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TESAMORELIN (*EGRIFTA*[™]) BRIEFING DOCUMENT

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LIST OF ABBREVIATIONS AND ACRONYMS

| | |
|----------------------|--|
| ADA | American Diabetes Association |
| Adj. | adjusted |
| AE | adverse event |
| AIDS | Acquired Immune Deficiency Syndrome |
| ALT | alanine aminotransferase |
| ANCOVA | analysis of covariance |
| ANOVA | analysis of variance |
| ARIC | Atherosclerosis Risk in Communities |
| ART | antiretroviral therapy |
| AST | aspartate aminotransferase |
| AUC | area under the curve |
| AUC _{0-inf} | area under the concentration-time curve at steady-state from 0 to infinity |
| AUC _{0-t} | area under the concentration-time curve at steady-state carried out to 24 hours |
| AUC _{t/inf} | area under the concentration-time curve at steady-state where t is divided by infinity |
| AUEC | area under the effect curve |
| bid | twice daily |
| BIIM | Body Image Impact Module |
| BiPAP | bilevel positive airway pressure |
| BL | Baseline |
| BMI | body mass index |
| CAD | coronary artery disease |
| CD | cluster of differentiation |
| CFI | Company Fit Index |
| CHD | coronary heart disease |
| CI | confidence interval |
| Cl/F | unbound oral clearance |

| | |
|-------------------|---|
| C _{max} | maximum plasma concentration |
| Company | Theratechnologies Inc. |
| COPD | chronic obstructive pulmonary disease |
| CRP | C-reactive protein |
| CT | computed tomography |
| CV | coefficient of variation |
| CV RF | cardiovascular risk factor |
| CVD | cardiovascular disease |
| Division | Division of Metabolism and Endocrinology Products |
| DM | diabetes mellitus |
| ELISA | enzyme-linked immunosorbent assay |
| E _{max} | maximum effect |
| ET | early termination |
| FBG | fasting blood glucose |
| FDA | US Food and Drug Administration |
| FPI | Full prescribing information |
| FRAM | Fat Redistribution and Metabolic Change in HIV Infection |
| GAS | Global Analogue Scale |
| Geo. | geometric |
| GH | growth hormone |
| GHRH | growth hormone-releasing hormone |
| GRF | growth-hormone releasing factor, also known as GH-releasing hormone |
| HbA _{1c} | glycosylated hemoglobin |
| HDL | high-density lipoprotein |
| HDL-C | high-density lipoprotein-cholesterol |
| hGRF | human hypothalamic growth hormone-releasing factor |
| HIV | human immunodeficiency virus |
| HOMA-IR | homeostasis model assessment-insulin resistance |
| HRQOL | health-related quality of life |
| HTN | hypertension |

| | |
|-----------------|--|
| ICU | intensive care unit |
| IGF-1 | insulin-like growth factor-1 |
| IGFBP-3 | Insulin-like growth factor binding protein 3 |
| IgG | immunoglobulin G |
| IGT | impaired glucose tolerance |
| IND | investigational new drug |
| ITT | intent-to-treat |
| IV | intravenous |
| KAB | knowledge, attitude, behavior |
| K _{el} | elimination rate constant |
| LBM | lean body mass |
| LDL | low-density lipoprotein |
| LDL-C | low-density lipoprotein-cholesterol |
| Ln | natural logarithm |
| LOCF | last observation carried forward |
| LSM | least-squares mean |
| M | million |
| MI | myocardial infarction |
| MID | minimal important difference |
| MRD | minimal required dilution |
| NAb | neutralizing antibody |
| NDA | new drug application |
| NFI | normed fit index |
| NHANES | National Health and Nutrition Examination Survey |
| NNRTI | non-nucleoside reverse transcriptase inhibitor |
| NOAEL | No observed adverse effect level |
| non-HDL-C | non-high-density lipoprotein cholesterol |
| NRTI | nucleoside reverse transcriptase inhibitor |
| NTx | cross-linked N-telopeptides of type I collagen |
| OGTT | oral glucose tolerance test |

| | |
|--------------------|---|
| OC | observed case |
| OL | open-label |
| PAI-1 | plasminogen activator inhibitor-1 |
| PD | pharmacodynamic |
| PEA | pulseless electrical arrest |
| PI | protease inhibitor |
| PK | pharmacokinetic |
| PP | per-protocol |
| PRO | patient-reported outcomes |
| P-T | placebo-tesamorelin |
| PY | patient-years |
| qd | once daily |
| QOL | quality of life |
| r | reliability |
| R | randomized |
| REMS | Risk Evaluation and Mitigation Strategy |
| rhGH | recombinant human GH |
| RMSEA | root mean square of approximation |
| SAE | serious AE |
| SAS [®] | Statistical Analysis Software |
| SAT | subcutaneous adipose tissue |
| SC | subcutaneous |
| SD | standard deviation |
| SDS | standard deviation score |
| SEM | standard error of measurement |
| SPA | Special Protocol Assessment |
| T _{1/2el} | terminal elimination half-life |
| T _{Emax} | time to maximum effect |
| TK | toxicokinetic |
| T _{max} | time to maximum plasma concentration |

| | |
|-------------------|---------------------------------|
| T-P | tesamorelin-placebo |
| tPA | tissue plasminogen activator |
| T-T | tesamorelin-tesamorelin |
| ULN | upper limit of normal |
| V _d /F | apparent volume of distribution |
| VAT | visceral adipose tissue |
| WC | waist circumference |

EXECUTIVE OVERVIEW

Note to Readers

This Executive Overview provides a quick preview of the development program supporting tesamorelin (*EGRIFTA*[™]) 2 mg for **subcutaneous** (SC) daily injection to induce and maintain a reduction of excess abdominal fat in **human immunodeficiency virus** (HIV)-infected patients with lipodystrophy. Tesamorelin is manufactured by Theratechnologies Inc. (also referred to as the Company); should it be approved for marketing in the United States, it will be commercialized by EMD Serono Inc.

NOTE: The Overview is cross referenced to data in the Briefing Document. The Overview is only a guide to the Briefing Document and is intended to provide a framework for the reader. The Briefing Document that follows is a stand-alone document that includes graphical representation of key findings, followed by appendices covering methods for **patient-reported outcomes** (PRO), statistical methods and considerations, death and special **adverse event** (AE) case narratives, and additional baseline demographic data.

Lipodystrophy in Patients with HIV Infection

Patients who suffer from HIV-associated lipodystrophy experience disfiguring body composition changes including excessive accumulation of fat in the visceral compartment, breasts, and the upper back (lipohypertrophy) and/or noticeable loss of subcutaneous fat in the trunk, face and extremities (lipoatrophy) (**Figure 1**), HIV-infected men and women with these negative body shape changes have significantly poorer body image compared with HIV-infected patients without lipodystrophy ([Lichtenstein 2005](#), [Marin 2006](#)). In particular, affected patients see themselves as disfigured, isolated, and stigmatized ([Blanch 2004](#), [Peterson 2008](#), [Guaraldi 2008](#)). Patients with this syndrome describe lives distorted by discomfort, self-hate, depression, stigmatization, and social alienation. These changes are of such concern that patients may sometimes choose not to take prescribed **antiretroviral therapy** (ART) or to delay the initiation of ART despite their

knowledge of the serious consequences of this choice in terms of HIV infection and its associated complications ([Vergel 2008](#)).

One of the hallmarks of HIV-associated lipodystrophy is this accumulation of **visceral abdominal tissue** (VAT), which typically manifests as a noticeable increase in **waist circumference** (WC) ([Brown 2009](#)). Increased abdomen size in particular has been shown to adversely affect body image perception, social functioning, interpersonal relationships, psychological well-being and overall **health-related quality of life** (HRQOL) ([Guaraldi & Baraboutis 2009](#), [Marin 2006](#), [Santos 2005](#), [Turner 2006](#)). **Subcutaneous adipose tissue** (SAT), however, may remain unchanged or be decreased in other parts of the body. Moreover for the same **body mass index** (BMI), HIV-infected men in the normal and overweight categories have increased VAT and reduced SAT compared with the non-infected population ([Joy 2008](#)).

Data from a community-based survey of patients suffering from lipodystrophy revealed that 87% of responders experienced depression or anxiety; 63% of the responders self-reported abdominal fat accumulation, and 25% had suicidal thoughts in the past because of perceived body changes ([Vergel 2008](#)). In addition, over 50% of responders stopped socializing, had decreased self-image, and changed clothing style. In short, the physical manifestations of lipodystrophy cause major disturbances in normal daily activities.

The consequences of this complex syndrome also frequently include significantly worse general perceived health scores in HIV-infected patients with excess truncal fat compared with age- and sex-matched HIV-negative patients with other chronic conditions known to adversely affect **quality of life** (QOL) ([Malon et al, 2002](#)).

These serious QOL effects are compounded by additional physical health risks presented by metabolic abnormalities of HIV-associated lipodystrophy. This syndrome frequently includes multiple metabolic disturbances like dyslipidemia and insulin resistance ([Capeau 2005](#), [Brown 2008](#), [Lichtenstein 2005](#), [Grinspoon 2005](#)). HIV-infected patients receiving ART are already at increased risk of developing type 2 diabetes mellitus and **cardiovas-**

cular disease (CVD) compared with the general population and both the dyslipidemia and altered glucose metabolism of lipodystrophy compound that risk ([Currier 2004](#), [d'Arminio 2004](#), [Friis-Møller 2003](#), [Friis-Møller 2007](#), [Klein 2007](#)). Specifically, metabolic abnormalities associated with lipohypertrophy and increased VAT include glucose intolerance, insulin resistance, elevated **low-density lipoprotein cholesterol** (LDL-C), hypertriglyceridemia, possibly low **high-density lipoprotein cholesterol** (HDL-C), and increased levels of **C-reactive protein** (CRP) ([Grinspoon 2005](#), [Hsue 2008](#)).

Excess VAT has been shown to be an independent predictor of all-cause mortality in men in the general uninfected population ([Kuk 2006](#), [Pischon 2008](#)). In this population, enlarged waist size or excess central fat has been associated with significantly increased cardiovascular risk ([Yusuf 2004](#), [Onat 2004](#)). In addition, increased VAT has been associated with an increased long-term risk of CVD and diabetes in both infected and uninfected populations. ([Larsson 1984](#), [Rexrode 2001](#), [Donahue 1987](#), [St. Pierre 2002](#), [Wohl 2008](#)). Consequences of HIV-associated lipodystrophy include an increased risk of premature atherosclerosis and cardiovascular complications. Most recently, a direct link between VAT and cardiovascular risk in the HIV-positive population was demonstrated by [Guaraldi \(2009\)](#), who found that VAT was a predictor of subclinical atherosclerosis, as evaluated by coronary calcium atherosclerosis imaging. Results by [Lo \(2010\)](#) demonstrate a significant association between VAT and coronary calcium score in HIV-positive patients. [Guaraldi \(2010\)](#) observed that VAT, but not general adiposity, was an independent predictor of prior CVD (myocardial infarction, coronary revascularization, stroke or peripheral vascular disease).

Figure 1. Clinical Manifestations of Lipodystrophy



Images courtesy of Drs Domingo and Guaraldi.

Estimates of the prevalence of lipodystrophy in HIV-infected patients vary but indicate that the syndrome is by no means rare-about 30% ([Lichtenstein 2001](#), [Bernasconi 2002](#), [Miller 2003](#), [Leow 2003](#), [Cofrancesco 2009](#)). Abdominal lipohypertrophy is a grueling fact of life for a substantial segment of HIV-infected patients.

The symptoms associated with lipohypertrophy can also potentially lead to more devastating consequences. In addition to social stigmatization and related psychological distress, individuals who self-report the symptoms of HIV-associated lipodystrophy are less likely to adhere to ART ([Duran 2001](#), [Ammassari 2002](#), [Vergel 2008](#)), with related risks to successful treatment and the resultant negative health consequences. Discontinuation of ART can lead to increased mortality, opportunistic disease, and other complications ([SMART Study Group 2006](#), [Ananworanich 2006](#)).

Limitations of Current Treatment Approaches

Because of the consequences of this syndrome for patients, clinicians have made significant efforts both to reduce VAT and to maintain or increase SAT in HIV-infected patients with abdominal lipohypertrophy. Unfortunately, no strategy has effectively addressed the various parts of the syndrome. Dietary and exercise therapy as well as cosmetic surgery have been tried with limited success ([Schambelan 2002](#), [Dolan 2006](#)). A large number of switch studies have been conducted to investigate whether substitution of one component of an HIV treatment regimen with an alternative potent drug, usually from a different class of antiretrovirals, may result in improvements in body composition. Overall, these studies have resulted in modest improvements in lipoatrophy and metabolic abnormalities, but none has been shown to result in VAT reduction ([Martinez 2000](#), [Drechsler 2002](#), [Martinez 2003](#)).

Recent studies involving HIV-infected patients with evidence of hyperinsulinemia and/or dyslipidemia whose protease inhibitors (PIs) were switched reported conflicting results ([Stanley 2009](#), [Molina 2010](#)). Similarly, treatment with the insulin-sensitizing agent metformin has produced inconsistent effects and may worsen lipoatrophy ([Hadigan 2000](#), [Driscoll 2004](#), [van Wyk 2005](#)).

Because VAT has been associated with impaired growth hormone (GH) secretion in patients with HIV-associated lipodystrophy ([Vigano 2003](#), [Rietschel 2001](#)), recombinant human GH (rhGH) has also been evaluated as a therapy. It does reduce VAT and improve lipid metabolism, but it also decreases limb fat and produces significant side effects, including symptoms of interstitial fluid retention and hyperglycemia ([Mulligan 1993](#), [Clark 1996](#), [Kotler 2004](#), [Kotler 2006](#), [Grunfeld 2007](#), [Bryant 2002](#)). Increases of fasting serum insulin were observed in this population treated with rhGH 4 mg for 12 weeks ([Grunfeld 2007](#)). In addition, there were significantly higher rates of peripheral edema in patients treated with rhGH 4 mg compared to placebo ($p < 0.001$ for both AE). Recently, use of low-dose rhGH was associated with a modest decrease in VAT but resulted in significant

deterioration in 2-hour glucose on oral glucose tolerance testing ($p=0.009$ vs. placebo) (Lo 2008).

Patients with HIV-associated lipodystrophy actively search treatment for its physical symptoms; however, clinicians have few treatment options and none that treat even a cluster of the syndrome's symptoms. Based on the data available to date, a clear medical need remains for a safe and effective therapy to treat the various consequences of abdominal lipohypertrophy by reducing VAT in HIV-infected patients.

Tesamorelin for VAT Reduction in HIV-Associated Lipohypertrophy

Because of its mechanism of action and the promise of **growth-hormone releasing factor** (GRF) in the treatment of excess abdominal fat in HIV-infected patients with lipodystrophy, tesamorelin was developed as a novel synthetic analogue of **human hypothalamic growth hormone-releasing factor** (hGRF).

This 44 amino-acid polypeptide incorporates a hydrophobic side chain that increases resistance to enzymatic degradation in human serum and has been shown to have a binding affinity to hGRF receptors comparable with that of endogenous hGRF. Consequently, tesamorelin is able to induce GH secretion in a pulsatile and physiological manner. Tesamorelin reduces VAT while preserving SAT with fewer of the side effects associated with pharmacological doses of rhGH.

Safety and toxicology studies supported the safe use of tesamorelin in patients with HIV-associated lipodystrophy. These results suggest that tesamorelin, similar to natural GRF, acts on the pituitary gland to release GH and subsequently releases **insulin-like growth factor-1** (IGF-1) through the somatotrophic axis.

Theratechnologies tested tesamorelin in several conditions known to be related to the GRF/IGF-1 axis, including HIV-associated lipodystrophy.

The dose used in the Phase 3 trials was based on the determination in Phase 1 and Phase 2 studies of the dose that could be well tolerated while keeping IGF-1 levels comparable to those measured in young adults ([Maggio 2006](#)). A daily dose of 2 mg tesamorelin injected SC once daily was chosen as optimal because it:

- was well tolerated.
- increased IGF-1 levels more than the 1-mg dose, but these increased levels remained comparable to those measured in young adults.
- induced greater decreases in VAT and trunk fat and a greater increase in IGF-1 levels after 12 weeks of treatment, compared with the 1-mg dose in HIV-infected patients with lipodystrophy.

On the basis of the consistent results of Phase 1 and 2 studies, the Company initiated planning for further clinical development for the treatment of excess abdominal fat in patients with HIV-associated lipodystrophy, an unmet medical need that demanded a development program focused on physical, psychological, and metabolic endpoints.

Tesamorelin Development and Regulatory History

In March 2005 the Company consulted with the Division of Metabolism and Endocrinology Products of the FDA and reached agreements on the proposed design of a Phase 3 study, the dose to be tested, and the measurement of VAT as the primary endpoint. The agreement also defined the clinically relevant difference between tesamorelin and placebo in VAT decrease as 8%, applying the recommendations from a roundtable discussion organized by the Forum for Collaborative HIV Research ([Snyder 2004](#)) (**Sections 3.1 and 3.5**).

