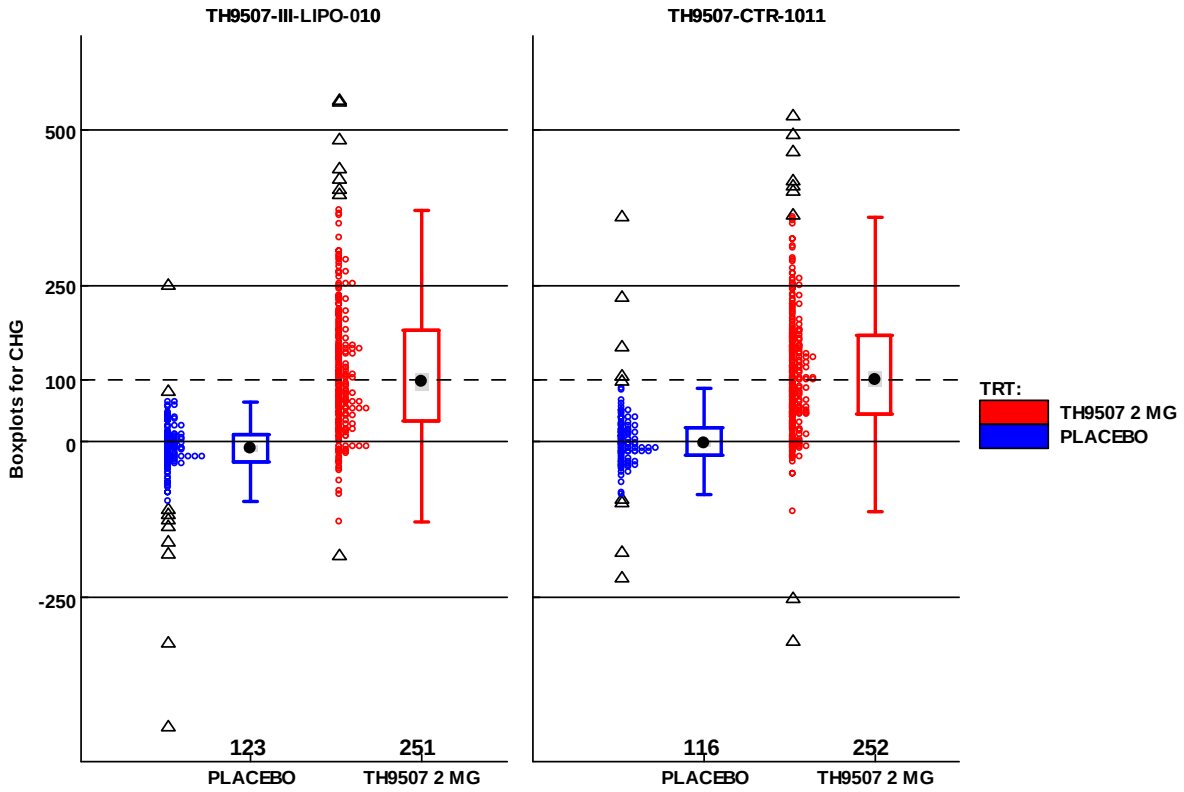


Figure 9 Boxplots for IGF-1 change from baseline to Week 26 – ITT excluding patients with baseline carried forward



Other Secondary Efficacy Variables:

Trunk Fat, Lean Body Mass (LBM) and Total Body Fat were statistically significantly different between TH9507-treated patients and placebo-treated patients (Table 5-7).

Table 5 ANCOVA* results for trunk fat change (kg) from baseline to Week 26 – ITT, LOCF

Study		TH9507 (2 mg)		Placebo		Treatment difference
		n	Mean	n	Mean	LSM, (SE), [95% CI], p-value
10	Baseline (SD)	261	14.9 (5.6)	130	15.3 (5.8)	
	Change (SE)		-1.0 (0.1)		+0.4 (0.16)	**-1.4 (0.19) [-1.8, -1.0] p<0.001**
11	Baseline (SD)	264	15.3 (5.3)	123	15.2 (5.1)	
	Change (SE)		-0.8 (0.12)		+0.2 (0.17)	**-1.0 (0.21) [-1.4, -0.6] p<0.001**

*Analysis of covariance model with treatment as fixed effect and baseline trunk fat as covariate. LSM=least-square mean

Figure 10 Cumulative distributions of trunk fat % change from baseline to Week 26 – ITT excluding patients with baseline carried forward

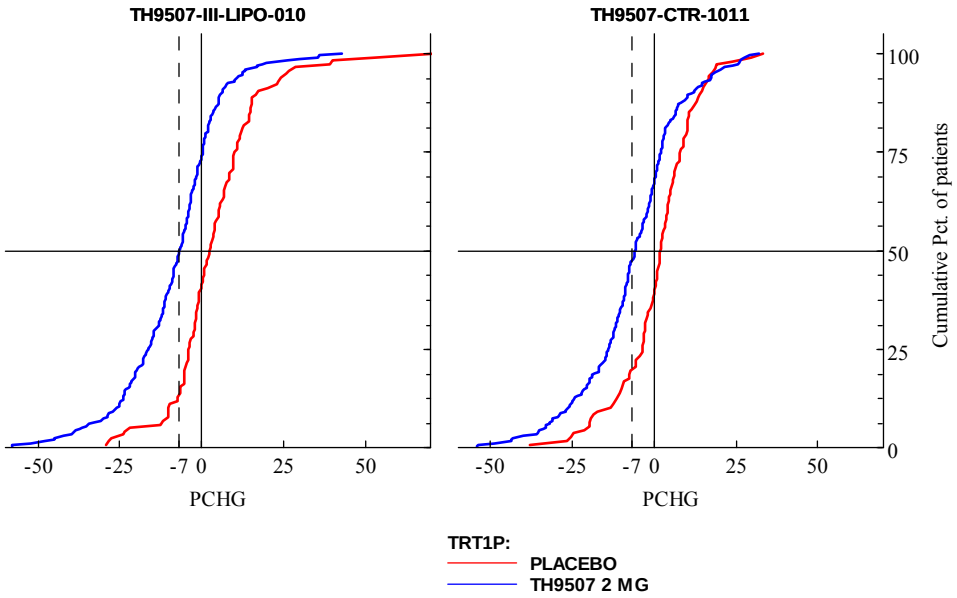


Table 6 ANCOVA* results for Lean Body Mass change (kg) from baseline to Week 26 – ITT, LOCF

Study		TH9507 (2 mg)		Placebo		Treatment difference
		n	Mean	n	Mean	LSM, (SE), [95% CI], p-value
10	Baseline (SD)	261	62.0 (10.1)	130	61.4 (9.6)	
	Change (SE)		1.3 (0.1)		-0.2 (0.2)	**1.6 (0.2) [1.1, 2.0] p<0.0001**
11	Baseline (SD)	264	62.4 (10.3)	123	60.5 (11.2)	
	Change (SE)		1.2 (0.1)		-0.1 (0.2)	**1.3 (0.2) [0.8, 1.8] p<0.0001**

*Analysis of covariance model with treatment as fixed effect and baseline LBM as covariate
LSM=least-square mean

Table 7 ANCOVA* results for Total Body Fat change (kg) from baseline to Week 26 – ITT, LOCF

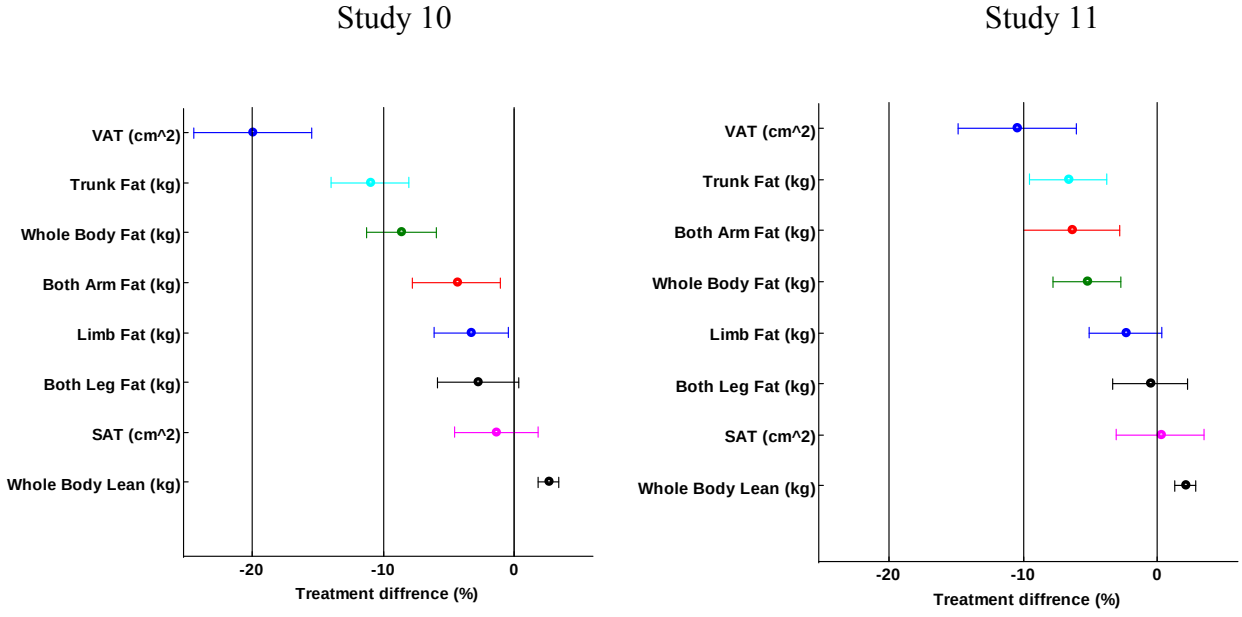
Study		TH9507 (2 mg)		Placebo		Treatment difference
		n	Mean	n	Mean	LSM, (SE), [95% CI], p-value
10	Baseline (SD)	261	22.9 (9.5)	130	23.9 (9.9)	
	Change (SE)		-1.1 (0.2)		0.6 (0.2)	**-1.7 (0.3) [-2.2, -1.2] p<0.0001**
11	Baseline (SD)	264	23.6 (9.4)	123	23.3 (8.4)	
	Change (SE)		-0.9 (0.2)		0.3 (0.2)	**-1.2 (0.3) [-1.8, -0.6] p<0.0001**

*Analysis of covariance model with treatment as fixed effect and baseline total body fat as covariate
LSM=least-square mean

Imaging and laboratory variables

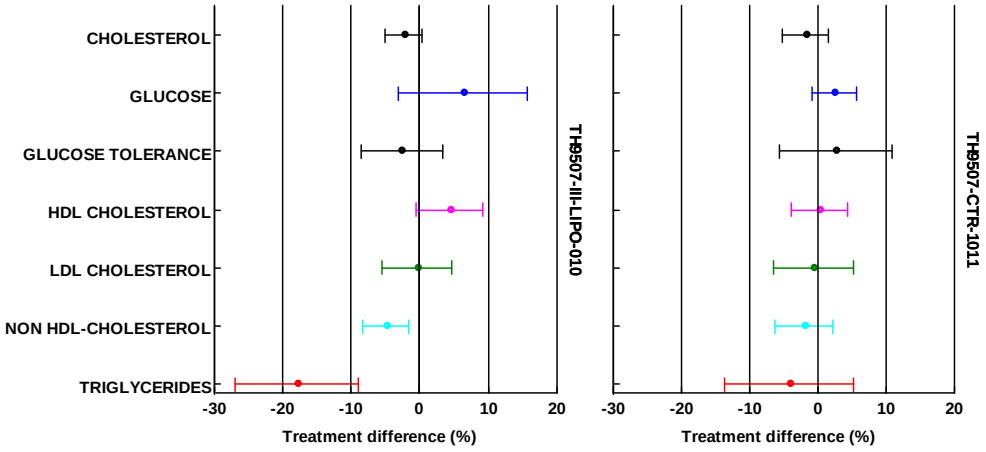
Figure 11 summarizes the least-squared-mean treatment differences between TH9507 2 mg and placebo for percent change from baseline to week 26 in all image variables. Figure 12 shows the treatment differences for selected laboratory variables.

Figure 11 LS Mean treatment differences [95% CI] for % change from baseline to Week 26 for all image variables – ITT, LOCF



Treatment effects for lipid and glucose variables were neutral (Fig. 12).

Figure 12 LSMean treatment differences [95% CI] for % change from baseline to Week 26 for laboratory variables – ITT, LOCF



Extension Phase:

In both studies, the initial randomized phases of 26 weeks were followed by an extension phase consisting of a randomized withdrawal period of 26 weeks. Completers in the TH9507 treatment group at Week 26 were re randomized to TH9507 or placebo for another 26 weeks. The purpose of the extension was to collect long-term safety data and to explore the duration of the effect after the main study. The treatment comparisons between placebo and TH9507 during the extension period were exploratory. Patients originally randomized to placebo were switched to TH9507 after Week 26.

For the TH9507–TH9507 treatment sequence, VAT percent changes from Week 26 to Week 52 were +4.5% and -0.4%, respectively, for Studies 10 and 11/12. For the TH9507–placebo treatment sequence, VAT percent changes were +25% and +23.5%, respectively.

For patients switching from placebo to TH9507 at week 26, VAT percent changes from week 26 to week 52 were -15% and -12%, respectively, for studies 10 and 11/12.

Table 8 displays the ANCOVA results for the re randomized groups. The difference between the T-T and T-P treatment sequences was statistically significant. Figure 13 displays cumulative distributions for VAT % change from week 26 to week 52 in the ITT population of the extension phase. Figure 14 displays boxplots for VAT % change in the extension phase.

Table 8 ANCOVA* results for VAT % change from Week 26 baseline to Week 52 – ITTE, LOCF

Study	T - T		T - P		Treatment difference
	n	LSM (SE)	n	LSM (SE)	LSM, (SE), [95% CI], p-value
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

*ANCOVA included treatment as fixed effect and Week 26 baseline VAT as covariate
LSM=least-square mean

Figure 13 Cumulative distribution of VAT % change from Week 26 to week 52 – ITTE, LOCF

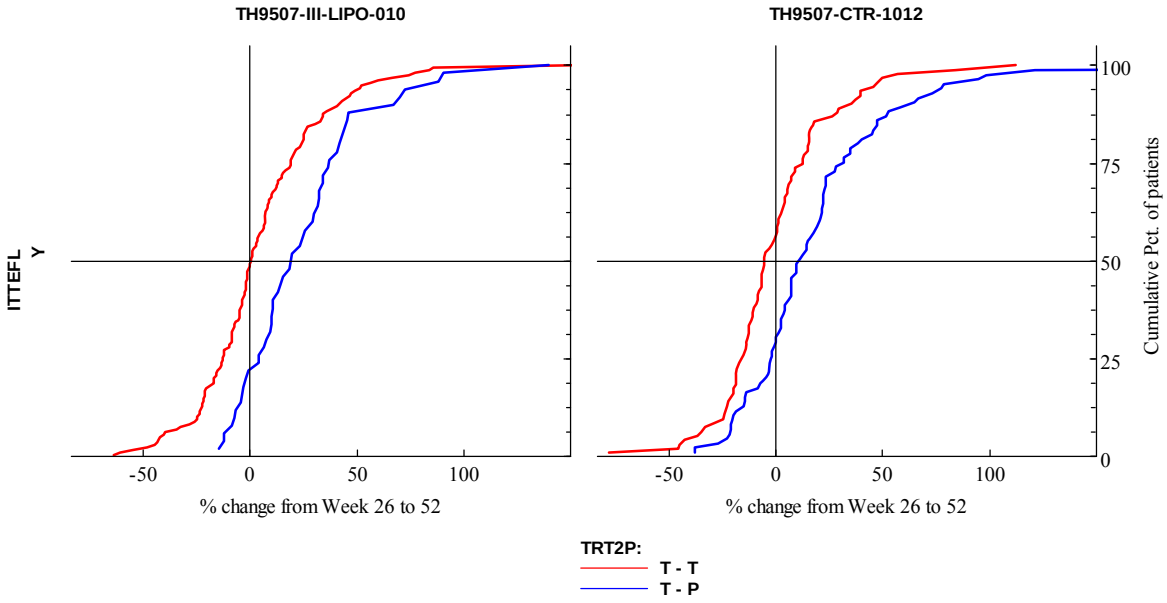


Figure 14 Boxplots for VAT % change from Week 26 baseline to Week 52 – ITTE, LOCF

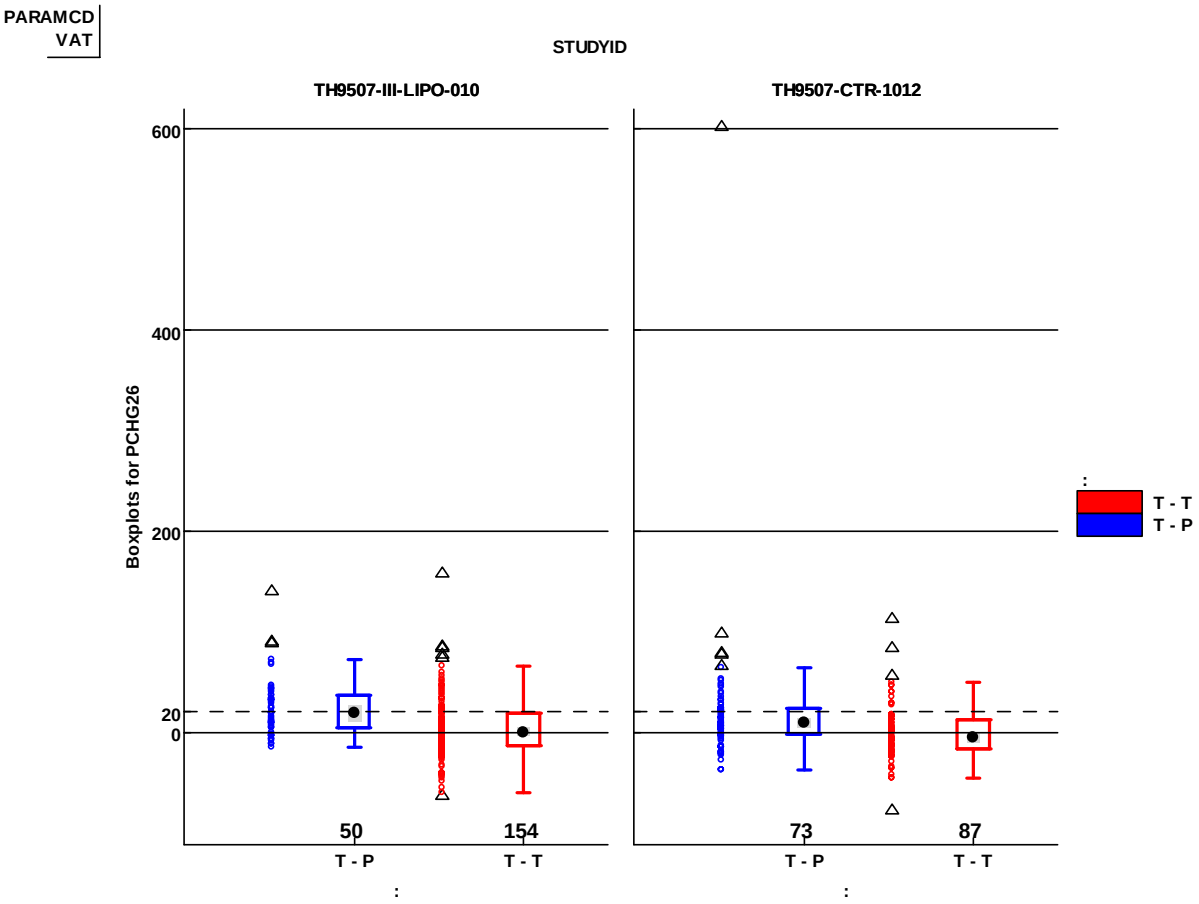


Figure 15 displays VAT (cm^2) levels over time by treatment sequence during the main phase and the extension phase for patients who completed 52 weeks of treatment. Figure 16 displays VAT percent changes over time with sample sizes for each treatment group in the main phase and in the extension phase for the completers at week 52. The efficacy of TH9507 was clearly reversed within 13 weeks after drug discontinuation.