The two also agreed to follow the Forum's recommendations that safety evaluations should demonstrate no worsening of peripheral lipoatrophy, no decrease in the percentage

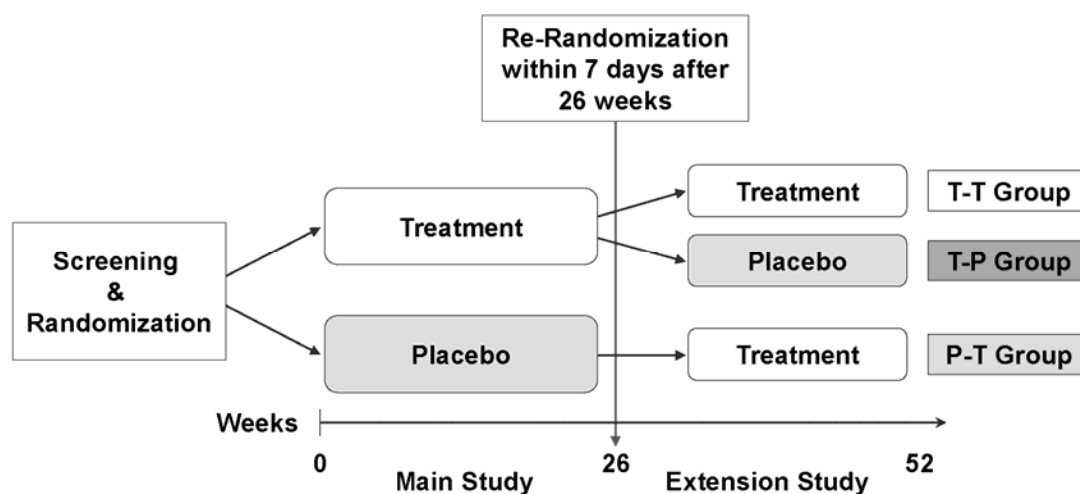
of lean body tissue, and no worsening of metabolic outcomes. Additional safety assessments agreed on were the means and distribution of the IGF-1 standard deviation score (SDS), with an SDS value greater than +2 considered to be potentially undesirable. The FDA also agreed to assess PRO as secondary endpoints and recommended a validated questionnaire developed by Phase V Technologies Inc. ([Phase V Technologies, Inc., 2003](#)) to assess PRO related to body image and HRQOL (**Appendix I, Section 11.1**).

The Company received a **Special Protocol Assessment** (SPA) for a second Phase 3 study in August 2006, whereby the FDA reconfirmed the primary endpoint as an 8% reduction in VAT. The Agency also approved the statistical analysis approach to measure the change from baseline in VAT (**Section 3.1**).

Tesamorelin Clinical Program in HIV-Infected Patients

The tesamorelin Phase 3 program included 2 multicenter, randomized, double-blind, parallel-group trials in patients with HIV infection and excess abdominal fat. Each trial consisted of 26-week, placebo-controlled main phases (LIPO-010 main and CTR-1011) followed by 26-week extension phases to assess long-term safety and duration of effects (LIPO-010 extension and CTR-1012, respectively) (**Figure 2**). Both phases of LIPO-010 were conducted in 43 sites in North America (United States and Canada), while CTR-1011 and CTR-1012 were conducted in 48 sites in North America (United States and Canada) and Europe.

Figure 2. Tesamorelin Phase 3 Program



The primary enrollment criteria were HIV infection, currently receiving ART, and the presence of excess abdominal fat as assessed by anthropometric measurements (WC and waist to hip ratio). Safety and efficacy were assessed in both main and extension phases. Patients who had a **fasting blood glucose** (FBG) level of ≤ 150 mg/dL at the beginning of the main or extension phases were eligible to enter those phases of each study.

Phase 3 Efficacy of Tesamorelin in Patients with HIV Receiving ART

Overall, a total of 816 patients were randomized in the two Phase 3 studies (**Section 4.3**). A total of 543 patients received daily SC injection of tesamorelin 2 mg: 273 in study LIPO-010 main and 270 in CTR-1011; 137 received placebo in LIPO-010 main and 126 in CTR-1011. Seventy-six percent of the tesamorelin patients and 79% of the placebo patients completed the initial 26-week study periods. At Week 26, patients who received placebo during the main phase studies were switched to tesamorelin (N=197); patients who received tesamorelin in the main phase studies were re-randomized to continue to receive tesamorelin (N=246) or to be given placebo (N=135) (**Figures 8A and 8B**), (**Section 4.3**).

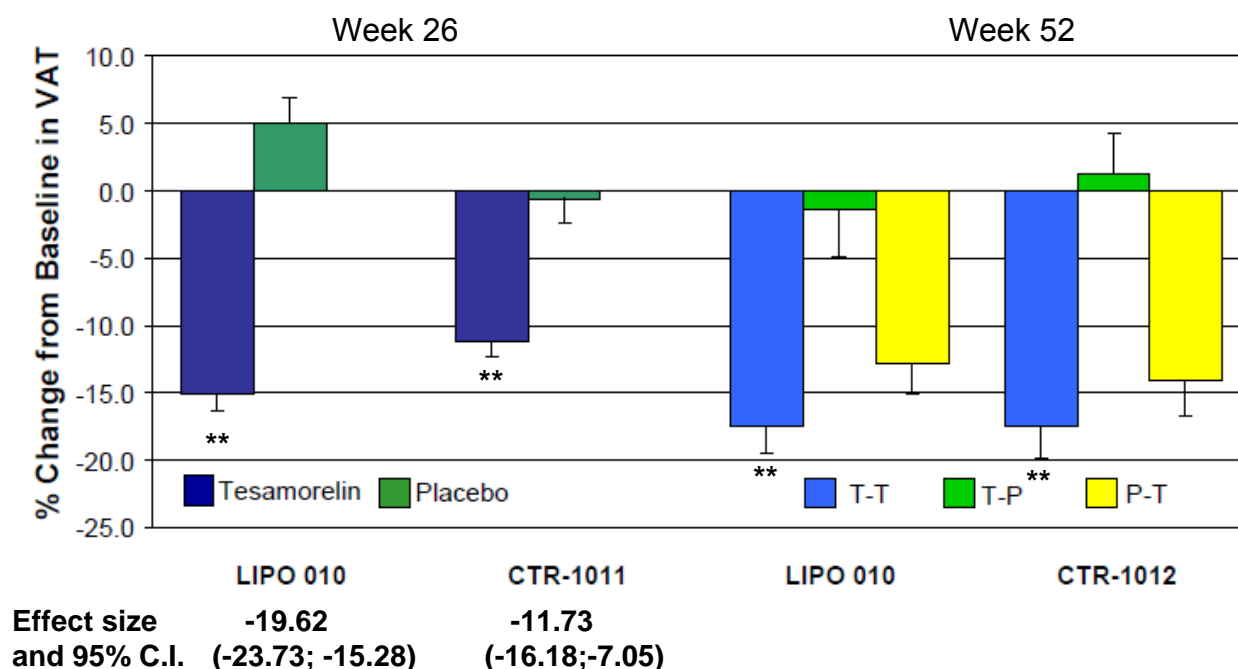
The primary endpoint in both of the pivotal Phase 3 studies was the percent change from baseline in VAT measured by **computed tomography** (CT) scan at the L4 and L5 level. Analyses included all patients who had received at least 1 dose of study drug, and the **last observation** was **carried forward** (LOCF). If a patient had no post-baseline value during the main study, his baseline value was carried forward for all post-baseline evaluations during the main study. In the case that no post-Week 26 measurements were taken during the extension study, Week 26 was not carried forward during the extension, but baseline from the main study was carried forward.

Tesamorelin significantly reduced VAT after 26 weeks of treatment compared with placebo ($p < 0.001$) in both Phase 3 studies (> 800 HIV-infected patients with excess abdominal fat in the context of ART). Mean decreases from baseline in VAT of 15%¹ and 11%¹ were achieved after 26 weeks of treatment in the 2 studies, respectively ($p < 0.001$ vs placebo), with a mean reduction in VAT of 13%¹ for the 2 studies combined ($p < 0.001$ vs placebo) (**Figure 3**).

In patients who received tesamorelin for 52 weeks, the overall mean percent changes from baseline in VAT were: -17.5% in LIPO-010 extension and -17.5% in CTR-1012. Patients who switched from tesamorelin to placebo regained VAT lost at Week 26. VAT decreased by around 13.3% overall in patients who switched from placebo to tesamorelin (**Figure 3**), (**Section 1.7** and **Section 5**).

¹ The means reported are arithmetic means calculated from the intent-to-treat (ITT) population, using the last observation carried forward (LOCF) method for missing observations. The last observation was carried forward from baseline when no post-dose evaluation was performed. Thus, the means reported are very conservative. Adjusted means (LSMEANS) led to decreases of 18%, 14%, and 16%, for LIPO-010, CTR-1011, and the 2 studies combined, respectively.

Figure 3. Percent Change from Baseline in VAT at Weeks 26 and 52 per Study (ITT Population, LOCF)



Data are mean ± SEM. Tesamorelin refers to tesamorelin 2 mg/day. CI, confidence interval; ITT, intent-to-treat; LOCF, last observation carried forward; P-T, placebo-tesamorelin; T-P, tesamorelin-placebo; T-T, tesamorelin-tesamorelin; SEM, standard error of the mean; VAT, visceral adipose tissue. ** p≤0.001 vs placebo at Week 26 and ** p≤0.001 T-T vs T-P at Week 52.

In the **intent-to-treat** (ITT) population using LOCF, 57.4% of patients in the tesamorelin group vs. 29.3% in the placebo group were considered as VAT responders, i.e., lost at least 8% of their baseline VAT, at Week 26 of treatment (p<0.001 for tesamorelin vs. placebo). In the **per-protocol** (PP) population-**Observed Case** (OC) analysis, the proportions of VAT responders at Week 26 were 68.8% and 32.6% in tesamorelin and placebo groups, respectively (p<0.001).

The main PRO endpoint used, as agreed with the FDA was “belly appearance distress”, a specific subscale from the body appearance distress scale focusing on the primary symptom of lipodystrophy. For the belly appearance distress scale, patients rated their current

level of distress over the size of their belly. Other PRO endpoints that focused on the belly were “belly profile” as assessed by the patient and separately by the physician, and “belly size,” a specific subscale of the “body size” scale. For the patient-rated belly profile scale, patients chose from 6 belly profile silhouettes the one that best represented their current look. For the physician-rated belly profile scale, the treating physician chose from the 6 profiles the one that best represented the patient’s current look. For the belly size scale, patients were asked to compare the size of their current belly to their “healthy look” (**Appendix I, Section 11.1**).

Over 26 weeks in the main phase studies, the improvements in the “belly appearance distress” and “belly profile” scale scores were significantly greater ($p=0.002$, $p=0.003$ and $p<0.001$, respectively) in the tesamorelin-treated patients. These differences were clinically significant on the basis of a responsiveness units analysis (**Section 5.1.4.1**), which is a well-established approach in the QOL literature ([Guyatt 1987](#), [Tuley 1991](#), [Testa 1993](#), [Testa 1996](#), [Zou 2005](#)). No significant differences were observed between tesamorelin- and placebo-treated patients for belly size assessment.

In addition, as per the FDA Guidance for Industry on PRO measures ([FDA 2009](#)), a responder analysis was conducted on the PRO belly parameters using an anchor-based method characterizing individual patients as responders based on the difference between their body profile at baseline and their baseline judgment of the smallest amount of improvement in belly profile considered to be beneficial. A significantly greater proportion of tesamorelin-treated patients were PRO responders. In addition, tesamorelin-treated patients who lost at least 8% of their baseline VAT were 2 to 3 times more likely to be responders to the main PRO. In the extension phase, the treatment effects on “belly appearance distress” and “belly profile” scale scores observed were sustained for the full 52 weeks of treatment (**Section 5.1.4.1**).

Serum lipid measures (fasting triglycerides, total cholesterol, **non-high-density lipoprotein cholesterol** [non-HDL-C], and **high-density lipoprotein cholesterol** [HDL-C]) ei-

ther were significantly improved or tended to improve in the main phase studies. Overall, triglyceride levels, which were above the normal range at baseline (mean of 261 mg/dL), decreased by a mean of 48 mg/dL in the patients who received tesamorelin from baseline to Week 52 ($p < 0.001$).

Treatment with tesamorelin also resulted in improvements in bone and inflammatory markers, with significant increases in osteocalcin and adiponectin levels and significant decreases from baseline in **tissue plasminogen activator** (tPA) and **plasminogen activator-inhibitor-1** (PAI-1) antigen levels.

Patients who received tesamorelin exhibited significant ($p < 0.001$ vs placebo) decreases in trunk fat, total fat, and WC and a significant increase in **lean body mass** (LBM) at Week 26. All these changes were sustained during the additional 26 weeks of treatment.

Previous experimental treatments of VAT often have the undesired clinically significant side effect of reducing SAT, thereby contributing to the lipoatrophy that affects patients' negative body image. In the tesamorelin program, there was a small difference in the mean change from baseline to Week 26 in limb fat between tesamorelin and placebo (-2.8% treatment effect of tesamorelin relative to placebo); however, based on values in the literature, it was not considered clinically significant ([Podzamczer 2008](#), [Cameron 2007](#)).

The results of subgroup analyses were generally consistent with the overall results for gender, age, race, geographic region, **impaired glucose tolerance** (IGT) or **diabetes mellitus** (DM2), baseline VAT, ART regimen, anti-tesamorelin **immunoglobulin G** (IgG) antibody status [Section 8.0], and testosterone use.

In conclusion, clinically meaningful changes in VAT were sustained over 52 weeks of tesamorelin treatment and were consistent across patient subgroups. In these studies tesamorelin significantly reduced VAT and improved the debilitating body image dysmorphia in HIV-infected patients with excess abdominal fat. The results of other measure-

ments, such as trunk fat, total fat, WC, and serum triglycerides, add further evidence for positive effects in this population.

Safety and Tolerability of Tesamorelin

Safety data from the tesamorelin clinical program included a range of doses in a variety of patient populations and provide adequate data for the evaluation of safety. A total of 1419 clinical study participants, including 798 HIV-infected patients, received at least 1 dose of tesamorelin (≤ 1 , 2, or 4 sc mg/day; or 0.2 iv mg/day).

In the HIV Phase 3 studies to evaluate 2 mg/day tesamorelin, 610 patients completed 26 weeks of treatment with tesamorelin, and 209 patients completed 52 weeks of treatment with tesamorelin. Overall, the mean cumulative exposure to tesamorelin was 30.5 weeks (**Section 6**).

In the total safety population, including both HIV and non-HIV-infected patients, demographic variables were not different between groups. Mean ages ranged from 40 to 56 years, and 16% of patients in the tesamorelin groups and 27% in the placebo groups were at least 65 years of age.

The proportion of patients who completed the Phase 3 studies was similar between the tesamorelin 2-mg and the placebo groups. No clinically meaningful differences were observed between the groups in the primary reasons for discontinuation. In the total safety database, total AEs and **serious AEs** (SAEs) were similar.

Overall, 10 deaths occurred, 6 in elderly, non-HIV-infected patients. Three deaths occurred during the main and extension phases of the Phase 3 program in HIV patients: 2 among tesamorelin-treated patients (2/740; 0.27%), 1 in the placebo group (1/398; 0.25%). The treating physician did not consider any of these deaths to be related to study

treatment. One death occurred in a tesamorelin-treated patient 9 months after the last dose of study drug.

In the Phase 3 main studies, the most common reasons for discontinuation in both groups were AEs (9.6% and 6.8%, respectively) and withdrawal of consent. AEs were reported in 78% and 71%, and SAEs were reported in 3.7% and 4.2%, in the tesamorelin and placebo groups, respectively. The incidence of SAEs did not differ between treatment groups and was lower in the extension phase than in the main phase. No specific SAE was reported by ≥ 2 patients in any treatment group, except sepsis. Among tesamorelin-treated patients in the main phase studies, the most common AEs were injection-site reactions, reported in 25% of tesamorelin- vs 14% of placebo-treated patients, and reactions thought to be related to GH secretion (peripheral edema, arthralgia, pain in extremity, and myalgia), reported in 26% of tesamorelin- vs 14% of placebo-treated patients. The treating physician considered most AEs to be mild or moderate in severity. No important differences were observed in the AE profiles of subgroups by concomitant medications, type of ART, type of lipid-modifying medication, or baseline demographic and clinical characteristics.

Special safety topics in patients with HIV infection

There has been a theoretical concern that high circulating IGF-1 levels for a prolonged period of exposure may be associated with the occurrence of cancer. The literature is controversial, and no link has been established between IGF-1 levels and the occurrence of cancer ([Cutting 1999](#), [Colao 2000](#), [Colao 2000a](#), [Serel 2000](#), [Kurek 2000](#), [Jernstrom 1999](#), [Renehan 2000](#)). GH or GH secretagogue administration would be expected to increase IGF-1 levels, which occurred in the tesamorelin Phase 3 studies. IGF-1 levels rose rapidly during the first 2 weeks, and mean values remained relatively stable thereafter: 262 ng/mL at 26 weeks and 238 ng/mL at 52 weeks.

For the purpose of safety assessments, IGF-1 levels were also expressed as IGF-1 SDS; the SDS describes how far the observation is above or below the mean of a population of similar age and gender. After 26 weeks of tesamorelin treatment, 47.4% and 35.6% of patients had an IGF-1 SDS $>+2$ and $>+3$, respectively, which decreased by 52 weeks to 33.7% (IGF-1 SDS $>+2$) and 22.6% (IGF-1 SDS $>+3$). No notable or clinically significant differences were observed for the overall incidence rates of AEs by IGF-1 SDS categories during the main and extension phases. However, GH-related AEs examined by IGF-1 SDS categories occurred in a greater percentage of patients in the IGF-1 SDS $>+2$ and $>+3$ categories, compared with the ≤ 2 category (peripheral edema, myalgia, pain in extremity, arthralgia, and paraesthesia).

In the HIV Phase 3 studies, 15 patients were diagnosed with cancer: 5 treated with tesamorelin (5/543; 0.92%) and 3 with placebo (3/263; 1.14%) in the main phase, and 7 tesamorelin or placebo in the extension phase (7/740; 0.95%). All cancers were considered by the treating physician to be unrelated, except in 1 tesamorelin patient and 1 placebo patient, each with Hodgkin's disease. Exposure to tesamorelin prior to the cancer event did not exceed approximately 6 months, except in 1 patient. Of the 5 tesamorelin patients in the main phase who were diagnosed with cancer, 2 had an IGF-1 SDS $>+2$ at their last visit. Of the 7 patients who were diagnosed with cancer in the extension phase, 3 (1 T-T, 1 T-P, and 1 P-T) had an IGF-1 SDS $>+2$ at their last visit. In summary, based on data from the Phase 3 studies, there was no evidence of a causal relationship among tesamorelin, increased IGF-1 levels and SDS, and any type of reported cancers.