Figure 15 VAT levels over time by treatment sequence (main and extension) in 52-week completers

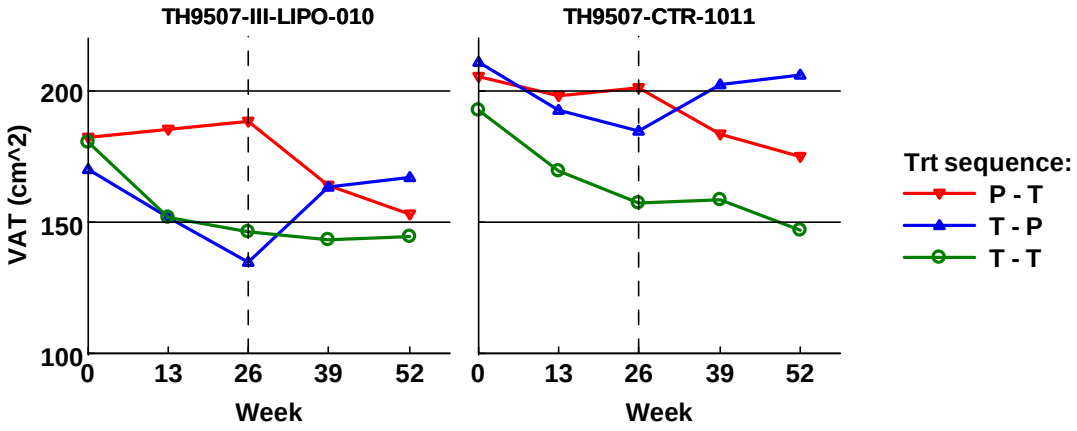
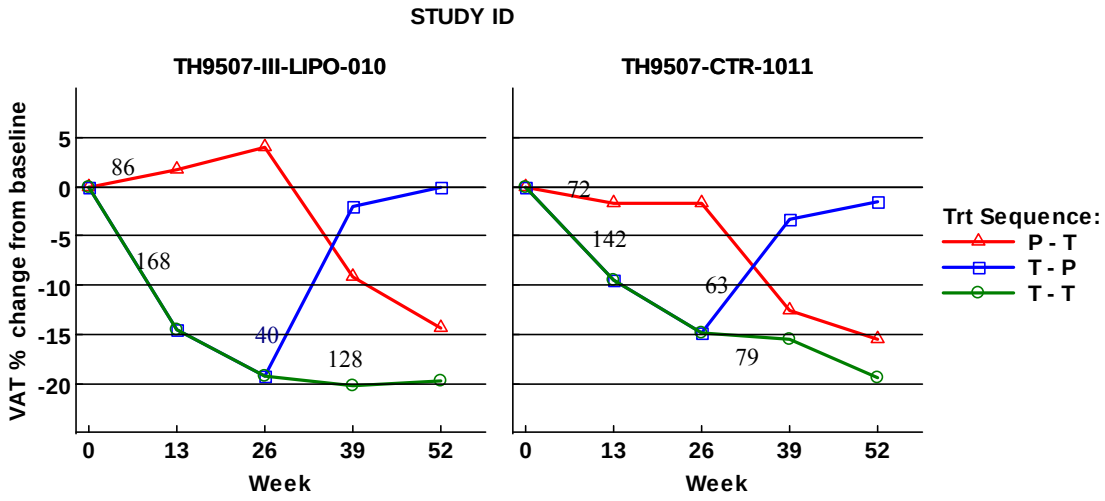
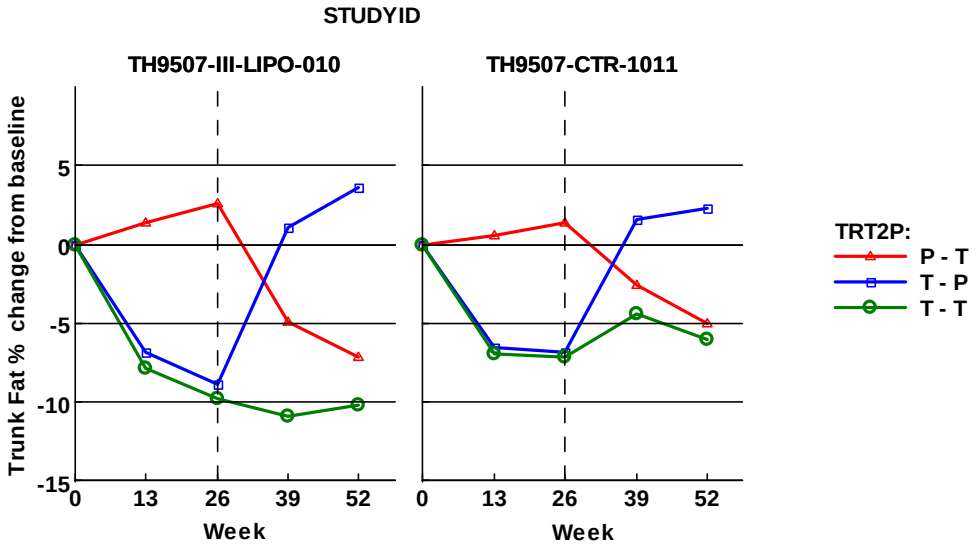


Figure 16 Mean VAT % change by treatment sequence (main and extension) in Week 52 completers



Similar to VAT, the efficacy of TH9507 with respect to trunk fat was reversed within 13 weeks of study drug discontinuation (Fig. 17 blue).

Figure 17 Mean Trunk Fat % change by treatment sequence (main and extension) in Week 52 completers



Patient Reported Outcomes (PRO)

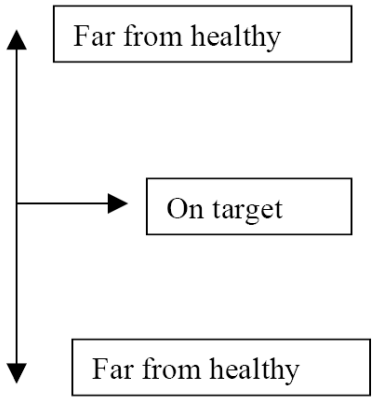
Secondary efficacy PRO variables were belly size evaluation (BSE), belly appearance distress (BAD) and belly profile assessment (BPA) scales. The primary analysis was parametric ANCOVA for BAD and BSE and the Mann-Whitney test for (BPA) for study 10 and ranked ANCOVA for study 11 for all 3 PRO endpoints, BSE, BAD and BPA. This reviewer reported p-values from these agreed-upon, prespecified analyses. A summary of p-values are found at the end of this section following descriptive data for each endpoint.

1. Belly Size Evaluation (BSE)

The Body Size Scale below consists of bi-directional responses which measure deviation from a healthy look. Patients compared their 'current appearance' to their perceived 'healthy look'.

Compared to my "healthy look", my current amount or size is….

Scored	Patient Selects Phrase
-100	A great deal less/very smaller or thinner
-75	A lot less/much smaller or thinner
-50	Somewhat less, smaller or thinner
-25	A little less, smaller or thinner
0	About right
+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



The bi-directional response used a corrected change score, negative of the (absolute (final) - absolute(baseline)) to yield consistently positive scores for improvement and negative scores for worsening and 0 for staying the same distance from 'about right' (Table 9) .

Table 9 BSE bi-directional

	1	2	3
Possible Score Category	Baseline and final values>0 (bigger than 'about right')	Baseline and final values<0 (smaller than 'about right')	Values fall on opposite sides of 0 (smaller than 'about right' at one time and bigger than 'about right' at another time
Change from baseline: Final – baseline	+ = worsening - = improvement	+ = improvement - = worsening	NA

	1	2	3
Possible Score Category	Baseline and final values>0 (bigger than 'about right')	Baseline and final values<0 (smaller than 'about right')	Values fall on opposite sides of 0 (smaller than 'about right' at one time and bigger than 'about right' at another time
Corrected change from baseline: - (absolute(final)-absolute(baseline))	+ = improvement - = worsening	+ = improvement - = worsening	+ = improvement - = worsening 0 = staying the same distance

Table 10 displays the descriptive statistics for BSE. At baseline, the median BSE score was 75 (belly size 'much bigger' than the 'healthy look') (Fig 18). At week 26, both groups improved toward the target look. The difference between treatment groups was not statistically significant. P-values were p=0.75 for study 10 and p=0.21 for study 11. Figure 19 displays the cumulative distribution for BSE change from baseline to week 26 and Figure 20 the percentage of patients by BSE change.

Table 10 Descriptive statistics for Belly Size Evaluation – ITT, LOCF

Protocol	TRT	N	Label	Mean	Std Dev	Median	Min	Max
LIPO-010	Placebo	137	BL	55.8	52	75	-100	100
			Wk 26	35.4	55	50	-100	100
			Change*	13.1	31.4	0	-100	100
	Th9507	272	BL	59.8	47.7	75	-100	100
			Wk 26	35.3	54.9	50	-100	100
			Change*	14.6	30.1	0	-75	100
CTR-1011	Placebo	126	BL	56.9	57.2	75	-100	100
			Wk 26	47.6	53.7	75	-100	100
			Change*	11.7	25.2	0	-75	100
	Th9507	268	BL	56	54.2	75	-100	100
			Wk 26	33.4	58	50	-100	100
			Change*	14.6	27.6	0	-75	100

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

Figure 18 Percentage of patients by BSE score at baseline - ITT

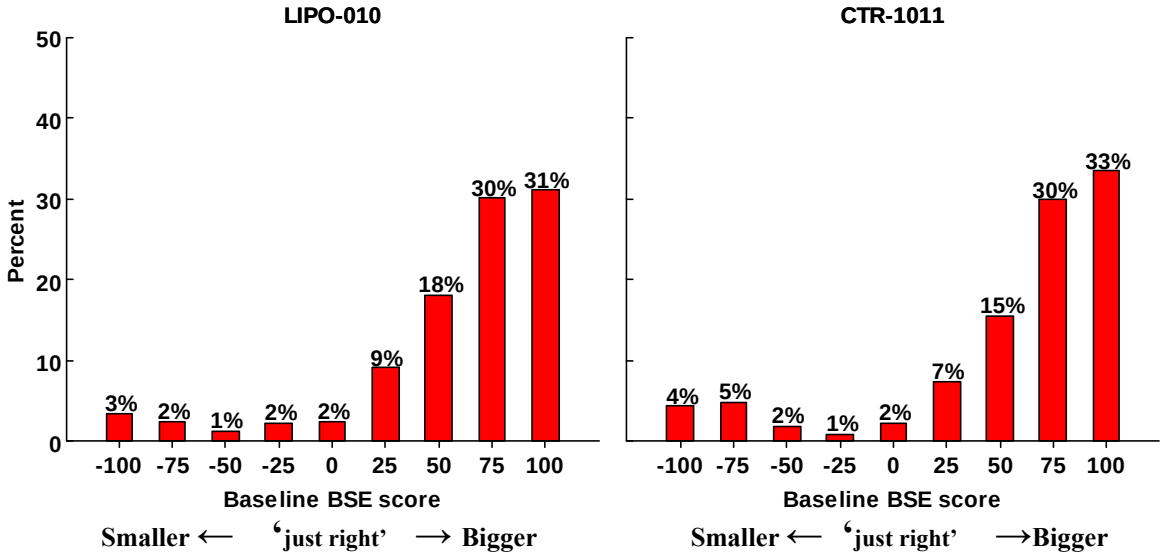


Figure 19 Cumulative distribution of Belly Size Evaluation change from baseline to Week 26 – ITT, LOCF

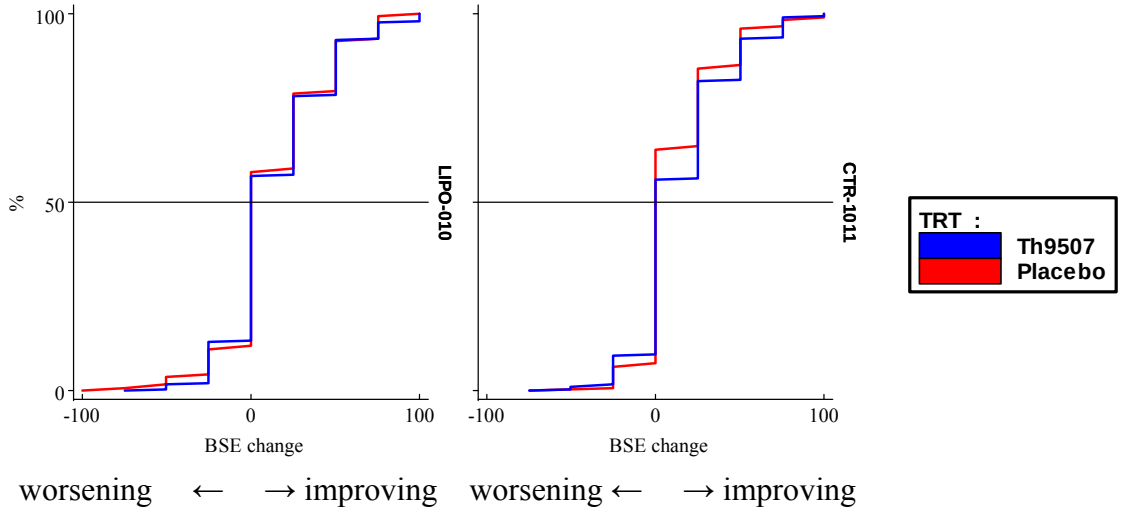
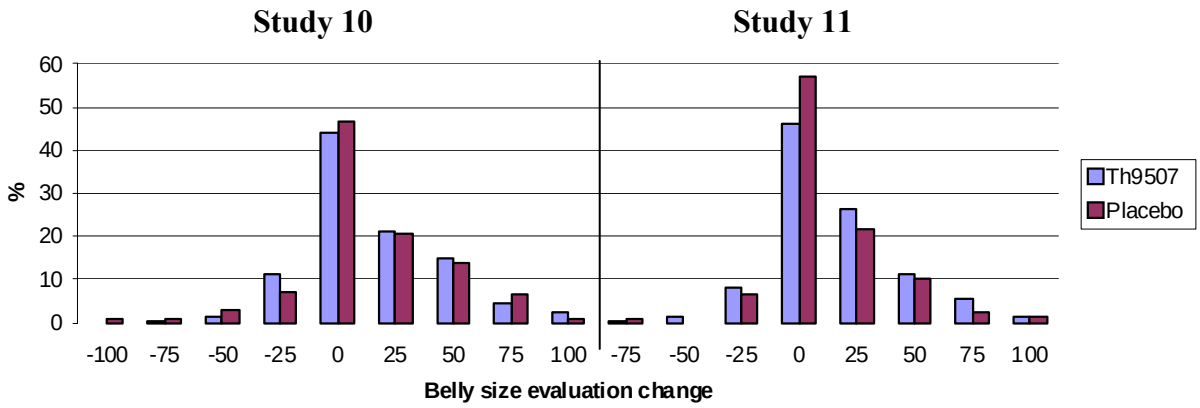


Figure 20 Percentage of patients by BSE change from baseline to Week 26 – ITT LOCF



Negative=worsening and positive=improving

2. Belly Appearance Distress

The 0 to 100 scale ranged from extremely upsetting and distressing to extremely encouraging with a score of 50 being neutral. A positive change indicated improvement.

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

Score	**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

Table 11 displays the descriptive statistics for BAD. More than 50% of patients reported 'extremely upsetting and distressing (30%)' or 'very upsetting and distressing (24%) at baseline for belly appearance distress (Fig 21). At week 26, the scores in both groups improved (Figs 22. 23). The treatment difference was not statistically significant for study 10 (p=0.076) and was significant for study 11 (0.022).

Table 11 Descriptive statistics of Belly Appearance Distress – ITT, LOCF

Protocol	TRT	N	Label	Mean	Std Dev	Median	Min	Max
LIPO-010	Placebo	137	BL	24	25.7	12.5	0	100
			Wk 26	30.2	27.3	25	0	100
			Change	6.2	25.8	0	-87.5	100
	Th9507	273	BL	22.1	22.2	12.5	0	100
			Wk 26	33.8	25.9	25	0	100
			Change	11.6	26.9	0	-87.5	87.5
CTR-1011	Placebo	126	BL	20.2	22.1	12.5	0	100
			Wk 26	25.4	25.1	25	0	87.5
			Change	5.2	26.6	0	-87.5	87.5
	Th9507	268	BL	22.4	24.2	12.5	0	100
			Wk 26	30.6	25.4	25	0	100
			Change	8.3	29	0	-100	100

Figure 21 Percentage of patients by BAD score at baseline – ITT, LOCF

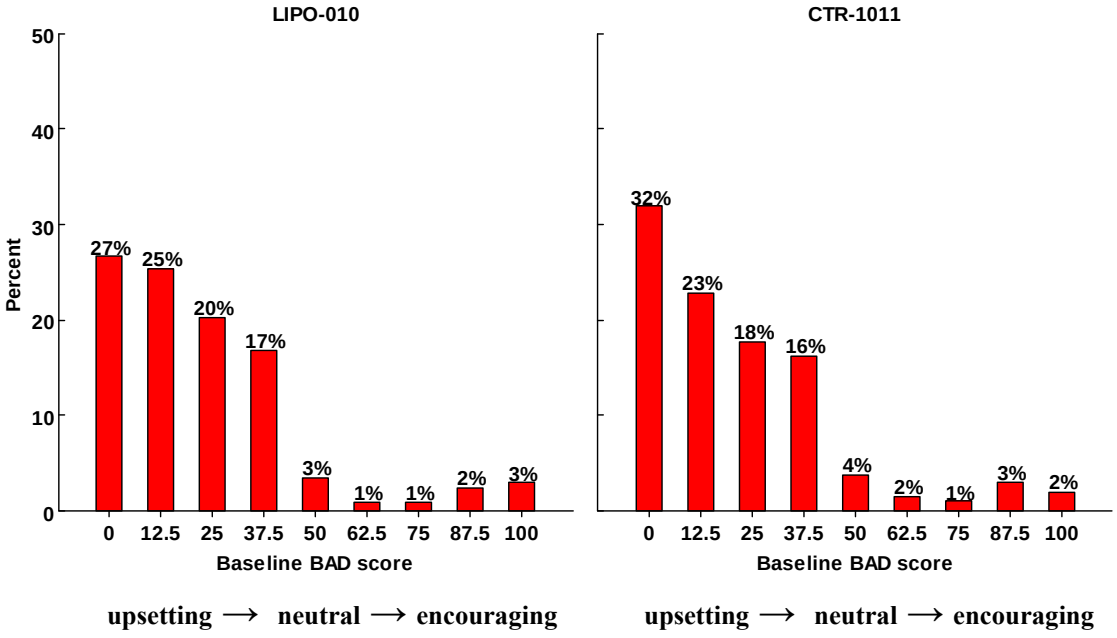


Figure 22 Cumulative distribution of Belly Appearance Distress change from baseline to Week 26 – ITT, LOCF