Another theoretical safety concern was the possible effect on glucose homeostasis. However, among patients with type 2 diabetes in a Phase 2 safety study, no clinically significant effect was observed in any glucose metabolism assessment. At baseline in the HIV Phase 3 studies, approximately 39% and 8% of patients in each of the treatment groups had IGT² and diet-controlled diabetes³, respectively. The proportion of patients with IGT

² (2006 ADA Definition) IGT=140 mg/dL \leq 2-hour oral glucose tolerance test [OGTT] \leq 199 mg/dL and/or 100 mg/dL \leq FBG \leq 125 mg/dL

or diabetes was generally comparable between the T-T and T-P groups at baseline, Week 26, and Week 52. However, when looking at data from 0-26 weeks, there appeared to be an increase of 4.7% in the proportion of patients with IGT in the tesamorelin group. This observed increase seems to be transient because long-term data showed stabilization over time in the percentage of patients with IGT as reflected in the T-T group.

In line with the new 2010 ADA definition, HbA_{1c} individual patient trends were analyzed across 52 weeks. During Weeks 0-26, the proportion of patients with a post-BL HbA_{1c} $\geq 6.5\%$ was slightly greater in the tesamorelin than placebo group among those with a baseline HbA_{1c} $< 6.5\%$, but comparable among patients with a baseline HbA_{1c} $\geq 6.5\%$. Overall, only 2.3% of patients in the tesamorelin group had at least one HbA_{1c} value $\geq 7\%$ regardless of the baseline value. In the subsequent 26 weeks, HbA_{1c} stabilized in the T-T group as shown by comparable percentages of patients in the T-T and T-P groups with at least one post-baseline value $\geq 6.5\%$ or $\geq 7\%$. Only 1.63% of patients in the T-T group had at least one HbA_{1c} value $\geq 7\%$ regardless of the baseline value. Shifts in normal, pre-diabetes, and diabetes categories were also analyzed across 52 weeks in study completers (defined as patients with HbA_{1c} data at every visit). Very few patients in the tesamorelin group (1.3%) and no patients in the placebo group shifted from baseline normal to the diabetes category at Week 26, whereas slightly more tesamorelin than placebo patients shifted from baseline normal to prediabetes and from baseline pre-diabetes to diabetes. In the subsequent 26 weeks, HbA_{1c} decreased as shown by a substantially smaller proportion of patients experiencing shifts in HbA_{1c} categories in both the T-T and T-P groups at Week 52 compared to baseline. Of note, many examples of improvement in HbA_{1c} category were also observed throughout 52 weeks of treatment.

Other glucose parameters, such as FBG, insulin, **homeostasis model assessment of insulin resistance** (HOMA-IR), and **glycosylated hemoglobin** (HbA_{1c}), were assessed at Week 26 and Week 52. Only mean HbA_{1c} showed a slight change from baseline at Week

³ (2006 ADA Definition) Diabetes=2-hour OGTT ≥ 200 mg/dL and/or FBG ≥ 126 mg/dL

26, while remaining in a normal range. The change in HbA_{1c} was not clinically significant at Week 26 and by Week 52 was neither statistically nor clinically significant. Overall, there were slight differences in glycemic parameters between groups, which can be readily managed in clinical practice.

Hypersensitivity reactions (**Section 3.1**) occurred in 27/740 (3.6%) tesamorelin-treated HIV-infected patients in the Phase 3 studies. Of these, 21 cases were reported spontaneously to the sponsor and 6 were identified during a retrospective review of all reported rash and urticaria events. None of the hypersensitivity reactions were considered to be anaphylaxis, defined as a systemic life-threatening allergic reaction. The patients who reported systemic symptoms noted that the symptoms resolved either spontaneously or simply with an antihistamine or topical corticosteroid application. None of the patients were treated with epinephrine, bronchodilators or systemic corticosteroids nor needed any emergency medical care. None of the hypersensitivity reactions were considered as SAE or resulted in a serious outcome (**Appendix IV and Section 11.4**).

Immunogenicity

Antibody formation, a common response to peptide therapeutics when administered SC ([Schnabel 2006](#)), could potentially lead to undesirable clinical effects, such as a decrease in drug efficacy or an increase in SAEs. Therefore, as part of the Phase 3 program, extensive monitoring was conducted to detect the development of antibodies if present (**Section 7**).

Anti-tesamorelin IgG antibodies were detected in 51% of tesamorelin-treated patients at 26 weeks. The proportion of patients with anti-tesamorelin IgG antibodies remained essentially unchanged among tesamorelin-treated patients from Weeks 26 through 52. Most of the patients with detected IgG antibodies had low titers (<400). In addition, the pro-

portion of patients with anti-tesamorelin IgG antibodies was reduced from 56% to 18% in the T-P patients, suggesting that ceasing treatment results in seroreversion over time.

The presence of *in vitro* detected **neutralizing antibodies** (NAb) against endogenous GRF and against tesamorelin was assessed in T-T patients who were anti-tesamorelin IgG antibody-positive at Week 52 or early termination. Five percent of these patients were found to be hGRF NAb-positive, and 10% of these patients were found to be tesamorelin NAb-positive.

The presence of anti-tesamorelin IgG antibodies and *in vitro* detected hGRF and tesamorelin NABs had no impact on the efficacy and safety of this product either during treatment or after treatment was stopped.

Conclusions

The results from the Theratechnologies development program suggest that tesamorelin has the potential to assist patients and physicians meet the challenges associated with increases in VAT in the context of HIV-associated lipodystrophy [Section 2]. This persistent medical condition has physical and psychological sequelae that cause emotional distress and a reduced QOL, interfere with life-saving HIV disease management, and further increase metabolic and cardiovascular risk in individuals already at greater than normal risk because of ART.

Clinical trial evidence supports the potential benefits of tesamorelin:

- reduces VAT
- preserves abdominal SAT and limb fat
- improves “belly appearance distress” and “belly profile”
- reduces waist circumference
- improves other body composition measures

- increase lean body mass
- decrease trunk fat
- shows improvement in lipid parameters
 - triglycerides
 - total cholesterol
 - total cholesterol/HDL ratio
 - non-HDL cholesterol

The possible risks associated with tesamorelin treatment were clearly identified in the Phase 3 program:

- increase in IGF-1 levels associated with a theoretical risk of cancer
- small number of patients with worsening of glucose homeostasis
- hypersensitivity reactions
- presence of antibodies

Tesamorelin offers patients and physicians the means to combat one of the most devastating side effects of ART, thus offering not only improved QOL and reduced risk of other health consequences associated with lipohypertrophy, but also potentially removing an obstacle in the decision by the affected patients to continue ART.

For a complete discussion of Risk Management and Benefit Risk Assessment (see **Section 8 and 9**).

For ease of review of the document, we are providing in **Appendix VII** several key articles for consultation.

1 INTRODUCTION AND MEDICAL NEED

NOTE: The remainder of this document presents a more detailed discussion of the material introduced in the Executive Overview, including graphical representation of key findings, followed by appendices covering methods for patient-reported outcomes (PRO), statistical methods and considerations, and death and special adverse event (AE) case narratives.

1.1 Lipodystrophy in HIV-Infected Patients

HIV-associated lipodystrophy is a medical condition characterized by abnormalities in body shape and composition in association with multiple metabolic abnormalities, including dyslipidemia and insulin resistance ([Capeau 2005](#), [Brown 2008](#), [Lichtenstein 2005](#), [Grinspoon 2005](#)). This condition is associated with a range of physiological and psychological complications beyond the significant health and mortality risks of the HIV infection itself. In HIV-infected patients with lipodystrophy, fat changes can include lipoatrophy or lipohypertrophy, or both ([Lichtenstein 2005](#), [Grinspoon 2005](#), [Bacchetti 2005](#), [FRAM 2006](#)) (see **Figure 1**).

A significant physical feature of lipohypertrophy is abdominal fat accumulation, which manifests as a noticeable increase in abdominal girth. In HIV-infected patients, abnormal fat accumulation may also occur in breast tissue, in the dorsocervical tissues leading to “buffalo hump,” or appear as lipomas. Lipoatrophy or loss of SAT is particularly stigmatizing and is most noticeable in the face, limbs, and buttocks, but can also occur in the trunk ([Brown 2008](#)). Dyslipidemia may manifest as high plasma levels of triglycerides and LDL-C, and low levels of HDL-C ([Brown 2008](#)).

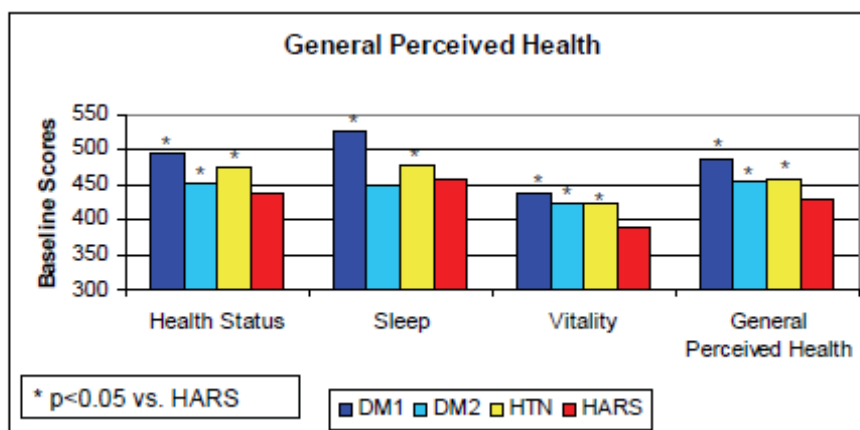
The causes of lipodystrophy in HIV-infected patients may include factors related to the HIV infection and its comorbidities, duration of ART, and host factors such as age, genetics, and gender ([Martinez 2001](#), [Lichtenstein 2005](#)). Recent data suggest that different

pathophysiological mechanisms are involved in the development of lipohypertrophy and lipoatrophy in these patients. A review of the literature ([Lichtenstein 2005](#)) indicated that the most common statistically significant independent risk factors identified for lipohypertrophy were duration of ART, markers of disease severity, and protease inhibitor (PI) use. However, lipodystrophy overall has not been associated with specific antiretroviral medications or classes of medications ([Martinez 2001](#)).

1.2 Effects of lipodystrophy on body image, psychosocial functioning, and health-related quality of life in HIV-infected patients

Because highly active ART prolongs life, HRQOL has become an important consideration in HIV-infected patients, as evidenced by the increasing number of studies addressing these issues. In a recent review, [Guaraldi et al \(2008\)](#) adapted [Testa & Simonson's \(1996\)](#) conceptual model of HRQOL to body image impact and its consequences for health perceptions and psychosocial functioning. Results from descriptive and qualitative studies support the concept that a substantial distortion of body image as a result of lipodystrophy is associated with significant impairment in psychosocial and affective domains of HRQOL. [Lichtenstein et al \(2005\)](#) reported that HIV-infected patients with body shape changes have significantly poorer body image compared to HIV-infected patients without lipodystrophy. This was confirmed in a cross-sectional study by [Marin et al \(2006\)](#) reporting reliability and validity of a lipodystrophy-specific questionnaire. In particular, HIV-infected patients with lipodystrophy see themselves as disfigured, isolated, and stigmatized ([Blanch 2004](#), [Peterson 2008](#), [Guaraldi 2008](#)). Among body shape changes, increased belly size has been shown to adversely affect body image, social functioning, interpersonal relationships, psychological well being and overall QOL ([Guaraldi & Baraboutis 2009](#), [Marin 2006](#), [Santos 2005](#), [Turner 2006](#)) (**Figure 4**).

Figure 4. General Perceived Health in HIV-Positive Patients with Excess Abdominal Fat Compared to Patients with Diabetes or Hypertension



DM1, type 1 diabetes mellitus; DM2, type 2 diabetes mellitus; HTN, hypertension; HARS, HIV-Associated Redistribution Syndrome (Excess Abdominal Fat).

Turner RR, et al. Presented at the 8th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, San Francisco, USA, September 2006.

Marin et al (2006) found that HIV-infected patients with lipodystrophy were more significantly impaired than HIV-infected patients without lipodystrophy in depression, anxiety, social distress, and social support. Qualitative data from structured focus groups of HIV-infected patients showed that the primary concerns of patients across groups were physical discomfort, impairment, and psychological and social distress caused by body changes (Reynolds 2006). Patients also had a significant concern that the syndrome would lead to unintended disclosure of their health status. Collins et al (2000) assessed qualitatively the experiences of 33 HIV-infected patients with lipodystrophy through open-ended questions. An analysis of the major themes included poor self-image and self-esteem, problems in social and sexual relations, and demoralization and depression. Patients used words such as “grotesque,” “deformed,” or “damaged goods” to describe their body image. A comment from another patient was, “This lipodystrophy thing has affected me at this point more than HIV itself.” A significant disruption and impairment in sexual functioning has been reported among patients with lipodystrophy syndrome (Dukers 2001, Guaraldi 2007).

[Santos et al \(2005\)](#) made a strong association between ART use, body image distortion, and impairment in social function and relationships among HIV-infected patients. Although [Steel et al \(2006\)](#) reported no differences in HRQOL or depression between HIV-infected patients with or without a diagnosis of lipodystrophy, data were collected with the Medical Outcomes Study Short-Form 36 (SF-36) health survey and the 5-item Center for Epidemiological Studies – Depression (CES-D) screening instrument. Neither instrument would necessarily be expected to detect differences within HIV-infected patients due to lipodystrophy given the presence of other significant morbidities among HIV-infected patients with or without lipodystrophy.

Among body shape changes, increased abdomen size has been shown to adversely affect body image perception, social functioning, interpersonal relationships, psychological well-being and overall HRQOL ([Guaraldi & Baraboutis 2009](#), [Marin 2006](#), [Santos 2005](#), [Turner 2006](#)). Data from a community based survey revealed that depression or anxiety was present in 87% of responders, of which 63% self-reported abdominal fat accumulation, and 25% had suicidal thoughts in the past because of perceived body changes ([Vergel 2008](#)). In addition, over 50% of the survey respondents stopped socializing, had decreased self-image, and changed clothing style.

In the setting of randomized controlled trials, [Turner \(2006\)](#) reported significant improvement in body size evaluation, body appearance distress, and belly profile assessment as well as composite mental health and psychological distress among HIV-infected lipodystrophy patients treated with 2 mg somatropin qd compared with placebo. These results are summarized in the somatropin ([Serostim](#)[®]) labeling.

Taken together, these studies provide a conceptualization of the significant impact of lipodystrophy on body image, with significant evidence for substantial body image distortion that is associated with impairment in psychosocial and affective domains of HRQOL. The evidence also suggests that reduction in the clinical signs and symptoms of the lipodystrophy syndrome (e.g., reduction in VAT, improvement in lipoatrophy in the

extremities) results in improved body image and, subsequently, in psychosocial and affective functioning.

Compliance with ART

In addition to social stigmatization and related psychological distress, individuals who self-report the symptoms of HIV-associated lipodystrophy are less likely to adhere to ART, with related risks to health status. Discontinuation of ART can lead to increased mortality, opportunistic disease, and other complications ([SMART Study Group 2006](#), [Ananworanich 2006](#)).

[Duran et al \(2001\)](#) (Antiproteases Cohorte [APROCO] study) found that 30% of 277 patients who were initially adherent at 4 months of follow-up were non-adherent to ART at 20 months. At 20 months, 76% of patients reported ≥ 1 lipodystrophy symptom and 47% reported a “bigger belly or wider waist.” Non-adherent patients were more likely to report the lipodystrophy symptoms of “change in the body shape” (60% vs 46%; $p=0.03$), “bigger belly or wider waist” (55% vs 43%; $p=0.06$), and “bigger breast” (27% vs 13%; $p=0.008$) than adherent patients. After multiple adjustments by logistic regression for other variables related to non-adherence, the number of self-reported symptoms of lipodystrophy was significantly and independently associated with non-adherence, with an odds ratio of 1.13 (95% CI, 1.02, 1.26). Adherence to ART was examined in a longitudinal study in 207 patients who had been receiving ART for a median of 89 weeks and were followed for a median of 45 weeks ([Ammassari 2002](#)). Patient-reported fat accumulation and longer duration of ART were independently and statistically significantly associated ($p \leq 0.05$) with an increased risk of non-adherence. The results of a community-based survey indicate that 41% of responders had interrupted ART because of body changes in the past ([Vergel 2008](#)). In a recent study ([Plankey 2009](#)), self-perception of central fat gain was associated with 1.5-fold increased odds of highly active ART non-adherence compared with no change after multivariate adjustment. Importantly, self-

perception of fat gain in the abdomen was the strongest predictor of highly active ART non-adherence when the individual body sites were studied.

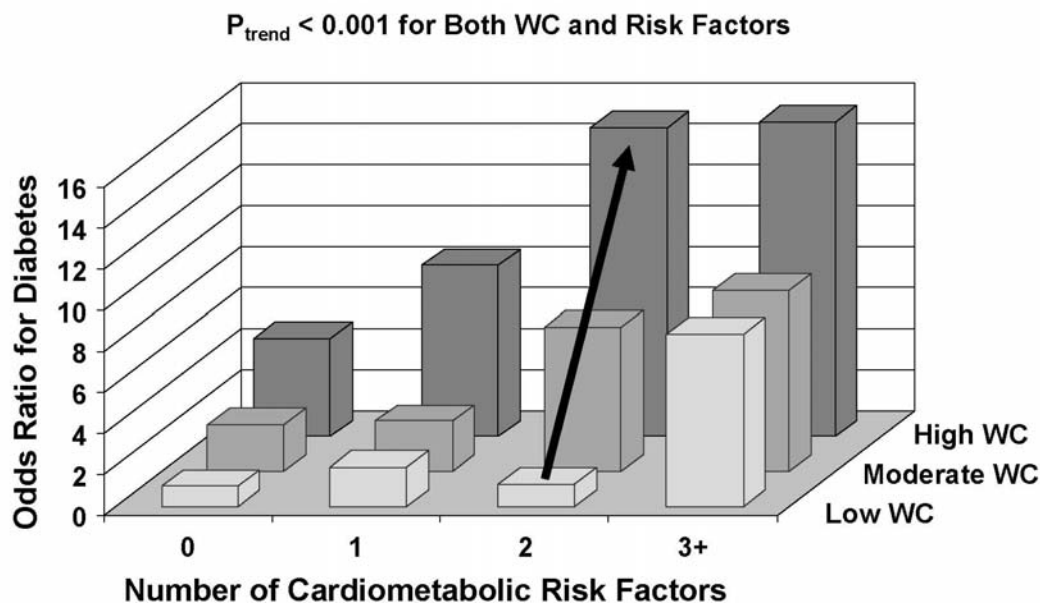
1.3 Health Risks Associated with Increased VAT and Waist Circumference

VAT, considered the most pathogenic adipose tissue, is an important component of abdominal obesity. Levels of VAT are associated with the metabolic disturbances that are risk factors for cardiovascular disease (CVD) and diabetes ([Pouliot 1994](#), [Onat 2004](#), [Fujimoto 2007](#)).

In the non-HIV population, several prospective, epidemiological or cross-sectional studies showed that abdominal obesity with increased VAT, is associated with a prothrombotic inflammatory state and metabolic abnormalities, which substantially increase the risk of type 2 diabetes and CVD ([Larsson 1984](#), [Rexrode 2001](#), [Donahue 1987](#), [St Pierre 2002](#)). [Pouliot et al \(1992\)](#) found that obese men with high VAT show significantly higher plasma glucose, insulin, and triglyceride levels and significantly lower plasma HDL levels compared to obese men with low VAT. In addition, data from several studies indicate that WC significantly correlates with VAT in the general population ([Onat 2004](#), [Pouliot 1994](#), [Ross 1996](#)).

An association between WC and both CVD and diabetes was shown in an analysis of the US 1999-2004 National Health and Nutrition Examination Survey (NHANES) ([Janiszewski 2007](#)). For a given number of cardiometabolic risk factors, the likelihood of having diabetes increases when moving from the low WC category (<90.9 cm) to the moderate (90.9-102.9 cm) or high WC (>102.9 cm) categories (**Figure 5**). [Balkau et al \(2007\)](#) recently reported a statistically significant graded increase in the frequency of diabetes mellitus with both BMI and WC, with a stronger relationship for WC than for BMI across categories for both genders.

Figure 5. Waist Circumference as a Predictor of Diabetes Beyond Commonly Evaluated Cardiometabolic Risk Factors



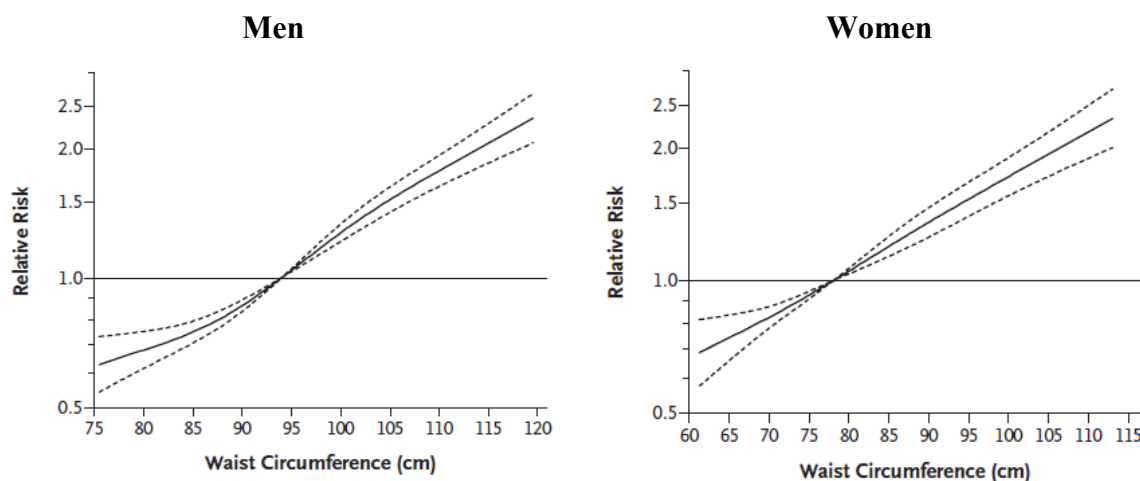
WC, waist circumference.

Janiszewski PM, et al. *Diabetes Care*. 2007;30:3105-3109.

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Recent data from a large European cohort with 359,387 participants indicate that both general and abdominal obesity, as assessed by waist circumference and waist-to-hip ratio, are independently associated with the risk of death. The results showed that the highest quintile of WC in men and women was associated with a relative risk of death of 2.05 (**Figure 6**), and the highest quintile of waist-to-hip ratio was associated with a relative risk of death of 1.68. For a given BMI, a WC 5 cm larger increased the risk of death by a factor of 1.17 among men and 1.13 among women ([Pischon 2008](#)).

Figure 6. Adjusted Relative Risk of Death Among Men and Women According to Waist Circumference



Solid lines indicate relative risks, and dashed lines indicate 95% confidence intervals derived from restricted cubic spline regression, with knots placed at the 5th, 25th, 75th, and 95th percentiles of the gender-specific distribution of each anthropometric variable.

The reference point for waist circumference is the gender-specific median of the variable. The graphs are truncated at the 1st and 99th percentiles. Age was used as the underlying time variable in the regression models, with stratification according to center and age at recruitment and additional adjustment for smoking status, educational level, alcohol consumption, physical activity, and height. The relative risks are plotted on a logarithmic scale.

Pischoon T, et al. *N Engl J Med.* 2008;359:2105-2120.

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1.4 Metabolic Effects of SAT

Increased amounts of SAT have been demonstrated to have direct and beneficial metabolic effects, including improvements in insulin sensitivity and dyslipidemia, which may lower the risk for diabetes mellitus and atherosclerosis (Tran 2008, Snijder 2006). Porter et al (2009) examined the relation between age-adjusted SAT tertiles within gender-specific tertiles of VAT and cardiometabolic risk factors in participants from the Framingham Heart Study (n=3001, 48.5% women). In the top VAT tertile, lower triglyceride levels were observed in men with increasing SAT (64.4% high triglycerides in SAT tertile 1 vs. 52.7% in SAT tertile 3, p=0.03). The prevalence of high triglycerides decreased significantly among obese women with increased SAT (48.8% in SAT tertile 1 vs. 33.0% in SAT tertile 3, p=0.02).

It has been suggested that SAT, especially in the femoral-gluteal region, plays a protective role by acting as a “sink” for circulating free fatty acids ([Frayn 2002](#)). Adipocytes in the femoral region are relatively insensitive to lipolytic stimuli and have a high sensitivity for anti-lipolytic stimuli. As a result of free fatty acids uptake in the femoral-gluteal region, detrimental fat storage in the liver, muscle and pancreas may be prevented ([Ravussin 2002](#)).

1.5 Metabolic Effects of Increased VAT and Decreased SAT in the HIV-Infected Patients

In a study comparing HIV-infected patients with controls who did not differ significantly in age, race, or BMI when stratified by gender, [Joy et al \(2008\)](#) found that VAT was significantly higher and that SAT was significantly lower among HIV-infected patients in the normal and overweight categories respectively, compared with controls in the same weight categories.

Increased VAT has been shown to be correlated with both fasting insulin and dyslipidemia in HIV-infected patients with lipodystrophy ([Saint Marc 2000](#), [Wohl 2008](#)). A comparison of HIV-infected patients with and without lipodystrophy showed that patients with lipodystrophy were more likely to have high triglyceride levels, insulin resistance, and diabetes ([Carr 1999](#), [Saint-Marc 2000](#), [Hadigan 2001](#), [Vigouroux 2003](#)). Of note, HIV-infected patients have been reported to have more metabolic abnormalities, including dyslipidemia, insulin resistance, high C-reactive protein (CRP), and low adiponectin levels than healthy controls ([Dolan 2005](#)). Overall, these data indicate that HIV-infected patients with lipodystrophy are at increased risk for CVD.

Many studies show that the incidence of CVD is high in HIV-infected patients and is more prevalent in HIV-infected patients who receive ART than in controls (**Table 1**). ART is associated with an increased incidence of cardiovascular and cerebrovascular

events, and the risks appear to increase with the length of exposure to ART (d'Arminio 2004, Friis-Møller 2007).

Table 1. Case-Control Studies Showing Prevalence of CVD in HIV+ Patients vs HIV- Patients

| | Study | Size/Control | Outcome | HIV+ vs HIV- | Adj. CV RF | Adj. PI |
|--------------------------------------|---------------------------------|----------------|----------|------------------------|------------|---------|
| Administrative Database | Klein, <i>JAIDS</i> , 2002 | 4159/39,877 | CAD adm | ↑ (6.5 vs 3.8/1000 PY) | Partial | No |
| | Klein, <i>CROI</i> , 2007 | 5000/43,000 | CAD adm | ↑ (4.5 vs 2.9/1000 PY) | Partial | No |
| | Currier, <i>JAIDS</i> , 2003 | 28,513/3 M | CAD adm | ↑ (only in young) | Partial | Yes |
| | Triant, <i>JCEM</i> , 2007 | 3851/1 M | MI adm | ↑ (75%) | Partial | No |
| | Obel, <i>CID</i> , 2007 | 3, 953/373,856 | CAD adm | ↑ (39%–112%) | Partial | No |
| | | | | | | |
| Prospective Surrogate Studies | Hsue, <i>Circulation</i> , 2004 | 121/27 | IMT/year | ↑ (7 μm vs 1 μm) | Yes | No |
| | Currier, <i>AIDS</i> , 2007 | 88/44 | IMT/year | ↔ (6 μm vs 9 μm) | Yes | Yes |

Adj., adjusted; Adm: admission; CAD, coronary artery disease; CV RF, cardiovascular risk factor; HIV, human immunodeficiency virus; M, million; MI, myocardial infarction; PI, protease inhibitor; PY, patient-years; IMT, intima media thickness.

Currier J, et al. *J Acquir Immune Defic Syndr*. 2003;33:506-512.

Currier J, et al. *AIDS*. 2007;21:1137-1145.

Hsue P, et al. *Circulation*. 2004;109:1603-1608.

Klein D, et al. *J Acquir Immune Defic Syndr*. 2002;30:471-477.

Klein D, et al. *CROI* 2007. Poster 807.

Obel N, et al. *Clin Infect Dis*. 2007;44:1625-1631.

Triant V, et al. *J Clin Endocrinol Metab*. 2007;92:2506-2512.

Accumulating evidence suggests a link between excess VAT and increased CVD risk in HIV-infected patients with lipodystrophy. Wohl et al (2008) showed that increased VAT and decreased leg SAT were associated with an increased 10-year Framingham CVD risk score in HIV-infected individuals. A direct link between VAT and cardiovascular risk in the HIV-positive population was demonstrated by Guaraldi et al (2009), who found that VAT was a predictor of subclinical atherosclerosis, as evaluated by coronary calcium atherosclerosis imaging in HIV-positive patients with lipodystrophy. This finding is in agreement with the results of Lo et al (2010) demonstrating a significant association between VAT and coronary calcium score in HIV-positive patients. More recently, using multivariable Poisson regression, Guaraldi et al (2010) reported that VAT, but not gen-

eral adiposity, was an independent predictor of prior CVD in a cohort of HIV-infected patients and, particularly, in patients with lipohypertrophy alone or both lipohypertrophy and lipodystrophy (Relative Risk 1.03, 95% CI: 1.01; 1.06, per 10 cm³ VAT increment, p-value=0.023).

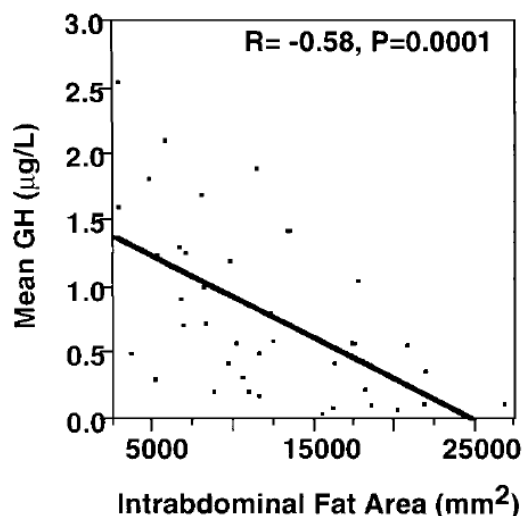
Given the deleterious effect of increased VAT and the protective effect of SAT on cardiovascular risk factors, the development of therapeutic strategies to reduce VAT while preserving SAT in HIV-infected patients with lipodystrophy represent an important unmet medical need.

In the HIV population, [Brown et al \(2009\)](#) observed that WC increases at a significantly faster rate in HIV-infected men with lipodystrophy (0.5 cm/year over 6 years of follow-up) than in HIV-infected men without lipodystrophy. Recently, [Guaraldi et al \(2010\)](#) showed that WC significantly correlates with VAT in HIV-infected patients with lipodystrophy. Taken together, these data indicate that WC is a surrogate measure of VAT in HIV-infected patients with lipodystrophy as observed in the general population.

1.6 Growth Hormone Deficiency in HIV-Infected Patients

[Rietschel et al \(2001\)](#) compared 21 HIV-infected men who had lipodystrophy with 20 HIV-infected men who did not have lipodystrophy and 20 control subjects; all were matched for age and BMI. Growth hormone (GH) was measured overnight. The results showed that VAT was significantly increased in the HIV-infected men with lipodystrophy compared with HIV-infected men without lipodystrophy and with the controls. Also, the HIV-infected men with lipodystrophy had a significantly lower mean GH concentration than the other groups had (**Figure 7**), and the differences remained significant when controlling for PI and nucleoside reverse transcriptase inhibitor (NRTI) use. In a multivariate regression model that controlled for age, BMI, body fat, and VAT, only VAT was a significant predictor of mean GH concentration.

Figure 7. Relationship of Intra-Abdominal Fat to Mean Overnight GH Concentration in HIV-Infected Patients with Lipodystrophy



GH, growth hormone.

Rietschel P, et al. *J Clin Endocrinol Metab*. 2001;86:504-510.

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HIV-infected adolescents with excess VAT were compared with those without excess VAT (Viganò 2003). These patients had received highly active ART for a mean of 55 months. The area under the curve (AUC) of the GH response (GH-AUC_{0-120 min}) was significantly lower in the increased VAT group compared with the low VAT group (16 µg•h/L vs 32 µg•h/L; p=0.002). Also, IGF-1 concentrations and lean body mass (LBM) were significantly lower and insulin levels were significantly higher in the excess VAT group.

1.7 Treatment of Lipodystrophy in HIV-Infected Patients

The main goals of therapy in HIV-infected patients with lipodystrophy have been to reduce VAT, maintain or increase SAT if it is reduced, and improve the metabolic parameters that are associated with CVD and diabetes. These approaches have included cosmetic surgery, lifestyle modifications, medication, switching antiretroviral agents, and administering hormones (including recombinant human GH [rhGH]). However, currently, no US Food and Drug Administration (FDA)-approved treatment exists for reducing VAT in

HIV-infected patients with lipodystrophy. Many approaches have been tried for treating lipodystrophy and its associated metabolic abnormalities in HIV-infected patients.

Exercise training in HIV-infected patients with lipodystrophy improves cardiorespiratory fitness and increases endurance and muscle strength, but has only a slight and limited effect on VAT ([Dolan 2006](#), [Driscoll 2004](#)). Also, exercise training has been shown to decrease serum triglycerides ([Leow 2003](#)), and dietary restriction can reduce overall body fat and improve the lipid profile ([Chen 2002](#)). Because of the known health benefits of diet and exercise, patients with HIV infection should be encouraged to maintain and increase healthy lifestyle habits, but effects on the symptoms of lipodystrophy are limited.

Thiazolidinediones (glitazones) are insulin-sensitizing agents used for the treatment of type 2 diabetes. Rosiglitazone improves insulin sensitivity, but adversely affects the lipid profile and produces conflicting results on body fat composition in HIV-infected patients with lipodystrophy ([Feldt 2006](#), [Sutinen 2003](#), [Hadigan 2004](#), [Carr 2004](#), [Macallan 2008](#)). In several studies ([Feldt, 2006](#), [Hadigan 2004](#)), rosiglitazone had beneficial effects on glucose metabolism and increased SAT but had no effect on VAT, while cholesterol and triglyceride levels increased. [Carr et al \(2004\)](#) found that rosiglitazone treatment for 48 weeks increased limb fat by a small amount, but it had no significant effect on any other lipodystrophy measure, including the waist-to-hip ratio, compared with placebo. [Macallan et al \(2008\)](#) also found that rosiglitazone induced a slow increase in limb fat over 48 weeks without any effect on VAT. Treatment of HIV-infected patients with lipodystrophy with pioglitazone 30 mg for 48 weeks increased limb fat and HDL-C, but had no effect on VAT ([Slama 2008](#)).

Metformin has been shown to improve insulin resistance if impaired in HIV-infected patients; however, it has a limited effect on VAT and may reduce SAT ([Hadigan 2000](#), [Kohli 2007](#)). In an open-label (OL) study ([van Wijk 2005](#)) comparing metformin with rosiglitazone, metformin was more effective in reducing VAT in patients with HIV lipodystrophy than rosiglitazone.

Statins have been shown to be effective in treating hypercholesterolemia, but few studies have assessed the effect of these medications on body composition. In a 16-week placebo-controlled study ([Mallon 2006](#)) with HIV-infected men, pravastatin 40 mg increased limb fat and SAT compared with placebo. However, no significant differences between the pravastatin and the placebo groups were observed for changes from baseline in BMI or VAT, or cholesterol or triglycerides ([Mallon 2006](#)). In another study ([Macallan 2008](#)), pravastatin 40 mg reduced total cholesterol and LDL-C during 48 weeks of treatment of HIV-infected patients with lipodystrophy, but it had no effects on body composition, including VAT.