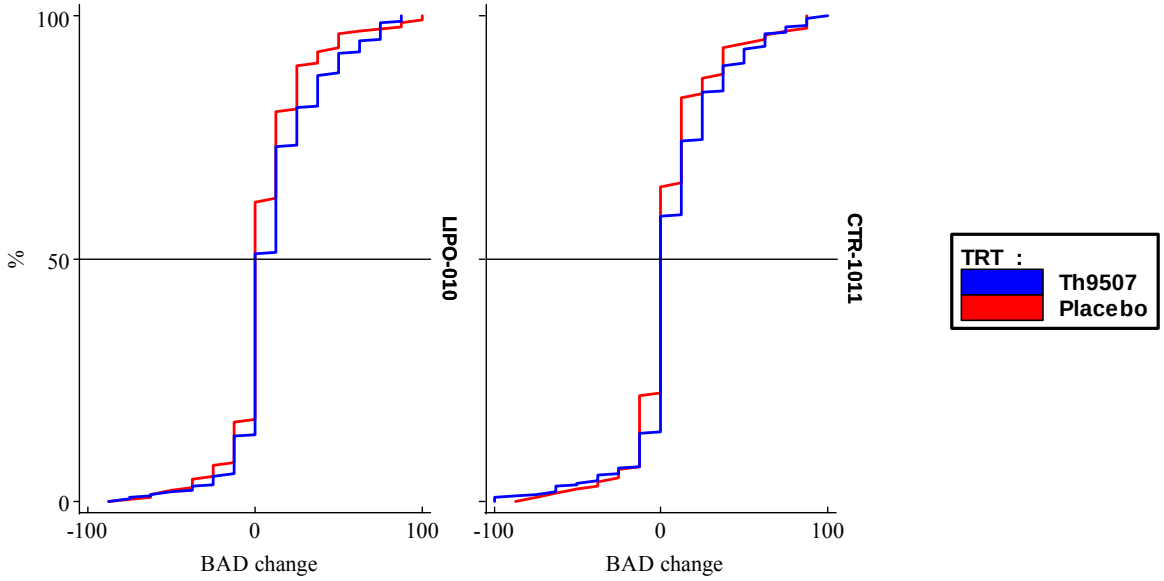
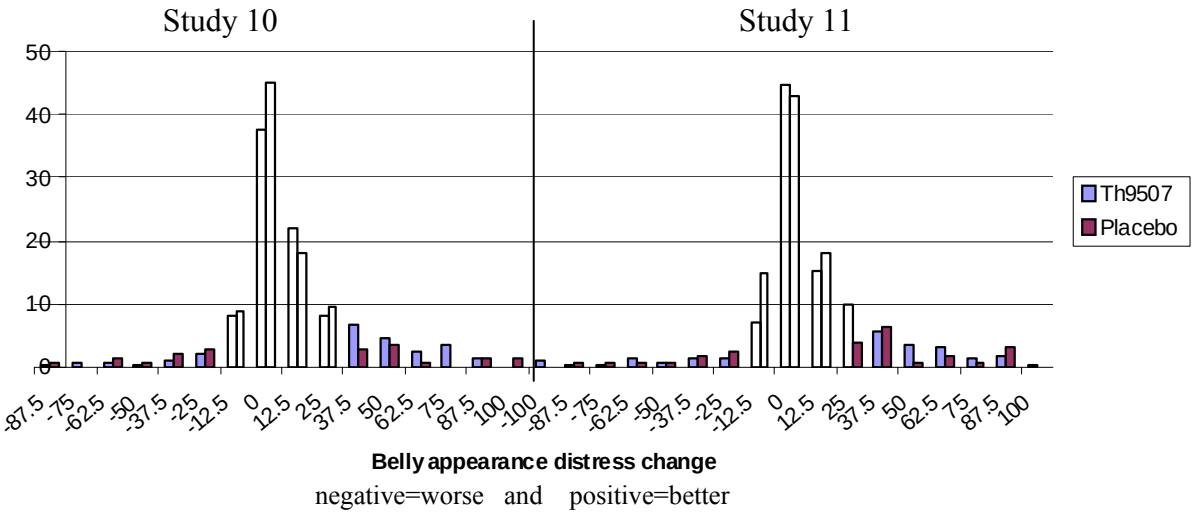


Figure 23 Percentage of patients by BAD change from baseline – ITT, LOCF



1. Patient rated Belly Profiles Scales

Patients and Physicians selected from 6 body profile images using a scale from 0 (normal) to 5 (the most dysmorphic) that reflected an increasing belly or hump.

Patients chose an image in response to each of three questions:

- Most how you think you look today?
- You would most like to look?
- Smallest amount of improvement that you consider beneficial to your health and well being?

Physician profile evaluations provided a clinical perspective to establish a standard for a 'minimally clinically important change.'

- Most how you think your patient looks today
- You would most like your patient to look
- Smallest amount of improvement that you consider beneficial to your patient's health and well being?

Table 12 displays the descriptive statistics for belly profiles today. Median current Belly Profile for baseline and week 26 was 3. P-values from the nonparametric Mann-Whitney test were p=0.031 for Study 10. The p-value from ranked ANCOVA was 0.075 for study 11.

Table 12 Descriptive statistics of Belly Profiles Today – ITT, LOCF

Protocol	TRT	N	Label	Mean	Std Dev	Median	Min	Max
LIPO-010	Placebo	137	BL	3.2	1.5	3	0	5
			Wk 26	2.8	1.5	3	0	5
			Change	-0.3	1.3	0	-4	5
	Th9507	273	BL	3.3	1.3	3	0	5
			Wk 26	2.6	1.4	3	0	5
			Change	-0.7	1.2	0	-5	4
CTR-1011	Placebo	126	BL	3.3	1.2	3	1	5
			Wk 26	3.1	1.4	3	0	5
			Change	-0.3	1	0	-4	2
	Th9507	268	BL	3.2	1.4	3	0	5
			Wk 26	2.7	1.6	3	0	5
			Change	-0.5	1.3	0	-5	4

Figure 24 Percentage of patients by BPA Today score at baseline – ITT, LOCF

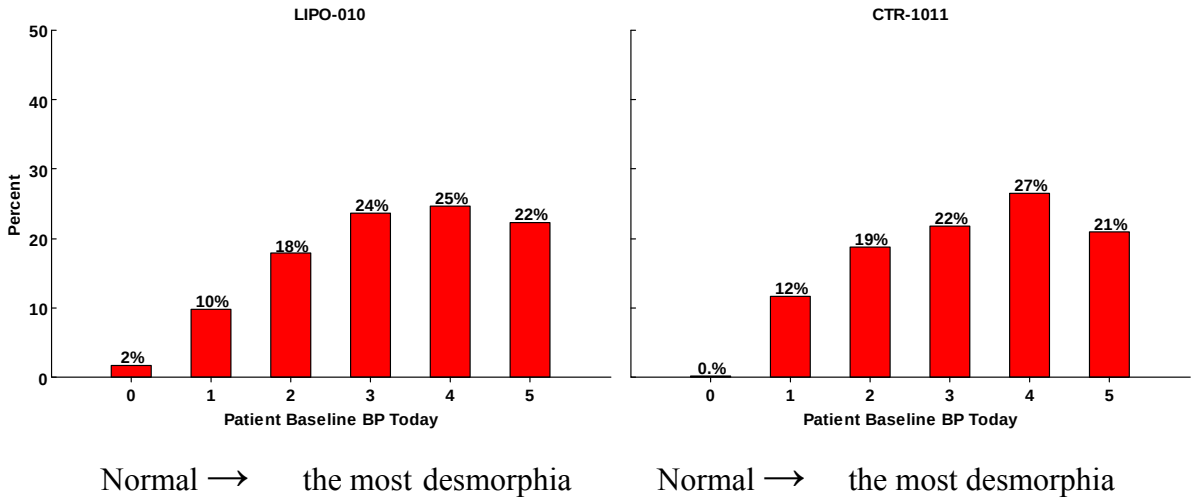


Figure 25 Cumulative distribution of Patient's Belly Profile Today change from baseline to Week 26 – ITT, LOCF