One class of antiretroviral agents, the PIs, has been implicated in the increase of lipodystrophy symptoms ([Carr 1998](#), [Carr 1999](#)), but switching from PIs to other agents has had little effect on symptom relief ([Martinez 2000](#), [Martinez, 2001](#), [Martinez 2003](#)), and patients not receiving PIs can also develop lipodystrophy symptoms ([Chen 2002](#)). Switching from the antiretrovirals stavudine or zidovudine to abacavir (which are all NRTIs) yielded improvement in SAT but did not reduce VAT ([Sutinen 2005](#)). A recent pilot study involving HIV-infected patients (n=15) with evidence of hyperinsulinemia and/or dyslipidemia demonstrated a decrease in VAT when patients were switched from the PIs lopinavir/ritonavir to the PIs atazanavir/ritonavir ([Stanley 2009](#)). However, in another recent study, [Molina et al \(2010\)](#) showed that switching from lopinavir to atazanavir had no effect on VAT. Discontinuation of ART is not an option because it leads to increased viral load, increases development of opportunistic disease, and can increase the all-cause mortality ([SMART Study Group 2006](#), [Ananworanich 2006](#)).

Decreased testosterone levels have been associated with visceral adiposity in HIV-infected men ([Hadigan 2000](#), [Schambelan 2002](#)). Testosterone for men who are hypogonadal has been beneficial for decreasing abdominal girth, but it is recommended for replacement only in patients who have low testosterone levels ([Schambelan 2002](#)).

Leptin is a hormone secreted by adipocytes and is associated with insulin resistance and central fat accumulation. [Nagy et al \(2003\)](#) found that mean leptin levels are low in HIV-infected patients with lipoatrophy only, but are significantly higher in patients with lipo-hypertrophy alone when compared to patients without lipodystrophy. Patients who had mixed lipodystrophy had intermediate levels of leptin. Therefore, leptin replacement is unlikely to address the problems of abdominal lipohypertrophy in HIV-infected patients.

The association of VAT with impaired GH secretion in patients with HIV-associated lipodystrophy ([Rietschel 2001](#), [Viganò 2003](#)) is a rationale for treatment with rhGH. Administration of rhGH 4 mg to HIV-infected patients with excess abdominal fat in 2 large studies was associated with a significant decrease in VAT. In the first study, VAT decreased from baseline to Week 12 by 18.8% in the group of patients treated with rhGH 4 mg ($p < 0.001$ vs. placebo), and significantly reaccumulated from Week 12 to Week 24 after cessation of active treatment (% change from baseline to Week 24: -1.6%) ([Kotler 2006](#)). In the second study, treatment with rhGH for 12 weeks was also associated with a significant decrease in VAT (-20.3%, $p < 0.001$ vs. placebo) ([Grunfeld 2007](#)). The mean percent change from baseline to Week 36 in VAT was -3.5% ($p = 0.018$) in the group of patients who received rhGH 4 mg for 12 weeks and then rhGH 2 mg on alternate days for 24 weeks ([Grunfeld 2007](#)). Treatment with rhGH 4 mg was also associated with significant decreases in abdominal SAT, total fat, trunk fat, and limb fat ([Kotler 2004](#), [Kotler 2006](#), [Grunfeld 2007](#)). Recently, administration of low-dose rhGH (average dose: 0.33 mg/day) over 18 months to HIV-infected patients with lipodystrophy and relative GH deficiency was associated with a modest decrease in VAT (8.5%) ([Lo 2008](#)). GH treatment also has beneficial effects on blood lipids in these HIV-infected patients. Significant decreases in total cholesterol and non-HDL-C and significant increases in HDL-C have been observed with 4 mg/day rhGH for 12 weeks ([Kotler 2004](#), [Grunfeld 2007](#)). Triglycerides significantly decreased but total cholesterol and HDL-C were unchanged in HIV-infected treated with low doses of rhGH ([Lo 2008](#)).

Although treatment with rhGH reduces VAT and improves lipid profile, it is also accompanied with significant side effects. Perturbation of glucose metabolism was an important safety issue across trials of rhGH in HIV-infected patients with lipodystrophy, including the 2 large studies (N=245 and N=326, respectively) from which glucose-intolerant and diabetic subjects were excluded (Kotler 2004, Grunfeld 2007). Kotler et al (2004) reported that mean fasting blood glucose and 2-h insulin AUC on OGTT worsened relative to baseline ($p<0.05$) in patients treated with rhGH for 12 weeks. Similarly, treatment with rhGH 4 mg daily for 12 weeks was associated with increases of 7.9% and 19.2% in fasting blood glucose and 2-hour glucose on OGTT ($p<0.05$ vs. placebo for both), respectively, in the study of Grunfeld et al (2007). Of note, fasting insulin rose by 133.5% in the group of patients receiving rhGH 4 mg ($p<0.001$ vs. placebo). Treatment of HIV-infected patients with low doses of rhGH was also associated with a significant increase in glucose levels 2 hours after an OGTT, although no changes in fasting blood glucose, fasting insulin, or HbA_{1c} were observed.

Treatment with rhGH in the studies by Kotler et al (2004) and Grunfeld et al (2007) was also associated with other significant GH-related side effects, including peripheral edema, arthralgia, limb pain, and hypoesthesia. In the study by Grunfeld et al (2007), 46.3% of rhGH-treated patients versus 4.9% of placebo experienced peripheral edema, and 38.9% of rhGH-treated versus 17.3% of placebo experienced arthralgia at Week 12 of treatment ($p<0.001$ vs. placebo for both). In addition, more patients in the rhGH group than the placebo group (17.2% vs. 8.6%, $p=0.073$) reported AEs of severe-grade toxicity (defined per toxicity guidelines as significant impairment of functioning). It has been previously observed that adults with GH deficiency who receive rhGH commonly experience fluid retention, which causes edema and arthralgia, and this side effect occurs in up to 17% of subjects in trials (Bryant 2002, Clark 1996). During the initial 12-week treatment periods of the 2 studies combined, the incidence of glucose-related AEs was 22% for the rhGH group and 4% for the placebo group. The incidence of arthralgia for the rhGH group was 37.1%, while the incidences of peripheral edema and hypoesthesia were 45.4% and 15.0%, respectively (Serostim[®] label).

Overall, these data indicate that use of rhGH in HIV-infected patients with lipodystrophy is associated with important safety issues and argue for the development of a product with an acceptable risk benefit profile to reduce VAT in this patient population.

2 TESAMORELIN DESCRIPTION AND CHARACTERIZATION

2.1 Product Description and Mechanism of Action

Tesamorelin is a synthetic analogue of human hypothalamic growth hormone-releasing factor (hGRF), also known as growth hormone-releasing hormone (GHRH). GRF is a hypothalamic peptide that acts on the pituitary cells to stimulate the synthesis and pulsatile release of endogenous GH.

The results of both experimental animal and human studies have shown that GH can reduce total fat mass through a combination of several actions, including inhibition of adipocyte differentiation ([Richelsen 1997](#), [Wabitsch 1996](#)) and stimulation of fat mobilization and oxidation ([Berneis 1996](#)). Also, GH is an anabolic agent that promotes urinary nitrogen retention, uptake of amino acids by muscle cells, and protein synthesis in various tissues ([Bauman 1982](#)). GH exerts its effect on protein metabolism either directly or indirectly through increased production of IGF-1 in the liver or in peripheral tissues ([Cummings 2003](#)). In various conditions, including AIDS, GH has been shown to increase LBM ([Clark 1996](#), [Mulligan 1993](#)). Basal GH concentrations and GH pulse amplitudes are reduced in HIV-infected patients with lipodystrophy ([Rietschel 2001](#)). However, the pulse frequencies of GH are normal. Also, the response of GH to GRF appears to be preserved ([Rietschel 2001](#)).

Impaired GH secretion is associated with visceral adiposity in patients with HIV-associated lipodystrophy ([Rietschel 2001](#), [Viganò 2003](#)). These results led to the use of GH in HIV-infected patients with lipodystrophy. As reported in **Section 1.7**, treatment of

HIV-infected patients with pharmacological doses of rhGH reduced VAT and trunk fat and increased LBM in 2 large randomized, placebo-controlled studies ([Kotler 2004](#), [Kotler 2006](#), [Grunfeld 2007](#)). However, rhGH administration also led to a decrease in limb fat and significant side effects, including symptoms of interstitial fluid retention and hyperglycemia, which resulted in treatment discontinuation in some patients.

Therapeutic strategies that induce a physiological pattern of GH secretion were therefore sought for the clinical management of lipodystrophy in HIV-infected patients. In contrast with GH, exogenous GRF induces a physiological pulsatile pattern of GH secretion and preserves IGF-1 feedback inhibition, thereby helping to prevent the adverse effects caused by GH excess ([Berelowitz 1981](#), [Hulse 1986](#)). SC administration of 1 mg GRF (GHRH[1-29]) twice daily (bid) to 31 HIV-infected men with lipodystrophy symptoms increased LBM, reduced trunk and visceral fat, and improved the ratio of abdominal fat to abdominal SC fat, with no significant changes in glucose parameters ([Koutkia 2004](#)). These results suggested that the use of GRF could be a beneficial treatment strategy for the treatment of lipodystrophy in HIV-infected patients.

Tesamorelin, as a synthetic analogue of hGRF, has the 44 amino-acid sequence of hGRF, but also a hexenoyl C6 chain, with a double bond at carbon position 3, anchored on tyrosine at the N-terminal end of the polypeptide. The addition of this hydrophobic side chain does not affect the binding affinity to hGRF receptors, but increases the resistance to enzymatic degradation in human serum. Pharmacological studies indicate that tesamorelin has an increased potency and a longer duration of action compared with hGRF. In both preclinical and clinical studies conducted by the Company, tesamorelin has been shown to increase circulating GH, IGF-1, and insulin-like growth factor binding protein-3 (IGFBP-3) levels. These results suggest that tesamorelin, like endogenous GRF, acts on the pituitary gland to release GH, which then induces the secretion of IGF-1 by the liver and peripheral tissues. Therefore, both GH and IGF-1 are considered effective surrogate pharmacodynamic (PD) endpoints for the pharmacological activity of tesamorelin.

2.2 Proposed Indication and US Trade Name

In large, multicenter, Phase 3 studies in HIV-infected patients with increased WC who were treated with ART, the reduction in VAT achieved by daily SC administration of 2 mg tesamorelin was both clinically and statistically significant. The least square means (LSM) reduction of VAT in the 2 studies was 16% over 26 weeks. Therefore, the proposed indication for tesamorelin is to induce and maintain a reduction of excess abdominal fat in HIV-infected patients with lipodystrophy. The US trade name of tesamorelin is *EGRIFTA*[™].

2.3 Dosage, Composition, and Administration

The recommended dose of tesamorelin acetate is 2 mg injected subcutaneously once a day, preferably in the morning. The recommended injection site is the abdomen. Injection sites should be rotated to different areas of the abdomen.

Tesamorelin is supplied in two vials containing 1.1 mg of tesamorelin each as a sterile, nonpyrogenic, lyophilized powder. The diluent (sterile water for injection) is provided in a separate vial. After reconstitution with sterile water for injection, the reconstituted solution concentration in each vial is 1 mg/mL. This solution should be injected immediately.

Tesamorelin vials should be protected from light and kept in the original 1-month box. Non-reconstituted tesamorelin must be stored at refrigerated temperature, between 2°C and 8°C (36°F and 46°F). The composition of tesamorelin dosage form is shown in **Table 2**.

Table 2. Composition of Dosage Form

| Component | Quantity (mg/vial) | Function |
|---|--------------------|----------------------------------|
| N-[trans-3-Hexenoyl]-human growth hormone-releasing factor (1-44) acetate, in-house | 1.1 | Active pharmaceutical ingredient |
| Mannitol USP | 55 mg | Bulking agent |

3 TESAMORELIN DEVELOPMENT OVERVIEW

3.1 Regulatory History

The Company discussed the development of tesamorelin with Regulatory Authorities from the US FDA on several occasions over the course of Investigational New Drug (IND) 61,226, which was submitted on October 15, 2001.

A face-to-face meeting was held with the FDA's Division of Metabolism and Endocrinology Products (Division) on March 30, 2005, to discuss the Company's plans for late-stage development of tesamorelin in HIV-associated lipodystrophy, including the pre-clinical and the Phase 3 programs that would be needed to support the proposed indication. The Division agreed with the proposed design of a Phase 3 study, the dose (2 mg) to be tested, and the measurement of VAT as the primary endpoint. The minimum difference in VAT needed to detect a clinically relevant difference between tesamorelin and placebo was considered to be 8%, according to the recommendations from a roundtable discussion organized by the Forum for Collaborative HIV Research ([Snyder 2004](#)). The Division agreed with the proposed secondary endpoints and recommended the use of a validated questionnaire developed by Phase V Technologies Inc. (Wellesley, MA, USA) to assess PRO related to body image. Demonstration of clinically meaningful improvement in body self-image using well-defined and reliable scales and indices appropriate for this population was considered to be an essential component of a new drug application (NDA) submission for this indication. The Division also encouraged the sponsor to examine whether improvements in body self-image were associated with enhanced com-

pliance with ART. The FDA recommended several approaches for determining the minimal important difference (MID), including identification of the magnitude of change in patient-reported self-image associated with a clinically meaningful reduction in VAT. According to the final version of the PRO guidance ([FDA 2009](#)), the MID is no longer recommended and instead, a responder analysis is emphasized; therefore the responder analysis is presented in this document (**Section 5.1.4.1**). The FDA also accepted the Company's proposed inclusion of glucose-intolerant patients and patients with type 2 diabetes in the Phase 3 studies provided that they were controlled by diet.

On June 14, 2006, the Company requested a Special Protocol Assessment (SPA) for their Phase 3 CTR-1011 study. In correspondence dated August 1, 2006, the FDA agreed with the Company's proposed primary and secondary endpoints and provided advice on statistical analysis issues.

In December 2007, the Company had an end-of-Phase 2 meeting with the FDA to obtain guidance on several clinical questions:

- The FDA agreed with the design of the pharmacokinetic (PK) and pharmacodynamic (PD) studies and requested drug-drug interaction studies to investigate potential CYP3A interactions with tesamorelin using a CYP3A substrate (simvastatin) and a CYP3A inhibitor (ritonavir). This advice was implemented with clinical studies CTR-1019 and CTR-1020, respectively.
- The FDA agreed that a formal QT/QTc study in humans would not be required, because *in vitro* studies and studies conducted in dogs showed no signal.
- The FDA acknowledged the Company's attempt to associate improved body self-image with enhanced compliance with ART (LIPO-010 main phase and CTR-1011), which was inconclusive, most likely because most patients were compliant with their ART throughout the study period. The FDA agreed that this would not be an obstacle to successful registration of tesamorelin.

In a pre-NDA meeting on September 19, 2008, FDA representatives agreed with the proposed indication for tesamorelin as treatment for the reduction of abdominal fat accumulation in ART-treated patients with HIV-associated lipodystrophy syndrome. Agreement was also reached that hypersensitivity reaction would be defined as follows: “A hypersensitivity reaction is a reaction that usually presents as an extended erythematous and pruritic rash on the abdomen where *EGRIFTA*[™] is injected, sometimes extending to other body parts such as chest, axillae, arms and back or associated with redness of other body parts including face, chest and hands. Occasionally large hives occur at the injection site, sometimes extending beyond the injection site and/or observed at previous injection sites, and sometimes associated with systemic symptoms.”

The NDA was submitted on May 29, 2009, and was accepted for review on August 10, 2009. The FDA encouraged the Company to develop an appropriate Risk Evaluation and Mitigation Strategy (REMS), which was submitted December 17, 2009. **(See REMS discussion below, section 8.1.5)**

3.2 Nonclinical Development

Tesamorelin was tested in a wide variety of toxicology studies, repeated-dose studies, *in vitro* and *in vivo* genotoxicity assays, reproductive toxicology studies, a local tolerance study, an immunotoxicology study, and degradant/impurity qualification studies. Overall, *in vitro* and *in vivo* non-clinical pharmacology studies have shown that tesamorelin does not behave as a prodrug and does not have higher potency or a longer duration of action compared with hGRF. Evaluations of the cardiovascular system, the respiratory system (in rats), and the central nervous system indicated no evidence of adverse effects. No significant test article-related effects were observed in these studies at SC doses of tesamorelin up to 50 mg/kg, the highest dose tested in the *in vivo* studies, or as high as 800

ng/mL, the highest concentration tested in the *in vitro* cardiovascular assay. These levels represent exposures well beyond those anticipated with the tesamorelin dose of 2 mg/day.

The PK/toxicokinetic (TK) profile of tesamorelin was evaluated primarily as part of the toxicology studies in rats and dogs. Species differences in PK were attributed to a faster rate of tesamorelin biodegradation in rat plasma compared with dog or human plasma. After SC injections, tesamorelin rapidly appeared in the circulation in both rats and dogs. Exposure was either dose proportional or less than dose proportional.

Tesamorelin was associated with low acute toxicity and was not genotoxic or mutagenic. No evidence of immunotoxicity or local irritation was found. The toxicological profile for tesamorelin-control and tesamorelin-stressed lots showed only a marginal difference in local injection-site irritation for the stressed lot. Tesamorelin produced no important developmental or reproductive toxicity in rats or rabbits, with the exception of a slightly increased incidence of litters of rats with hydrocephaly after administration of 1.2 mg/kg/day to the dams.

Anti-tesamorelin immunoglobulin G (IgG) antibodies appeared principally in rats and dogs after repeated administration. Despite this immunogenic response that resulted in a higher exposure to tesamorelin, the increase in the PD markers GH and IGF-1 overtime was not negatively affected by the presence of anti-drug antibodies and the pharmacological effects of the compound were still observed.

In the dog, tesamorelin administration over 52 weeks resulted in the development of a clinical condition sharing many of the characteristics of canine acromegaly, including morphological changes and the development of insulin resistance and/or diabetes. These findings were generally consistent with those reported after repeated administration of exogenous GH to dogs and are attributable to prolonged exposure to supraphysiological levels of IGF-1 (and/or GH). However, a no observable adverse effect level (NOAEL) was not established due to histopathological findings in the kidney (cortical tubular baso-

philia, medullary tubular dilatation, mononuclear cell infiltrate, and vacuolar degeneration in the collecting ducts), pancreas (epithelial degeneration of exocrine ducts), and gallbladder (basophilic fibrous material in the lumen and vacuolar epithelial degeneration), which could not be definitively attributed to prolonged exposure to high non-physiological levels of IGF-1 (and/or GH). The relevance of these findings in dogs is limited, as the clinical laboratory and AE results do not reveal any adverse effect of tesamorelin on hepatic, renal, or pancreatic function in human patients.