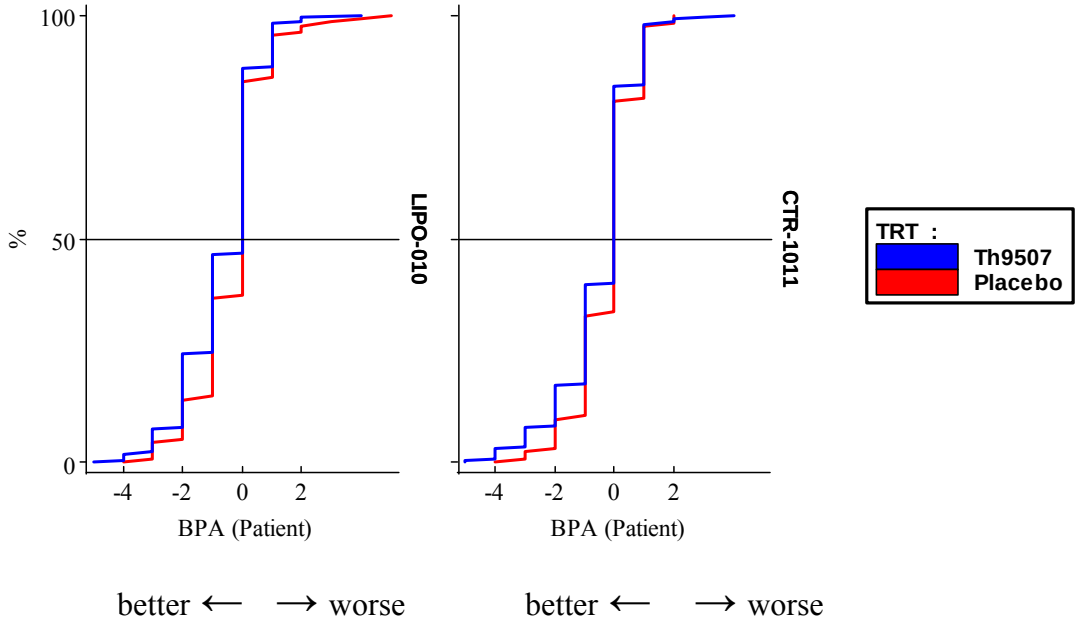
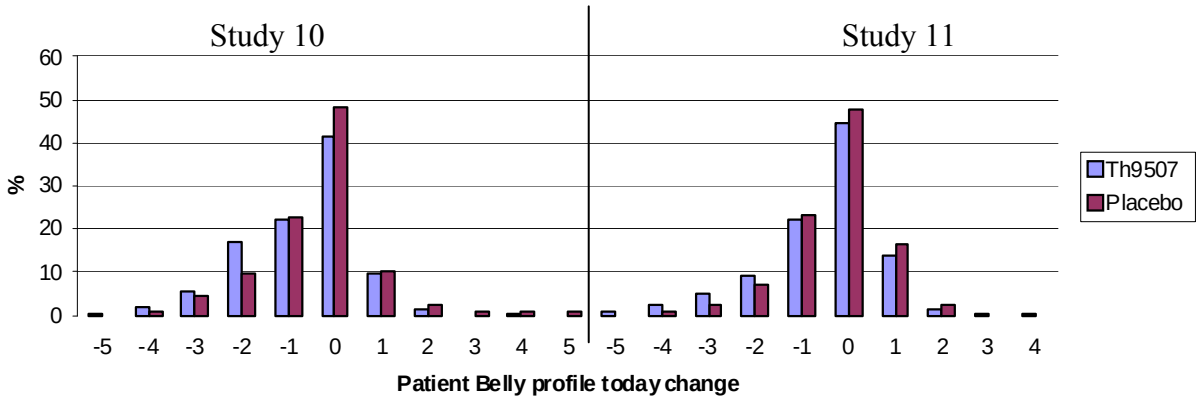


Figure 26 Percent of patients by patient BP change from baseline to week 26 – ITT, LOCF



better ← → worse **better ← → worse**

In conclusion, statistical evidence of TH9507 on PRO endpoints was not robust. More than 40% of patients perceived no change from baseline after 26 weeks of treatment for all 3 endpoints. Table 13 displays the p-values from the primary analyses, ANCOVA for BAD and BSE, and Mann-Whitney for BPA in study 10. Ranked ANCOVA was used to analyze all 3 endpoints in Study 11. There were no consistent significant results between studies.

Table 13 Summary of PRO p-values

PRO endpoint	Study 10	Study 11 Ranked ANCOVA
BAD	0.076*	0.022
BSE	0.750*	0.211
BPA	0.031**	0.075

*ANCOVA
**Mann-Whitney

Relationship between Anti-TH9507 antibodies and VAT percent change

Approximately half of the TH9507-treated patients developed anti-TH9507 antibody (Table 14). Figure 27 displays the scatter plot for VAT percent change from baseline at Week 26 versus anti-TH9507 antibody titer using a log scale in TH9507-treated patients with the antibody. Figure 28 presents boxplot of VAT % change by titer category.

Table 14 % of patients with anti-TH9507 antibody and by titer category

	Study 10						Study 11					
Treatment	TH9507			Placebo			TH9507			Placebo		
# patients with Anti-TH9507 antibody/total # (%)	104/209 (50%)			3/112 (3%)			96/197 (49%)			3/89 (3%)		
Titer:0, low (<400), high (≥400)	0	Low	High	0	Low	High	0	Low	High	0	Low	High
% of patients	50%	42%	8%	97%	3%	0%	51%	38%	11%	97%	3%	0%

Figure 27 Scatter plot of VAT % change by anti-TH9507 antibody titer

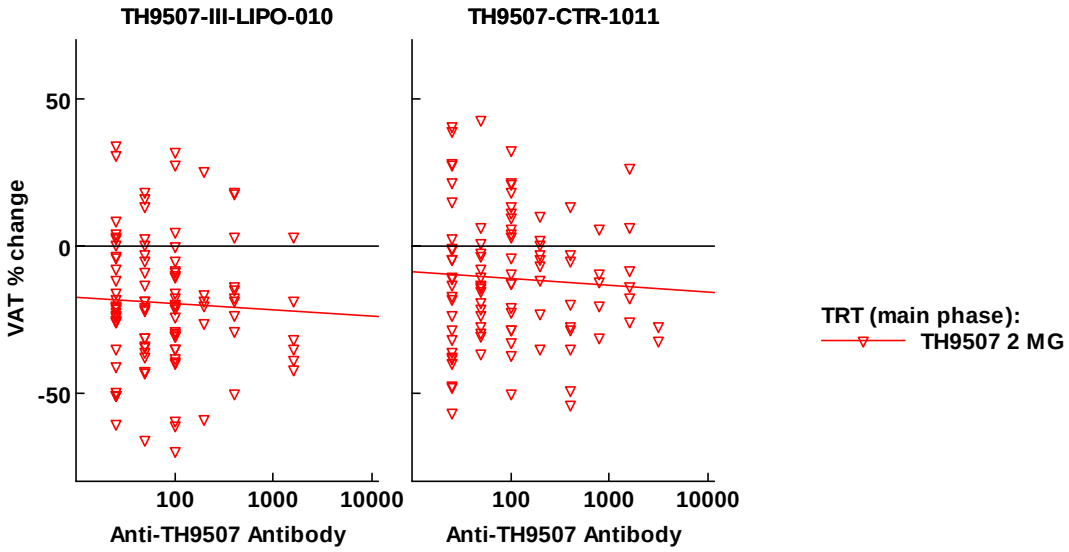
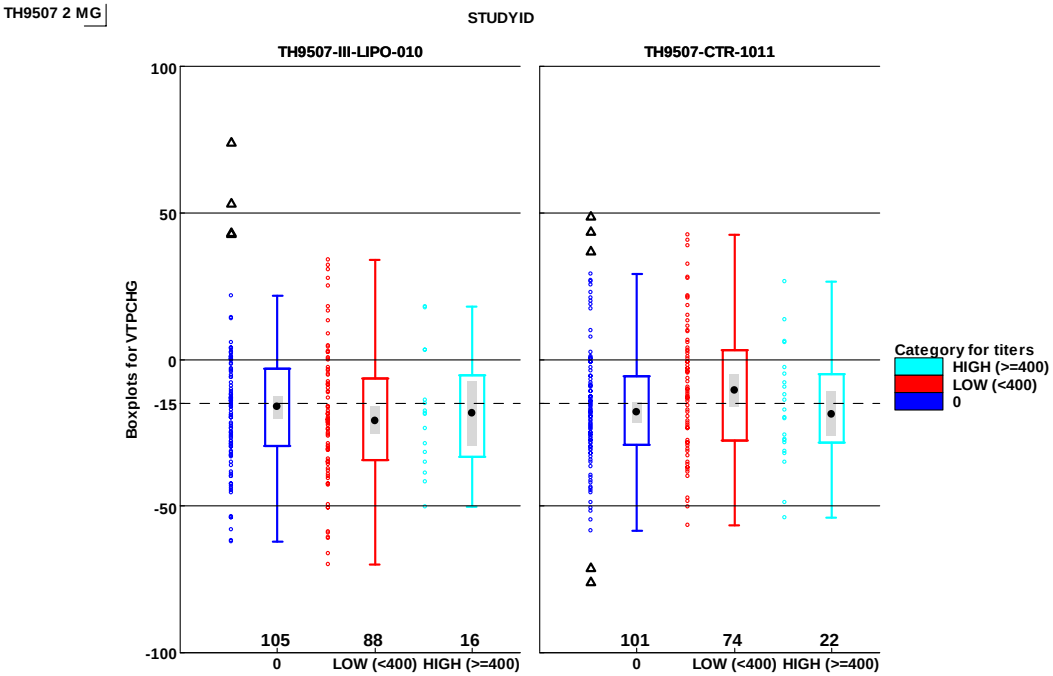


Figure 28 Boxplot of VAT % change by anti-TH9507 antibody titer category



DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

BACKGROUND INTRODUCTORY MEMORANDUM

From: **Susan Kirshner**

Through: **Amy Rosenberg**

Forum: Endocrinologic and Metabolic Drugs Advisory Committee meeting

Topic: Extrapolation of Immunogenicity Data between populations for Egrifta (rhGHRH) Advisory Committee

Therapeutic proteins, such as rhGHRH, have the potential to elicit antibody responses against the drug in treated patients. A variety of factors have been identified that impact the likelihood for developing antibodies. These include age, gender, immune competency status of the host, genetics, dose and route of drug administration, whether the drug is derived from an endogenous human protein or a non-human protein and impurities in drug product[1]. However, there are no reliable models or algorithms for predicting the development of antibody responses in patients. Furthermore, immunogenicity rates to the same drug have been found to differ between groups, depending on the patient factors delineated above. For example, less than 1% of immune suppressed cancer patients receiving chemotherapy developed antibodies to PEGylated recombinant human megakaryocyte growth and development factor (PEG-rhuMGDF) and thrombocytopenia, whereas 4% of healthy individuals, with intact immune systems, developed antibodies to PEG-rhuMGDF and thrombocytopenia[2], which is some cases lasted for years despite aggressive medical intervention. Therefore it is critical that product immunogenicity be rigorously assessed for each indication rather than extrapolating between populations.

As previously noted, although Egrifta elicited antibody responses in approximately 50% of treated subjects, no loss of efficacy was observed in antibody positive subjects. However, for the reasons noted above, neither the rate nor the impact of the immune response to Egrifta in HAART treated HIV patients ought to be extrapolated to other populations such as obese subjects.