In conclusion, non-clinical studies conducted by the Company have shown that tesamorelin increases circulating GH and IGF-1 levels in rats and dogs, respectively, which are considered effective surrogate endpoints of the pharmacological activity of tesamorelin. Furthermore, the safety and toxicology studies support the safe use of tesamorelin in patients with HIV-associated lipodystrophy. These results suggest that tesamorelin, similar to natural GRF, acts on the pituitary gland to release GH, and subsequently releases IGF-1 through the somatotrophic axis.

3.3 Clinical Pharmacology

Nine clinical pharmacology studies were conducted in healthy volunteers and 1 was conducted in HIV-infected patients receiving ART (**Table 3**). Tesamorelin PK was estimated in 7 PK and 2 drug-drug interaction studies. PD evaluations (GH and/or IGF-1) were done in 6 of the studies.

Table 3. Pharmacokinetic and Pharmacodynamic Clinical Trials

| Trial Number (abbreviation) | Patients (n), Age Range | Study Objective | Study Design | Tesamorelin Dosing and Duration |
|-----------------------------|--|-----------------------------|-----------------------|---|
| Core PK Studies | | | | |
| TH9507-CTR-1017 (CTR-1017) | Healthy men (26) and women (18), 18-65 years | Bioavailability, PK, safety | R, OL, parallel group | 2 mg SC, 200 µg IV, single doses on days 1 and 14 |
| TH9507-CTR-1016 (CTR-1016) | Healthy men (24), 45-60 years | PK, PD, safety | R, OL, parallel group | 1 or 2 mg qd SC, multiple dose, 14 days |

| Trial Number (abbreviation) | Patients (n), Age Range | Study Objective | Study Design | Tesamorelin Dosing and Duration |
|--|---|--|--|---|
| TH9507-CTR-1015 (CTR-1015) | HIV-positive men (14) and women (4) receiving ART, 26-58 years | PK, PD, safety | OL | 2 mg qd, SC, multiple dose, 14 days |
| Supplemental PK Studies | | | | |
| TH9507-CTR-1013 (CTR-1013) | Healthy men (76) and women (12), 18-65 years | BE, PK, PD, safety | R, OL, crossover | 2 mg SC (formulation testing) single dose |
| TH9507-CTR-1014 (CTR-1014) | Healthy men (4) and women (8), 25-62 years | PK, safety | R, OL, crossover | 2 mg SC, single dose |
| Early PK Studies | | | | |
| TCHUV 10-98 ^a (10-98) | Healthy men (6), 21-28 years | Bioavailability, PK, PD, safety | R, placebo- controlled, par- tially double- blind, crossover | 20, 40, 100, 200, 400 µg, 1.5 mg SC, and 200 µg IV Single dose |
| TH9507/I/HV/002 ^a (HV-002) | Healthy men (39), 50-60 years | PK, PD, safety | R, placebo- controlled, par- tially double- blind, parallel- group | 0.5 mg qd or bid, 1 mg or 2 mg qd SC, multiple dose, 7 days |
| TH9507/I/PKPD/009 (PKPD-009) | Healthy elderly men (12) and women (12), 70-77 years | PD, safety (<i>PK not done due to lack of a suitable tesamorelin assay</i>) | R, OL, crossover | 2 mg qd and bid SC, multiple dose, 14 days |
| Drug-Drug Interaction Studies | | | | |
| TH9507-CTR-1019 (CTR-1019) | Healthy men (54) and women (4), 20-60 years | Drug-drug interac- tion with simvas- tatin; PK, safety | R, OL, crossover | 2 mg qd SC, multiple dose, 7 days |
| TH9507-CTR-1020 (CTR-1020) | Healthy men (24) and women (8), 19-63 years | Drug-drug interac- tion with ritonavir; PK, safety | R, OL, crossover | 2 mg qd SC, multiple dose, 7 days |

ART, antiretroviral therapy; IV, intravenous; OL, open-label; PD, pharmacodynamic; PK, pharmacokinetic; R, randomized; SC, sub-
cutaneous.

^aEarly studies in which tesamorelin plasma concentrations were measured by a non-validated radioimmunoassay method. PK data
were used for information only.

From the tesamorelin clinical pharmacology program, 3 studies (CTR-1016, CTR-1017, and CTR-1015) were considered core studies and 2 (CTR-1014 and CTR-1013) were considered supplemental. Drug interactions were evaluated in 2 studies (CTR-1019 and CTR-1020). The enzyme-linked immunosorbent assay (ELISA) used to determine plasma tesamorelin concentrations in these clinical pharmacology studies, was validated and optimized for tesamorelin detection in plasma matrices from healthy and HIV-infected patients.

3.3.1 Pharmacokinetics

The PK of tesamorelin 1 mg was evaluated in 1 of the core studies (CTR-1016) with healthy volunteers. After multiple 1-mg doses (14 days), the geometric mean (CV%) of maximum plasma concentration (C_{\max}) was 960 pg/mL (37%) and the geometric mean (CV%) of $AUC_{0-\infty}$ was 318 pg·h/mL (86%). After 14 days of dosing, C_{\max} and $AUC_{0-\infty}$ seem to increase proportionally with doses of 1 mg and 2 mg tesamorelin. **Table 4** and **Table 5** present the PK of tesamorelin 2 mg evaluated in healthy volunteers (CTR-1016) and HIV-infected patients (CTR-1015), respectively, after 14 days of daily administration.

Table 4. PK Parameters for Tesamorelin 2 mg in Healthy Volunteers (CTR-1016)

| Parameters | Unit | Multiple Dosing (14 Days) N=12 | | | |
|----------------------------|-----------------|--------------------------------|--------|-----------|-----------------|
| | | Mean (SD) | CV, % | Geo. Mean | Geo. Mean CV, % |
| AUC_{0-t}^{\dagger} | pg·h/mL | 686.32 (465.91) | 67.88 | 557.80 | 78.17 |
| $AUC_{0-\infty}^{\dagger}$ | pg·h/mL | 828.54 (611.21) | 73.77 | 665.71 | 78.63 |
| $AUC_{t/\infty}^{\dagger}$ | % | 84.35 (9.83) | 11.65 | - | - |
| C_{\max} | pg/mL | 1843.2 (615.6) | 33.40 | 1744.9 | 36.54 |
| T_{\max} | h | 0.150 (0.043) | 28.43 | - | - |
| T_{\max}^{\ddagger} | h | 0.150 (0.013) | - | - | - |
| K_{el} | h ⁻¹ | 2.9734 (1.8073) | 60.78 | - | - |
| $T_{1/2el}$ | h | 0.43 (0.42) | 98.93 | - | - |
| Cl/F^{\dagger} | L/(h·kg) | 50.29 (29.82) | 59.30 | - | - |
| V_d/F^{\dagger} | L/kg | 22.32 (22.90) | 102.58 | - | - |

AUC_{0-t} , area under the concentration-time curve at steady-state carried out to 24 hours; $AUC_{0-\infty}$, area under the concentration-time curve at steady-state from 0 to infinity; $AUC_{t/\infty}$, area under the concentration-time curve at steady-state where t is divided by infinity; Cl/F , unbound oral clearance; C_{\max} , maximum plasma concentration; CV, coefficient of variation; Geo., geometric; K_{el} , elimination rate constant; PK, pharmacokinetic; SD, standard deviation; T_{\max} , time to maximum plasma concentration; $T_{1/2el}$, apparent mean elimination half-life; V_d/F , apparent volume of distribution.

[†] N=11.

[‡] Median and interquartile ranges are also presented.

“-” = Not applicable.

Table 5. PK Parameters for Tesamorelin 2 mg in HIV-Infected Patients (CTR-1015)

| Parameter, | Unit | Multiple Dosing (14 days) N=15 | | | |
|-------------------------------|-----------------|--------------------------------|-------|-----------|-----------------|
| | | Mean (SD) | CV, % | Geo. Mean | Geo. Mean CV, % |
| AUC _{0-t} | pg·h/mL | 1117.23 (953.40) | 85.34 | 794.68 | 108.59 |
| AUC _{0-inf} | pg·h/mL | 1312.60 (1124.19) | 85.65 | 940.40 | 104.73 |
| AUC _{t/inf} | % | 84.73 (6.39) | 7.54 | - | - |
| C _{max} | pg/mL | 2333.3 (1185.0) | 50.78 | 2013.2 | 66.52 |
| T _{max} | h | 0.157 (0.042) | 26.61 | - | - |
| T _{max} [*] | h | 0.150 (0.025) | - | - | - |
| K _{el} | h ⁻¹ | 2.5071 (1.9692) | 78.54 | - | - |
| T _{1/2el} | h | 0.63 (0.61) | 96.54 | - | - |
| Cl/F | L/(h·kg) | 40.97 (31.15) | 76.04 | - | - |
| V _d /F | L/kg | 20.19 (9.87) | 48.90 | - | - |

AUC_{0-t}, area under the concentration-time curve at steady-state carried out to 24 hours; AUC_{0-inf}, area under the concentration-time curve at steady-state from 0 to infinity; AUC_{t/inf}, area under the concentration-time curve at steady-state where t is divided by infinity; Cl/F, unbound oral clearance; C_{max}, maximum plasma concentration; CV, coefficient of variation; Geo., geometric; K_{el}, elimination rate constant; PK, pharmacokinetic; SD, standard deviation; T_{max}, time to maximum plasma concentration; T_{1/2el}, apparent mean elimination half-life; V_d/F, apparent volume of distribution.

* Median and interquartile ranges are also presented.

“-” = Not applicable.

After repeated dosing of 2 mg tesamorelin for 14 days, C_{max} was achieved at mean times to maximum plasma concentration (T_{max}) of 0.15 hours in healthy volunteers (CTR-1016) and 0.16 hours in HIV-infected patients (CTR-1015). The apparent mean terminal elimination (T_{1/2el}) after repeated 2-mg doses was 26 minutes in healthy participants and 38 minutes in HIV-infected patients. Overall, estimates of the apparent T_{1/2el} phase were highly variable. These differences did not have a clinical effect based on the sustained effect of tesamorelin on IGF-1 and GH observed in Phase 1, 2, and 3 studies.

On the basis of the dose-adjusted AUC ratios after SC and intravenous (IV) administration (CTR-1017), the absolute bioavailability of tesamorelin was estimated to be less than 4%. A similarly low bioavailability (~6%) was estimated in the 10-98 study.

In summary, tesamorelin PK may be characterized as rapid with a low bioavailability and high variability among individuals, and it does not appear to differ between healthy volunteers and HIV-infected patients receiving ART.

In drug-drug interaction studies (CTR-1019 and CTR-1020), tesamorelin was co-administered with simvastatin (a CYP3A-substrate) or ritonavir (a CYP3A-inhibitor). Overall results showed that the effect of tesamorelin on CYP3A activity appears to be minimal, indicating that these drugs may be co-administered with tesamorelin without a change in their dosing regimen.

3.3.2 Pharmacodynamics

GH and/or IGF-1 response was measured in healthy participants and HIV-infected patients in 6 Phase 1 clinical studies (**Table 3**). In healthy participants (CTR-1016), the GH responses to multiple tesamorelin 2-mg doses (14 days) were a geometric mean (CV%) maximum effects (E_{\max}) of 13.2 ng/mL (52%), and a geometric mean (CV%) for the area under the effect curve (AUEC) of 29.3 ng•h/mL (60%). GH responses to tesamorelin 1 mg were a geometric mean (CV%) for E_{\max} of 8.0 pg/mL (56%), and a geometric mean (CV%) for AUEC values of 14.5 ng•h/mL (56%). GH (E_{\max}) was achieved at mean times to maximum effect ($T_{E_{\max}}$) of 0.42 and 0.61 hour after 14 days of 1 mg and 2 mg tesamorelin daily administration (CTR-1016), respectively. Similar PD results were obtained in healthy elderly participants (PKPD-009) treated with tesamorelin 2 mg once daily for 14 days. After multiple tesamorelin doses (14 days), E_{\max} and AUEC values were generally proportional to the dose of 1 mg versus 2 mg.

In HIV-infected patients receiving ART (CTR-1015), 2 mg/day tesamorelin increased IGF-1 levels by approximately 121% from baseline to 14 days. In healthy participants (CTR-1016), 2 mg/day tesamorelin increased IGF-1 levels by approximately 115% from baseline to 14 days. In both HIV-infected and healthy individuals, the greatest increase occurred over the first 7 days of treatment, and a lesser but still statistically significant increase occurred between Days 7 and 14.

In healthy elderly participants (PKPD-009), mean changes from baseline in IGF-1 levels were 121 and 182 ng/mL for those receiving tesamorelin 2 mg qd and 2 mg bid, respectively. In the early, HV-002 study, doses of tesamorelin 0.5 mg qd, 0.5 mg bid, 1 mg qd, and 2 mg qd increased IGF-1 levels by 37%, 104%, 89%, and 107%, respectively, over 7 days.

In the Phase 2 12-week studies in HIV-infected patients (LIPO-008) and patients with type 2 diabetes (DIABETIC-006), IGF-1 increased in a dose-dependent manner, with greater increases in the groups that received tesamorelin 2 mg vs the groups that received tesamorelin 1 mg. In the LIPO-008 study, IGF-1 levels increased by 59% and 80% in the 1- and 2-mg groups, respectively. In the DIABETIC-006 study, IGF-1 levels increased by 32% and 60% in the 1- and 2-mg groups, respectively.

3.4 Dosing Rationale

The Company considered that a daily dose of 2 mg tesamorelin was optimal for the Phase 3 clinical program in HIV-infected patients with excess abdominal fat. The main objective of the dose selection program was to determine the maximum dose of tesamorelin that could be administered, while keeping IGF-1 levels comparable to those measured in young adults and limiting the potential impact on glucose parameters.

The 2-mg dose was selected for the following reasons:

- The results from a Phase 1 study in healthy elderly subjects (PKPD-009) suggested that increasing the dose of tesamorelin above 2 mg qd could result in increased incidence of AEs.
- Clinical pharmacology data showed that daily administration of 2 mg tesamorelin was associated with an increase in IGF-1 levels, an integrated measure of GH and a surrogate endpoint of the biological activity of tesamorelin, comparable to the levels measured in young adults.

- In Phase 2 studies, including the study in HIV-infected patients with lipodystrophy, the 2-mg dose had a consistently superior effect on IGF-1 level, when compared with the 1-mg dose, and was overall well tolerated.
- The 2-mg dose was efficacious in reducing VAT and trunk fat in the target population and had a superior effect when compared with the 1-mg dose.
- Finally, the 2-mg daily dose did not affect glucose parameters when administered to type 2 diabetic patients for a period of 3 months.

Further supporting the selection of the 2-mg dose are the results of Study CTR-1016, a Phase 1, single-center, randomized, OL, multiple-dose study evaluating the PK and PD profiles of tesamorelin 1 and 2 mg, administered by SC injection after single and repeated administration once daily for 14 consecutive days in healthy subjects (mean age 52±5 years). The results from this study showed that GH production, as expressed in terms of AUEC, was approximately 68% higher after administration of tesamorelin 2 mg compared with tesamorelin 1 mg ($p=0.028$). Furthermore, on Day 14, baseline-adjusted IGF-1 production was approximately 40% greater for the tesamorelin 2-mg dose when compared with the tesamorelin 1-mg dose (145 ± 64 ng/mL vs 200 ± 66 ng/mL for 1 mg vs 2 mg, $p=0.029$).

3.5 Overview of Clinical Studies

The efficacy and safety of tesamorelin were investigated in various conditions in the Phase 2 program (**Table 6**) in double-blind, placebo-controlled, parallel-group studies. The conditions studied were those known to be affected by alterations in the GH/IGF-1 axis. In addition, potential adverse effects of special interest, such as glucose metabolism and IGF-1 levels, were assessed.

Table 6. Phase 2 Safety and Efficacy Studies^a

| Study Name (abbrev) | Subjects (n), Age Range | Kind of Study | Tesamorelin Dosage and Treatment Duration |
|---------------------------------------|---|------------------|---|
| TH9507/II/SLEEP/002 (SLEEP-002) | Healthy men with sleep disturbances (12), 51-63 years | Safety, efficacy | 0.1 or 1 mg/day, 7 days |
| TH9507/II/SLEEP/005 (SLEEP-005) | Healthy men (62) and women (20) with sleep maintenance insomnia, 34-60 years | Safety, efficacy | 0.1 or 1 mg/day, 14 days |
| TH9507/II/IR/007 (IR-007) | Elderly men (47) and women (40) who received influenza vaccination, 64-95 years | Safety, efficacy | 1 or 2 mg/day, 8 weeks |
| TH9507/II/COPD/003 (COPD-003) | Men (87) and women (22) with chronic obstructive pulmonary disease, 46-84 years | Safety, efficacy | 1 or 2 mg/day, 3 months |
| TH9507/II/HF/004 (HF-004) | Elderly men (23) and women (104) recovering from hip surgery, 69-98 years | Safety, efficacy | 2 mg/day, 8 weeks |
| TH9507/II/DIABETIC/006 (DIABETIC-006) | Men (35) and women (18) with type 2 diabetes, 50-79 years | Safety | 1 or 2 mg/day, 12 weeks |
| TH9507/II/LIPO/008 (LIPO-008) | HIV-infected men (54) and women (7) with excess abdominal fat, 32-60 years | Efficacy, safety | 1 or 2 mg/day, 12 weeks |

^a Randomized, double-blind, parallel-group, placebo-controlled studies.

The DIABETIC-006 study was a safety study to assess the effects of tesamorelin 1 mg and 2 mg on glycemic parameters in individuals with type 2 diabetes. The lack of an effect on glycemic indices in this study served as the rationale for including HIV-infected patients with lipodystrophy and IGT or diet-controlled diabetes in the Phase 2 study LIPO-008. LIPO-008 was a 12-week, multicenter study (in the United States and Canada) that compared tesamorelin 1 mg and 2 mg and placebo. In this study, tesamorelin significantly decreased VAT, trunk fat, and triglycerides while preserving abdominal SC fat and limb fat. These data are consistent with the effects of GRF (GHRH[1-29]) on HIV-infected patients reported by [Koutkia et al \(2004\)](#). With regards to safety, tesamorelin 2 mg did not adversely affect glucose homeostasis in the HIV-infected patients in LIPO-008, including those with IGT or diet-controlled type 2 diabetes.

The results from the Phase 2 program were the rationale for initiating a Phase 3 program to assess the efficacy and safety of daily SC tesamorelin 2 mg in patients with HIV-

associated lipodystrophy. This program included 2 multicenter, randomized, double-blind, parallel-group, placebo-controlled Phase 3 studies.

- Study LIPO-010, a 26-week main phase study (LIPO-010 main) that compared 2 mg tesamorelin with placebo with a 26-week extension (LIPO-010 extension) conducted in 37 sites in the United States and 6 sites in Canada
- Study CTR-1011, a repeat of the main phase of LIPO-010, conducted in 26 sites in the United States, 9 sites in Canada, and 13 sites in Europe (United Kingdom, France, Spain, Belgium), with a 26-week extension, study CTR-1012, which had a separate protocol (repeat of LIPO-010 extension phase)

The objective of the extension phases was to assess long-term safety and examine the duration of effects of tesamorelin 2 mg. In the extension phase studies, patients who received tesamorelin 2 mg in the main phase were re-randomized to tesamorelin 2 mg or placebo and the group that received placebo was switched to tesamorelin 2 mg.

The primary endpoint in these studies was percent change in VAT as assessed by CT scanning. According to the recommendations of the roundtable discussion organized by the Forum for Collaborative HIV Research ([Snyder 2004](#)), a minimum difference of 8% was needed to detect a clinically relevant difference between tesamorelin and placebo. These recommendations indicated that safety evaluations should demonstrate no worsening of peripheral lipoatrophy, percentage of lean body tissue, and metabolic outcomes (e.g., no worsening of baseline glucose). Additional safety assessments were to include the means and distribution of the IGF-1 response SDS, with an SDS value greater than +2 considered to be potentially undesirable. Secondary efficacy endpoints were chosen to address the associated metabolic and clinical consequences of lipodystrophy and included changes in lipids, IGF-1, and PRO related to body image. PRO related to body image were assessed with well-defined and reliable scales and indices appropriate for this population that were recommended by the FDA and developed by Phase V Technologies Inc. The scales and indices, that were originally validated in the HIV-infected patients with

abdominal lipohypertrophy enrolled in studies of rhGH (Serostim[®] [somatotropin]), are included in **Appendix I**.

4 CLINICAL DEVELOPMENT PROGRAM IN LIPODYSTROPHY

4.1 Endpoints

The primary efficacy endpoint of the 2 main phase studies (LIPO-010 main and CTR-1011) of tesamorelin 2 mg in HIV-infected patients with excess abdominal fat accumulation was percent change in VAT after 26 weeks. The sustainability of this endpoint was assessed in 26-week extensions in 2 studies (LIPO-010 extension and CTR-1012, respectively). Secondary efficacy endpoints included IGF-1, a surrogate marker for biological activity of GH, triglycerides, total cholesterol-to-HDL-C ratio, and PRO related to body image.

Safety endpoints included AEs, glycemic parameters (FBG, insulin, and 2-hour OGTT test), immunogenicity, and safety laboratory assessments.

4.2 Measurements and Analyses

VAT was measured by CT scanning from a single 5-mm slice obtained between L4 and L5. This measurement is closely associated with visceral fat volume ([Kobayashi 2002](#)). LBM and fat volume in the trunk and limbs were measured using total-body dual-energy x-ray absorptiometry. Standard laboratory methods were used to assess blood parameters. A validated questionnaire (Phase V Technologies) was used to measure self-perceived body image (**see Appendix I**).

The statistical methods for both Phase 3 studies were comparable. See **Appendix II** for further details. Endpoints analyzed for the individual Phase 3 studies were also analyzed

for the combined studies using similar methods. Statistical tests were 2-sided, using $\alpha=0.05$, and interactions were tested at $\alpha=0.10$. The statistical power was based on the ability to detect a clinically meaningful difference of 8% between tesamorelin and placebo for VAT, as agreed upon with the FDA (see **Section 3.1**). The intent-to-treat (ITT) populations included all randomized patients who received at least 1 dose of study drug during the period of assessment and the last observation was carried forward for patients who did not complete the study. If a patient had no post-baseline value, his baseline was carried forward for all post-baseline evaluations in the main study. In the case that no post-Week 26 measurements were taken during the extension study, Week 26 was not carried forward during the extension, but baseline from the main study was carried forward. Analyses of the per-protocol (PP) population, which included all patients who received at least 1 dose of study drug and who had no major protocol violations and had at least 1 post-baseline VAT assessment, were done as secondary supportive analyses and are not reported in this document.

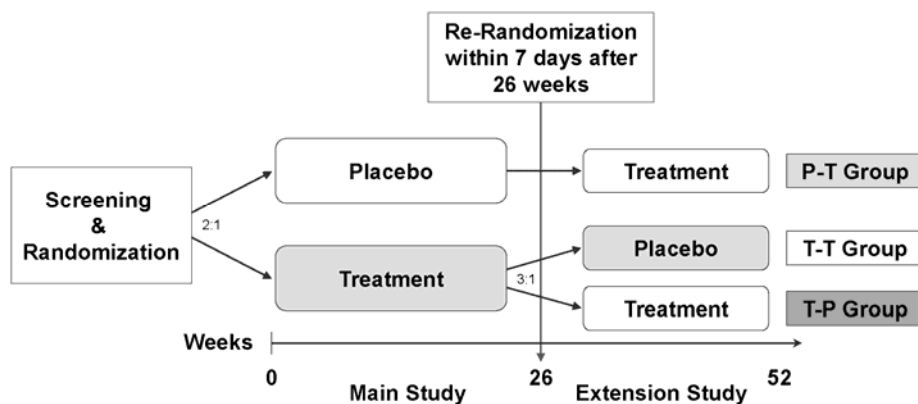
For both the main study and the extension study, analyses of covariance were used to test for treatment effects.

4.3 Study Design and Objectives

The Phase 3 main and extension phase studies (LIPO-010, CTR-1011, and CTR-1012) were randomized, double-blind, parallel-group, placebo-controlled studies. These studies were similarly designed; the main difference was in the randomization schedules for LIPO-010 extension and CTR-1012 (**Figures 8A and 8B**).

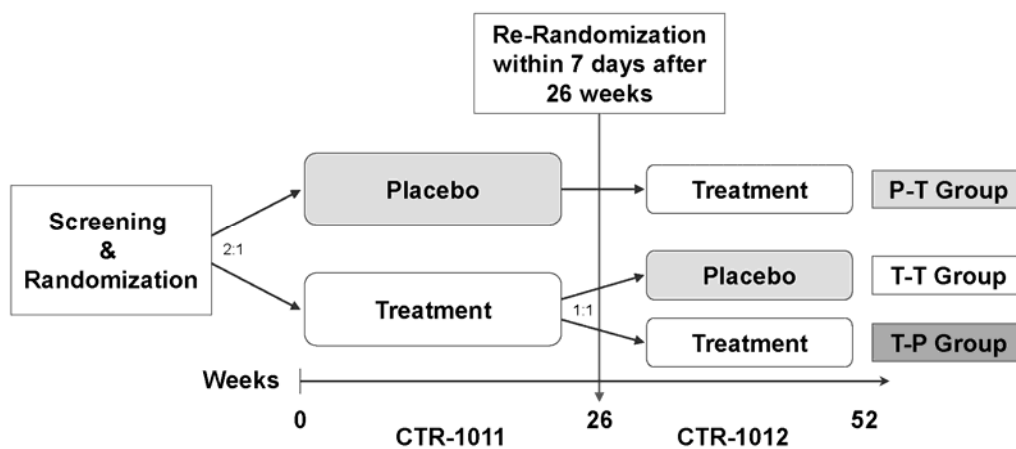
Figure 8. Phase 3 Study Designs

A. LIPO-010 (Main and Extension)



First patient: June 2005
 - 37 US sites
 - 6 Canadian sites

B. CTR-1011 and CTR-1012



First patient: February 2007
 - 26 US sites
 - 9 Canadian sites
 - 13 EU sites

4.3.1 LIPO-010 main and CTR-1011

In the main phase studies (LIPO-010 main and CTR-1011), patients were randomized in a 2:1 ratio (active-to-placebo) to receive either 2 mg tesamorelin or placebo daily by SC injection for 26 weeks. A total of 381 patients were planned for enrollment into the main phase of LIPO-010, and 400 patients were planned for enrollment into CTR-1011.

The major entry criteria for both main phase 26-week studies were men and women 18 to 65 years of age with HIV infection (CD4 cell counts >100 cells/mm³ and viral load $<10,000$ copies/mL within 8 weeks before randomization); stable ART for ≥ 8 weeks; abdominal fat accumulation in the context of treatment of HIV disease as indicated by a WC ≥ 95 cm and a waist-to-hip ratio ≥ 0.94 in men and a WC ≥ 94 cm and a waist-to-hip ratio ≥ 0.88 in women. FBG had to be ≤ 150 mg/dL (≤ 8.33 mmol/L). Patients with IGT and some patients with diet-controlled type 2 diabetes were included in the Phase 3 studies. Stable therapy with lipid-lowering medications (i.e., no changes within 3 months prior randomization) and physiological doses of testosterone were allowed. Exclusion criteria included BMI ≤ 20 kg/m², use of antidiabetic and insulin-sensitizing agents, and use of GH or GH agonists.

4.3.2 LIPO-010 extension and CTR-1012

LIPO-010 patients who received tesamorelin in the main phase of LIPO-010 were randomized in a 3:1 (active-to-placebo) ratio to receive tesamorelin or placebo in the extension phase, and those who received placebo in the main phase were switched to tesamorelin. CTR-1011 patients who received tesamorelin were randomized in a 1:1 ratio to receive tesamorelin or placebo in study CTR-1012, and patients who received placebo were switched to tesamorelin.

The objectives of the extension phase studies were to assess long-term safety and examine the duration of effects of tesamorelin assessed in the main phase studies. Eligibility

criteria for entry into the extension phases were completion of 26 weeks of treatment in the main phases and FBG ≤ 150 mg/dL (≤ 8.33 mmol/L).

4.3.3 LIPO-008 (supportive)

LIPO-008 was a 12-week, multicenter (7 sites in the United States and Canada), randomized, double-blind, parallel-group, placebo-controlled Phase 2 study. Sixty-one (61) patients were randomized to receive placebo (n=21), tesamorelin 1 mg/day SC (n=19), or tesamorelin 2 mg/day SC (n=21).

The principal inclusion criteria were men and women 18 to 65 years of age, HIV-associated lipodystrophy as assessed by a WC ≥ 95 cm and a waist-to-hip ratio ≥ 0.94 in men and a WC ≥ 94 cm and a waist-to-hip ratio ≥ 0.88 in women; stable highly active ART for ≥ 8 weeks; cluster of differentiation 4 (CD4) cell count > 100 cells/mm³; viral load $< 10,000$ copies/mL; and BMI > 20 kg/m².

The primary objective was to evaluate the reduction in VAT and the change in trunk-to-limb fat ratio at 6 and 12 weeks after treatment with tesamorelin 1 mg and 2 mg. Secondary objectives were to assess the effects of tesamorelin 1 mg and 2 mg on total cholesterol, HDL-C, the total cholesterol-to-HDL-C ratio, non-HDL-C, triglycerides, trunk fat, LBM, waist-to-hip ratio, IGF-1, and IGFBP-3 at baseline, Week 6, and Week 12. The waist-to-hip ratio had an additional assessment at Week 2.

5 CLINICAL EFFICACY IN HIV-INFECTED PATIENTS

The efficacy of tesamorelin 2 mg/day administered SC in patients with HIV infection and excess abdominal fat was assessed in 2 multicenter, randomized, double-blind, parallel-group, placebo-controlled Phase 3 studies, each consisting of 26-week main phases (LIPO-010 main and CTR-1011) followed by 26-week extensions to assess long-term

safety and duration of effects (LIPO-010 extension and CTR-1012, respectively). Tesamorelin efficacy and appropriate dosing in the same patient population were also studied in a multicenter, randomized, double-blind, placebo-controlled, 12-week Phase 2 study (LIPO-008).

5.1 Main Phase Studies (LIPO-010 Main, CTR-1011)

5.1.1 Patient disposition

Table 7 shows the disposition of patients in LIPO-010 main phase and CTR-1011, the 2 Phase 3 pivotal studies. In the ITT population, 76% in the tesamorelin group and 79% in the placebo group completed the first 26 weeks of treatment. The main reasons for early study discontinuation were AEs and withdrawal of consent. The overall early discontinuation rate was slightly higher in CTR-1011 (26%) than in LIPO-010 main (21%). The difference was mostly due to a higher discontinuation rate among placebo patients in CTR-1011 (27% vs 16% in LIPO-010). In LIPO-010 main, more tesamorelin-treated patients than placebo-treated patients discontinued due to AEs and lack of compliance. No notable differences between treatment groups for the primary reasons for early study discontinuation were observed in CTR-1011.

Table 7. Patient Disposition (Main Phase, ITT Population)

| | LIPO-010 | | CTR-1011 | | COMBINED | |
|---|----------------------------------|------------------|----------------------------------|------------------|----------------------------------|------------------|
| | Tesamorelin 2 mg/day N=273 | Placebo N=137 | Tesamorelin 2 mg/day N=270 | Placebo N=126 | Tesamorelin 2 mg/day N=543 | Placebo N=263 |
| Patient disposition, n (%) | | | | | | |
| Randomized population, N | 275 | 137 | 275 | 129 | 550 | 266 |
| ITT population ^{a, c} | 273 (99.3) | 137 (100.00) | 270 (98.2) | 126 (97.7) | 543 (98.7) | 263 (98.9) |
| PP population ^a | 208 (75.6) | 105 (76.6) | 194 (70.5) | 92 (71.3) | 402 (73.1) | 197 (74.1) |
| Patients who completed main phase^b (first 6 months) | | | | | | |
| Yes | 211 (77.3) | 115 (83.9) | 202 (74.8) | 92 (73.0) | 413 (76.1) | 207 (78.7) |
| No | 62 (22.7) | 22 (16.1) | 68 (25.2) | 34 (27.0) | 130 (23.9) | 56 (21.3) |

ITT, intent-to-treat; PP, per protocol.

^a Percentages based on number of randomized patients.

^b Percentages based on number of patients in ITT population.

^c Patients excluded from the ITT population did not receive any doses of study medication.

5.1.2 Baseline characteristics

Baseline demographic and lipodystrophy syndrome–related characteristics were not significantly different between groups, with the exception of differences between groups in LIPO-010 main for the type and duration of ART therapy, as well as type of ART therapy in the combined results (**Table 8**). The mean age of the patients was approximately 48 years, and most of the patients were men and white/Caucasian. About half of the patients in both groups reported taking an NRTI and a PI. However, more tesamorelin-treated patients reported taking an NRTI and an NNRTI with no PI than placebo-treated patients. Most patients (approximately 86%, combined results) showed signs of a buffalo hump, breast enlargement, or general lipodystrophy. Abdominal lipohypertrophy was present in all patients in both groups.

The mean baseline anthropometric values were nearly identical for the combined tesamorelin and placebo groups. Mean body weight was 89 kg, mean BMI was 29 kg/m², mean WC was 105 cm, mean hip circumference was 100 cm, and mean waist-to-hip ratio was 1.

The mean baseline CD4 numbers (T helper lymphocyte counts) were 603 and 592 cells/mm³ in the tesamorelin and placebo groups, respectively. The cluster of differentiation 8 (CD8) numbers (T suppressor lymphocyte counts) were 956 and 979 cells/mm³, respectively. Viral loads (HIV-1 RNA levels) were undetectable in most of the patients (75% and 78% in the tesamorelin and placebo groups, respectively).