1. Rosenberg, A. Immunogenicity of Biological Therapeutics: A Hierarchy of Concerns. Dev Biol. Basel, 2003; 112:15 – 21.

2. Li J, Yang C, Xia Y, Bertino A, Glaspy J, Roberts M, Kuter DJ. Thrombocytopenia caused by the development of antibodies to thrombopoietin. Blood, 2001; 98:3241 – 3248.

FDA Review of Patient-Reported Outcome Measures:
NDA 22-505
Egrifta (tesamorelin acetate for injection)

1 EXECUTIVE SUMMARY

This review focuses on the key patient-reported outcome (PRO) endpoints that were utilized in the Tesamorelin clinical trials to support the indication of induction and maintenance of a reduction of excess abdominal visceral adipose tissue (VAT) in HIV-infected AIDS patients with HIV-associated adipose redistribution syndrome (HARS). The conclusions in this review are based upon the principles described in the Guidance, "FDA Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims."[1]

The Body Image Impact module (BIIM) was used in the phase 3 clinical studies. The following PRO endpoints are derived from the BIIM and are described within the sponsor's proposed labeling: (a) Belly appearance distress (BAD); (b) Self-reported belly size estimation (BSE); and (c) Belly profile assessment (patient-reported BPA). Of these three PRO endpoints, the BPA was a non-key endpoint and was not intended for inclusion in labeling should the product be approved.

This review concludes that these PRO endpoints have questionable content validity and thus are of unclear utility in supporting interpretation of the clinical trial results. Content validity of a PRO instrument is evidence derived from qualitative research that the items and domains of an instrument are appropriate, comprehensive, and interpretable, relative to its intended measurement concept, population and use. PRO measurements are designed to capture the intended measurement concept from the patient's perspective, and thus, content validity includes patient input and documentation of this input using qualitative research that demonstrates the patient is reporting on the concept of interest and that all essential aspects of that concept are captured.

Two items from the BIIM are targeted as key study endpoints for analysis, the BSE and the BAD. The "belly size estimation" (BSE) item is not a true measure of "belly size" but rather asks the subject to compare his/her current belly size to his/her idea of a "healthy look." It is questionable whether (a) subjects can rate their belly size in the absence of more specific criteria and (b) whether the term "healthy look" will be interpreted the same way across subjects and within the same subject over time.

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf

The “belly appearance distress” item (i.e., BAD) may be a valid measure of that concept, but the PRO dossier provided minimal results from qualitative research to support the content validity of the PRO tool. The PRO dossier did not address whether qualitative research was done to evaluate patient understanding of the final instrument (e.g., cognitive interviews). Thus, the information provided does not meet the standards for instrument development as recommended within the FDA PRO Guidance for Industry including evidence of saturation and evidence of patient understanding during the qualitative research process. In addition to problems with study interpretation, inconsistencies in patient understanding (and therefore, problems with content validity) can lead to “noise” in the instrument and lessen the sensitivity to detect a treatment effect.

The sponsor derived a minimum responder definition for the BAD of a 25-point increase in transformed score (0-100) based upon calibration of the BAD to the patient-reported BPA responder interval in the clinical trial sample. Using similar methods, a minimum responder definition was calculated as a 50-point increase for the BSE on a 0-100 scale. These responder definitions may be applied to the appropriate cumulative distribution function curves to aid in their interpretation. See the FDA Clinical Review for the description and interpretation of the PRO results.

2 PATIENT REPORTED OUTCOME ENDPOINT REVIEW

2.1 Instruments

Representative copies of the BSE (Appendix A), the BAD (Appendix B) and the BPA (Appendix C) used in the phase 3 clinical studies are appended.

Note that the BSE and BAD are derived from a series of items that asked patients to also rate other body parts (e.g., face, legs, and arms) in addition to the belly. The BSE and BAD are items 4(d) and 5(d), respectively.

2.2 Item Description

Self-reported belly size estimation (BSE):

- The patient is instructed to compare the "current appearance" of the "size of my belly" to his/her "healthy look."

- Response options are from 1 to 9 (1=a great deal less/very smaller or thinner to 9 a great deal more or very much bigger).

Belly appearance distress (BAD):

- The patient is instructed to indicate the degree of his/her distress with the size of his/her belly. The patient is instructed to think about his/her "current appearance."

- **Response options** are on a 9-point scale from 1 to 9 (1=Extremely Upsetting and Distressing and 8=Extremely Encouraging) with the middle option "no feeling either way."

2.3 Content Validity

Content validity is defined in the final PRO guidance as evidence that the instrument measures the concept of interest including evidence from qualitative studies that the items and domains of an instrument are appropriate and comprehensive relative to its intended measurement concept, population, and use. The Guidance goes on to state that testing other measurement properties (e.g., reliability) will not replace or rectify problems with content validity.

According to the PRO Guidance, the FDA review considerations to support content validity include the following:

- Derivation of all items;
- Qualitative interview schedule;
- Interview or focus group transcripts;
- Items derived from the transcripts;
- Composition of patients used to develop content; and
- Cognitive interview transcripts to evaluate patient understanding.

The key PRO study endpoints were measures of some aspect of the subject's belly:

(a) **Self-reported belly size estimation (BSE):** Patient perceptions of their current belly size in comparison to their idea of a "healthy" look; and

(b) **Belly appearance distress (BAD):** Patient-reported distress concerning the appearance of their belly.

In addition to the PROs described above, there was also a patient-rated belly profile (patient-rated BPA) in which the patient was to choose among six belly profiles, the one that they feel most accurately depicts their actual profile. The BPA was included in the clinical studies to aid in interpretation of the BAD and BSE results.

The PRO dossier contains inadequate documentation of the qualitative research to support the content validity of the BAD and BSE. Insufficient information on qualitative research in patients representing the target patient population was provided. The stated objective of instrument development was to document self-reported body dysmorphia experiences and perceptions among persons diagnosed with HIV/AIDS.

Reviewer's comment: Note that the objective of the PRO development was a broad assessment of self-reported body dysmorphia. The main focus was not to document patient experiences and perceptions with "belly size."

Documentation of cognitive interviews with patients to support the interpretability and acceptability of the questionnaire items (i.e., that patients understand the items similarly and in the way that is intended) was not provided for Agency review.

The instructions to subjects for the subject-reported BPA did not make clear how the assessment of BPA was to be done. Factors that could affect the assessment might include the patient's posture while evaluating his/her profile, whether the rating was to be done while looking in the mirror, and type of clothing.

The reference to "belly size estimation" does not describe the item content. The item content is more accurately described as the patient's perception of his/her current belly size in comparison to their idea of a "healthy look." This variable did not

demonstrate improvement in the phase 3 studies. It is questionable whether (a) subjects can rate their belly size in the absence of more specific criteria and (b) whether the term "healthy look" will be interpreted the same way across subjects and within the same subject over time. It is also possible that while there may have been some decrease in VAT as measured by CAT scan, the degree of this change may not have approached the patient's concept of what looks healthy. It is also possible, that the patient's concept of what looks healthy may change over time.

It is likely that patients in the target patient population are bothered by belly size in combination with loss of adipose tissue (lipoatrophy) in other areas.

Evidence of qualitative research showing sufficient evidence for saturation was not provided. Details of qualitative studies including interview guides, protocols, and patient-level qualitative data were not provided for Agency review. The potential differences in perception between men and women with HIV-associated adipose redistribution syndrome (HARS) were not addressed in the information provided to the Agency.

2.4 Other Measurement Properties (reliability, construct validity, ability to detect change)

The instruments other measurement properties were derived from a sample of male and female HIV+ subjects participating in a clinical study of r-hGH treatment for lipodystrophy. A total of 327 subjects were screened and 238 were randomized in this study. A total of 87% of the subjects were male and the mean age was 44 years. All had evidence of excess abdominal adipose tissue and were receiving treatment with antiretroviral medications.

The internal consistency reliability data for the summary scales that were presented in the PRO dossier had limited relevance for this particular application, because single items (not summary scales) from the multi-item body image impact scale were utilized as endpoints in the phase 3 studies.

The PRO dossier states that the test-retest reliability for the BIM Body Size Scale ranged from 0.602 (arm size) to 0.784 (hump size). The test-retest reliability for the BAD showed a reproducibility coefficient of 0.616. The mean retest interval was 10.5 days.

The correlations of the PRO endpoints with the objective measure of VAT obtained in the clinical trials were also reviewed. From the NDA amendment dated December 7, 2009 (serial 13), for Study LIPO-010, the correlation between the percent change in VAT and the raw change in patient-assessed BPA for the active group resulted in a correlation coefficient, "r" of 0.33.

The correlation between the raw absolute change in BAD and change in VAT for the active treatment group was resulted in an "r" of 0.26.

The correlation between absolute change in BSE and change in VAT for the active treatment group resulted in an "r" of 0.15.

2.5 Interpretation of Scores: BAD and BSE

The patient-rated belly profile (BPA) (Appendix C) was used as a non-key study endpoint as an anchor in the development of a responder definition for the key secondary study endpoints, the BAD and the BSE.

In the patient-rated BPA, the patients choose among six images of belly profiles, the one that they feel most accurately depicts themselves.

Using the patient-rated BPA, the selection of the responder interval for patients was a 2.3 unit improvement or more based on a sample mean difference between "current look" minus "smallest benefit" at baseline. The responder criteria for BAD and BSE round off to 2 scale units (i.e., 25 points for BAD and 50 points for BSE).

The following method for defining response criteria was described in the sponsor's submission:

> *Method:*
> *The prespecified criterion for a responder was based on the belly profile assessment (BPA). Three choices were made as part of the belly profile assessment:*
>
> *1. Select the picture that most closely resembles how you think you look today.*
>
> *2. Select the picture that most closely resembles how you would most like to look.*
>
> *3. Select the picture that most closely resembles the smallest amount of improvement that you would consider beneficial to your heath and well being.*
>
> *The patient-reported belly profile assessment (BPA) Responder Interval was operationally defined as the sample mean difference between "current look" (choice 1) minus "smallest benefit" (choice 3) at baseline.*
>
> *Responder Calibrations:*
> *The responder calibrations were based on the clinical study samples. The method that the sponsor used involved three analytic steps.*

Step 1: Regress the Baseline-to-LOCF BSE (or BAD) change score onto the Baseline-to-LOCF patient-reported BPA Current Look change score.

Step 2: The unstandardized coefficient from the regression parameter estimates the number of raw BSE (or BAD) scale units changed per "one profile" change in the patient-reported BPA Current Look scale.

Step 3: Multiply the unstandardized coefficient by the BPA Responder Interval to obtain the BSE (or BAD) Responder Interval calibrated to the BPA.

Reviewer's comment: To evaluate treatment benefit, it is informative to examine the cumulative distribution function (CDF) of responses between treatment groups to characterize the treatment effect. The responder definition agreed upon with the Agency (i.e., 25 points for BAD and 50 points for BSE on a 0-100 scale) may be applied to the appropriate CDF curve.

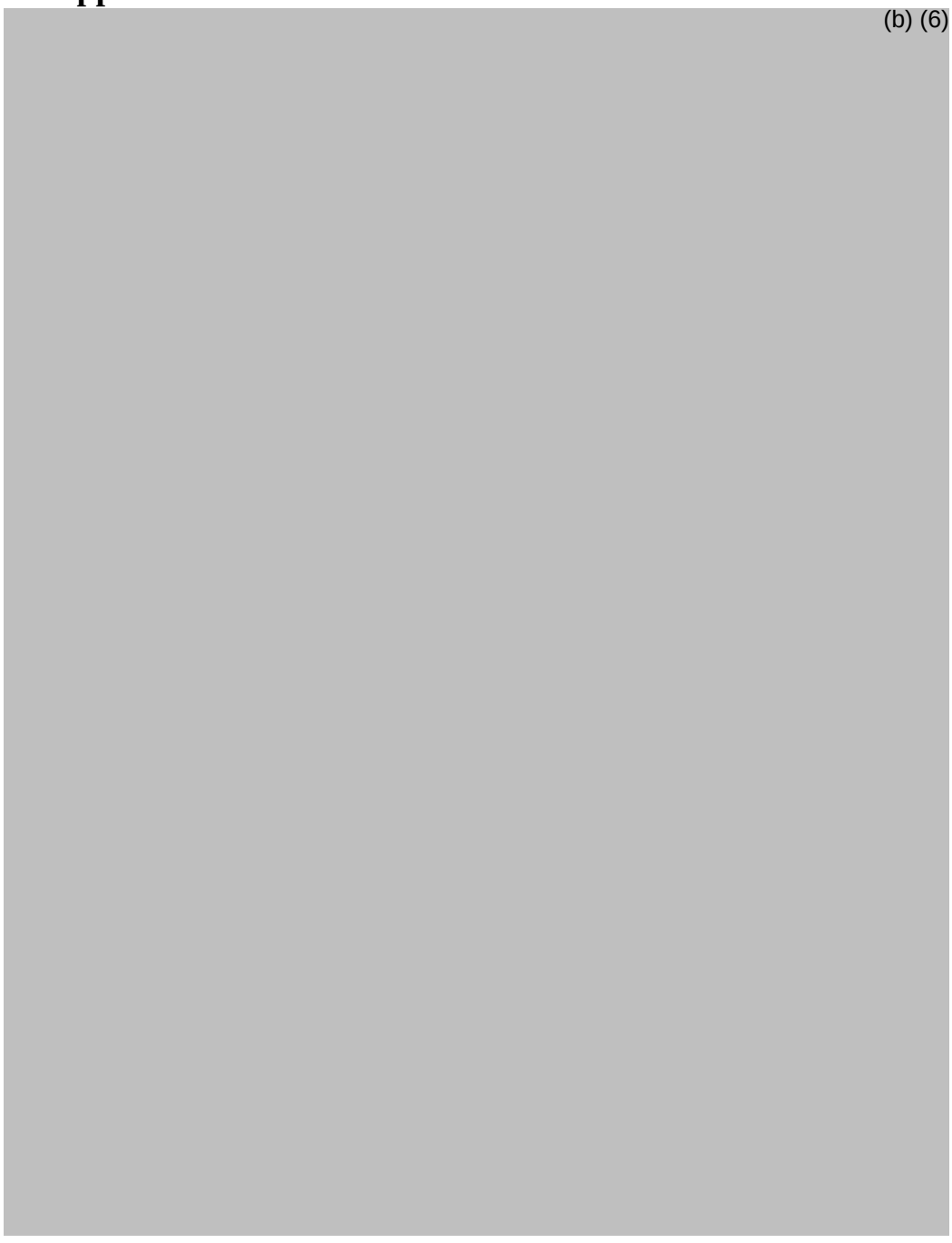
The purpose of the patient-rated BPA was as an anchor for interpretation of the BAD and BSE endpoints. The patient-rated BPA itself was not designated as a key study endpoint in the clinical trials.

The transformed scale for the BAD is shown below.

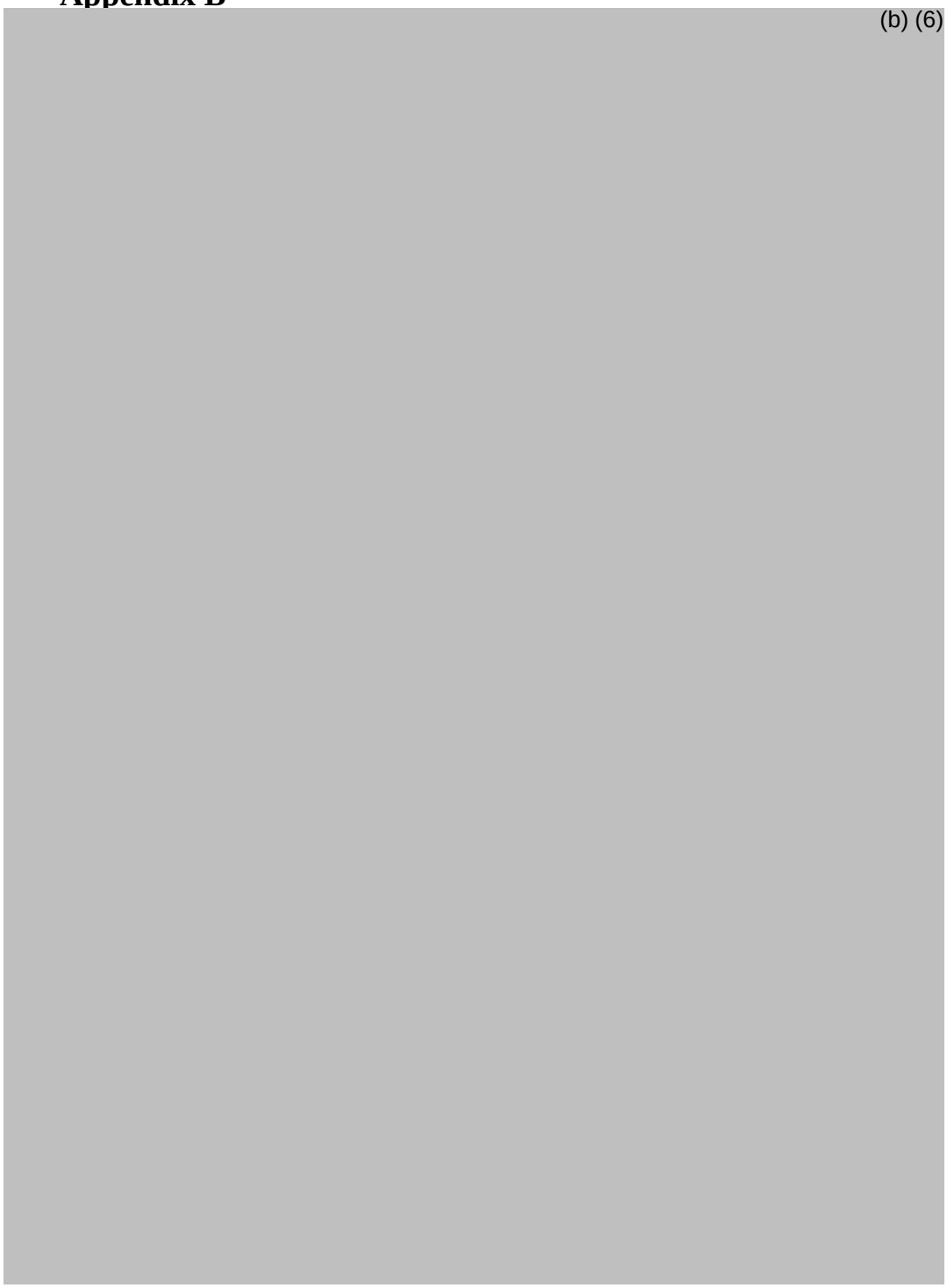
0.0	Extremely upsetting and Distressing
12.5	Very upsetting and Distressing
25.0	Quite upsetting and Distressing
32.5	A little Upsetting
50.0	No feeling either way
62.5	A little encouraging
75.0	Quite encouraging
87.5	Very Encouraging
100.0	Extremely Encouraging

Reviewer's comment: The responder definition agreed upon with the Agency was 25 points for BAD. Based upon this reviewer's interpretation of the graded descriptions provided above, any change less than 25 points on this scale does not appear to represent a meaningful responder definition for the BAD. For example, a 12.5 point change from "Very upsetting and Distressing" to "Quite upsetting and Distressing" does not appear to be clinically meaningful.

Appendix A



Appendix B



Appendix C