Table 8. Patient Demographics and Disease Characteristics at Baseline (Main, ITT Population)

| Characteristic | LIPO-010 | | CTR-1011 | | COMBINED | |
|---|----------------------------------|------------------|----------------------------------|------------------|----------------------------------|------------------|
| | Tesamorelin 2 mg/day N=273 | Placebo N=137 | Tesamorelin 2 mg/day N=270 | Placebo N=126 | Tesamorelin 2 mg/day N=543 | Placebo N=263 |
| 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) |
| Median | 46.0 | 48.0 | 47.0 | 47.0 | 47.0 | 48.0 |
| Range | 28–65 | 31–65 | 27–65 | 28–65 | 27–65 | 28–65 |
| Gender, n (%) | | | | | | |
| Men | 237 (86.8) | 115 (83.9) | 228 (84.4) | 105 (83.3) | 465 (85.6) | 220 (83.7) |
| Women | 36 (13.2) | 22 (16.1) | 42 (15.6) | 21 (16.7) | 78 (14.4) | 43 (16.3) |
| Ethnic origin, n (%) | | | | | | |
| White/Caucasian | 209 (76.6) | 99 (72.3) | 209 (77.4) | 96 (76.2) | 418 (77.0) | 195 (74.1) |
| Asian | 2 (0.7) | 0 | 1 (0.4) | 2 (1.6) | 3 (0.6) | 2 (0.8) |
| Black/African-American | 37 (13.6) | 22 (16.1) | 34 (12.6) | 12 (9.5) | 71 (13.1) | 34 (12.9) |
| Hispanic | 21 (7.7) | 13 (9.5) | 23 (8.5) | 12 (9.5) | 44 (8.1) | 25 (9.5) |
| Other | 4 (1.5) | 3 (2.2) | 3 (1.1) | 4 (3.2) | 7 (1.3) | 7 (2.7) |
| Duration of ART, months* | n=272 | n=136 | n=270 | n=126 | n=542 | n=262 |
| 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) |
| Median | 49.4 | 43.4 | 43.0 | 45.5 | 45.9 | 43.7 |
| Range | 6–231 | 5–154 | 4–179 | 4–146 | 4–231 | 4–154 |
| Type of ART regimen, n (%)† | | | | | | |
| NRTI and NNRTI (with no PI) | 111 (40.7) | 37 (27.0) | 79 (29.3) | 39 (31.0) | 190 (35.0) | 76 (28.9) |
| NRTI, NNRTI, and PI | 30 (11.0) | 19 (13.9) | 25 (9.3) | 5 (4.0) | 55 (10.1) | 24 (9.1) |
| NRTI and PI (with no NNRTI) | 114 (41.8) | 66 (48.2) | 125 (46.3) | 61 (48.4) | 239 (44.0) | 127 (48.3) |
| NRTI alone | 11 (4.0) | 12 (8.8) | 13 (4.8) | 4 (3.2) | 24 (4.4) | 16 (6.1) |
| Other | 7 (2.6) | 3 (2.2) | 28 (10.4) | 17 (13.5) | 35 (6.4) | 20 (7.6) |
| Time since lipodystrophy syndrome diagnosis, months | n=261 | n=135 | n=261 | n=123 | n=522 | n=258 |
| 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) |
| Median | 45.2 | 47.4 | 59.8 | 66.3 | 50.7 | 55.0 |
| Range | 0–223 | 0–192 | –5–211 | 1–259 | –5–223 | 0–259 |
| Lipodystrophy syndrome clinical assessment, n (%) | | | | | | |
| Facial lipoatrophy | 141 (51.6) | 70 (51.1) | 123 (45.6) | 56 (44.4) | 264 (48.6) | 126 (47.9) |
| Lower limbs lipoatrophy | 165 (60.4) | 81 (59.1) | 148 (54.8) | 72 (57.1) | 313 (57.6) | 153 (58.2) |
| Upper limbs lipoatrophy | 140 (51.3) | 58 (42.3) | 117 (43.3) | 57 (45.2) | 257 (47.3) | 115 (43.7) |
| General lipoatrophy ^a | 198 (72.5) | 99 (72.3) | 181 (67.0) | 83 (65.9) | 379 (69.8) | 182 (69.2) |
| Buffalo hump | 116 (42.5) | 63 (46.0) | 93 (34.4) | 44 (34.9) | 209 (38.5) | 107 (40.7) |
| Abdominal lipohypertrophy | 273 (100) | 137 (100) | 270 (100) | 126 (100) | 543 (100) | 263 (100) |
| Breast enlargement | 111 (40.7) | 60 (43.8) | 105 (38.9) | 39 (31.0) | 216 (39.8) | 99 (37.6) |
| Subjects with ≥1 of the following signs: general lipoatrophy, buffalo hump, or breast enlargement | 242 (88.6) | 125 (91.2) | 222 (82.2) | 101 (80.2) | 464 (85.5) | 226 (85.9) |

ART, antiretroviral therapy; ITT, intent-to-treat; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; SD, standard deviation.

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

* $p=0.027$ for treatment group difference in LIPO-010 (1-factor [treatment group] Analysis of variance (ANOVA)).

† $p=0.038$ for treatment group difference in LIPO-010 (Fisher's exact test); $p=0.032$ for treatment group difference in combined results (generalized linear model [specifying the distribution of the dependent variable as multinomial] with treatment group and study in the model); $p=0.042/0.188$ for treatment group difference in combined results (generalized linear model [specifying the distribution of the dependent variable as multinomial] with treatment group, study, and treatment group-by-study in the model. Treatment group/study-by-treatment group p -values.)

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

5.1.3 Primary endpoint: change in VAT

The primary efficacy endpoint was the percent change from baseline to Week 26 in VAT in the ITT population using the last observation carried forward (LOCF) analysis. Differences between treatments were significant ($p<0.001$) in both the individual studies and the combined studies (**Table 9 and Figure 9**). By 13 weeks of treatment, mean percent change in VAT was significantly greater ($p<0.001$) in the tesamorelin group (10.3%) than in the placebo group (1.4%). After 26 weeks, VAT had decreased by 13.1% (least-squares mean [LSM] -15.9%) compared with an increase of 2.3% (LSM 0.1%) in the placebo group ($p<0.001$). The effect size and 95% CI at Week 26 were -15.96% (-19.01;-12.80). Results were generally consistent in the individual studies. However, a smaller mean change was observed in the tesamorelin group in CTR-1011.

Table 9. VAT: Actual and Percent Change from Baseline to Week 26 (Main, ITT Population)

| Visit | LIPO-010 | | | | | | CTR-1011 | | | | | | COMBINED | | | | | |
|-------------------------------|----------------------------------|--------------------|------------------|------------------|--------------------|------------------|----------------------------------|--------------------|------------------|------------------|---------------------|------------------|----------------------------------|--------------------|------------------|------------------|--------------------|------------------|
| | Tesamorelin 2 mg/day N=273 | | | Placebo N=137 | | | Tesamorelin 2 mg/day N=270 | | | Placebo N=126 | | | Tesamorelin 2 mg/day N=543 | | | Placebo N=263 | | |
| | n | Mean (SD) | LSM ^a | n | Mean (SD) | LSM ^a | n | Mean (SD) | LSM ^a | n | Mean (SD) | LSM ^a | n | Mean (SD) | LSM ^a | n | Mean (SD) | LSM ^a |
| Baseline VAT, cm ² | 272 | 178.29 (76.942) | — | 136 | 170.96 (76.916) | — | 268 | 186.49 (86.555) | — | 126 | 194.94 (95.450) | — | 540 | 182.36 (81.881) | — | 262 | 182.49 (86.992) | — |
| Week 26 VAT, cm ² | 272 | 150.54 (74.070) | — | 136 | 176.00 (81.698) | — | 268 | 165.71 (87.010) | — | 126 | 194.12 (100.166) | — | 540 | 158.07 (81.033) | — | 262 | 184.71 (91.322) | — |
| % change | 272 | -15.13 (20.844) | -17.82 | 136 | 5.00 (23.434) | 2.23 | 268 | -11.06 (21.278) | -13.84 | 126 | -0.62 (18.904) | -2.39 | 540 | -13.11 (21.139) | -15.89 | 262 | 2.30 (21.520) | 0.08 |
| p-value ^b | <0.001 | | | | | | <0.001 | | | | | | <0.001 | | | | | |

ITT, intent-to-treat; LSM, least-squares mean; SD, standard deviation; VAT, visceral adipose tissue.

^aLSM is the exponentiation of the LSM from the statistical model minus 1, expressed as a percentage: $LSM = (\exp[LSM \text{ from model}] - 1) \times 100$.

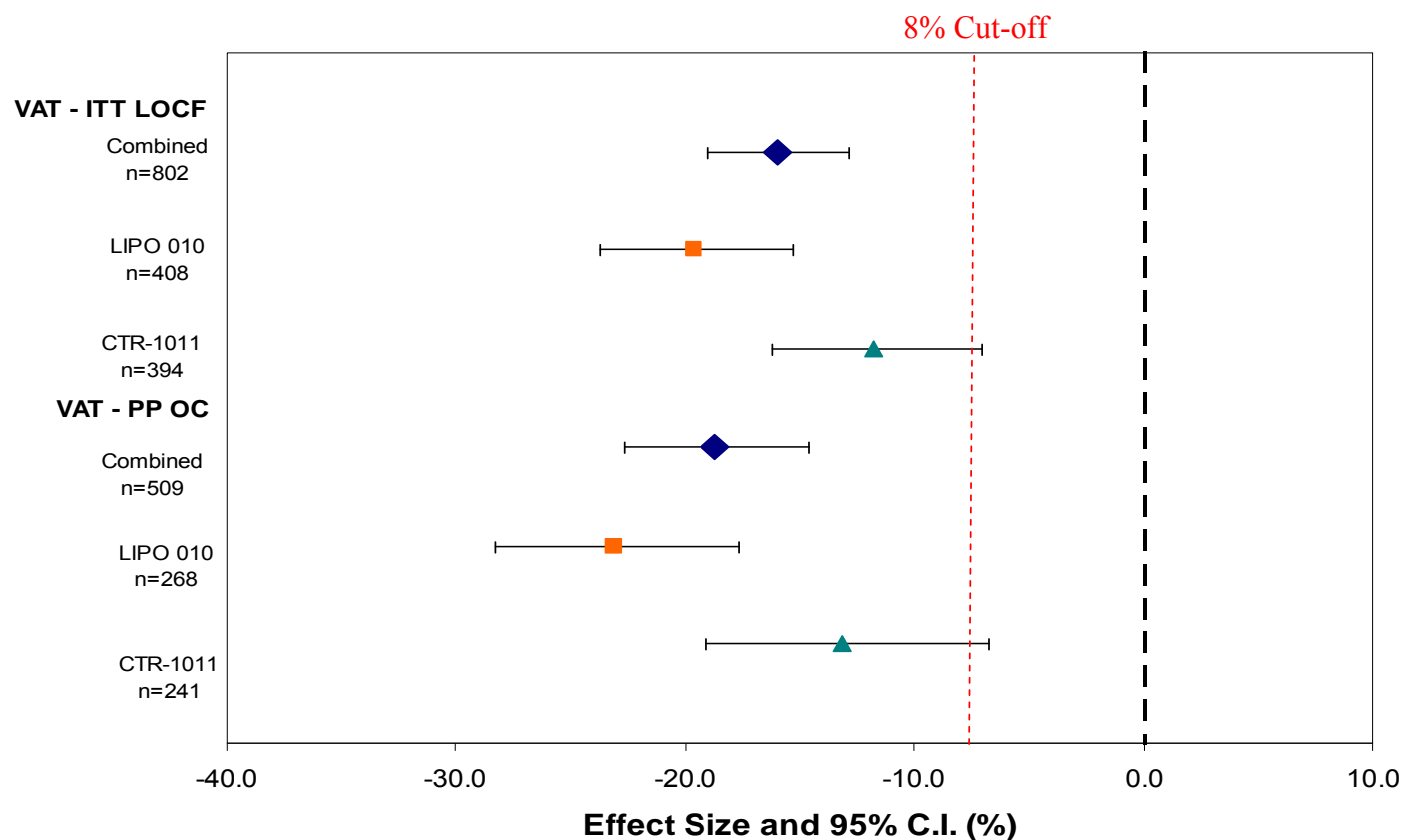
^bp-values are for treatment group difference. For the individual studies, the ANCOVA model is $\log(\text{VAT at baseline}) + \text{treatment}$. For the combined studies, ANCOVA model is $\log(\text{VAT at baseline}) + \text{study} + \text{treatment}$.

Consistency between Intent-to-Treat (ITT) and Per protocol analyses (PP)

A PP population was defined for each study before data unblinding, and analyses using PP patient data were done as supportive analyses. The PP population included all randomized patients who have been exposed to study medication (at least one dose), had at least one post-baseline assessment for the primary efficacy variable VAT and had no major protocol violations.

Figure 8 demonstrated consistent results between the ITT analysis using LOCF imputation for missing observations and the PP analysis using observed case (OC) (i.e., no imputation for missing observations).

Figure 9. Forest Plot of the Effect Size and 95% CI of the Percent Change from Baseline in VAT at Week 26

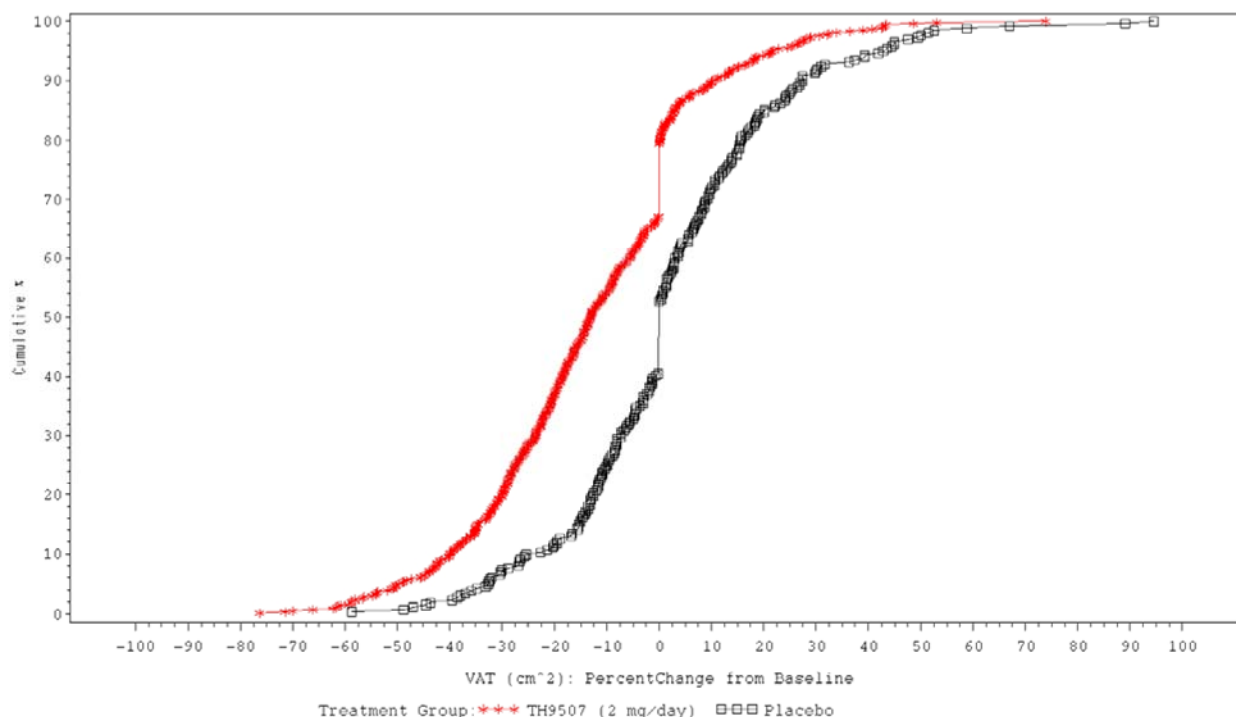


CI, confidence interval; ITT – LOCF, intent-to-treat last observation carried forward; PP – OC, per protocol – observed case; VAT, visceral adipose tissue.

In the ITT population using LOCF analysis, 57.4% of patients in the tesamorelin group vs. 29.3% of patients in the placebo group were responders, i.e., lost at least 8% of their baseline VAT, at Week 26 of treatment ($p < 0.001$ for tesamorelin vs. placebo). In the PP population-Observed Case (OC) analysis, the proportion of VAT responders at Week 26 was 68.8% and 32.6% in the tesamorelin and placebo groups, respectively ($p < 0.001$).

The cumulative distribution function (**Figure 10**) of the individual changes in VAT from baseline to Week 26 showed that a higher proportion of patients in the tesamorelin group than in the placebo group had a decrease in VAT.

Figure 10. Cumulative Distribution Function of the Percent Change in VAT by Treatment Group at Week 26 (Main, ITT Population)



ITT, intent-to-treat; VAT, visceral adipose tissue.

5.1.4 Secondary endpoints and other parameters

5.1.4.1 Patient-reported outcomes

The results for “belly appearance distress,” belly size”, and patient- and physician-rated “belly profile” are detailed in **Table 10**. At baseline, patients in both the tesamorelin and placebo groups reported considerable distress related to their belly appearance. Mean scores were both 22.1 for the tesamorelin and placebo groups, indicating feelings about current belly appearance ranged between “*Quite Upsetting and Distressing*” and “*Very Upsetting and Distressing*.” For patient-rated belly profile, patients in both the tesamorelin and placebo groups selected dysmorphic body profiles at baseline, with mean scores of 3.3. Mean baseline physician ratings of belly profile for the tesamorelin and placebo groups were the same, in the dysmorphic range with scores of 3.1. For baseline belly size, patients in both the tesamorelin and placebo treatment groups reported similar belly sizes, which were both larger than the “healthy look” (mean scores of 57.8 and 56.7, respectively).

The “belly appearance distress” score improved significantly from baseline ($p<0.001$) to 26 weeks in both the tesamorelin and the placebo groups (a positive change from baseline score indicates improvement, i.e., less distress), but the improvement was significantly greater in the tesamorelin group ($p=0.002$).

Patient-rated “belly profile” scores improved significantly more in the tesamorelin group than in the placebo group. The mean improvement in patient-rated belly profile was -0.6 units (a negative change from baseline score indicates improvement) in the tesamorelin group and -0.3 units in the placebo group ($p=0.003$). Physician-rated “belly profile” scores also improved significantly from baseline more in the tesamorelin group than in the placebo group ($p<0.001$). The mean improvement from baseline in physician-rated belly profile was -0.6 units in the tesamorelin group and -0.3 units in the placebo group ($p<0.001$). Belly size scores significantly improved ($p<0.001$) compared with baseline in

both the tesamorelin and the placebo groups. The difference between groups was not significant.

Table 10. PRO: Belly Appearance Distress, Belly Size, and Belly Profile at Week 26 (Main, ITT Population)

| Patient-Reported Outcome, Mean (SD) | LIPO-010 Main | | CTR-1011 | | COMBINED | |
|--|----------------------------------|---------------------|----------------------------------|--------------------|----------------------------------|---------------------|
| | Tesamorelin 2 mg/day N=273 | Placebo N=137 | Tesamorelin 2 mg/day N=269 | Placebo N=126 | Tesamorelin 2 mg/day N=542 | Placebo N=263 |
| Belly appearance distress^a | n=272 | n=137 | n=269 | n=126 | n=538 | n=262 |
| Baseline | 22.1 (22.23) | 24.0 (25.68) | 22.3 (24.19) | 20.2 (22.07) | 22.1 (22.99) | 22.1 (24.08) |
| Week 26 | 33.7 (25.93) | 30.2 (27.31) | 30.5 (25.40) | 25.4 (25.10) | 31.9 (25.60) | 28.1 (26.56) |
| Change from baseline ^d | 11.6 (26.93) | 6.2 (25.82) | 8.4 (28.99) | 5.2 (26.61) | 9.8 (27.95) | 5.9 (25.77) |
| p-value ^g | <0.001 [†] | 0.006 [†] | <0.001 [†] | 0.031* | <0.001 [†] | <0.001 [†] |
| p-value: baseline ^h | | 0.431 | | 0.416 | | 0.962 |
| p-value: change from baseline ⁱ | | 0.028* | | 0.022* | | 0.002* |
| Belly size^b | n=272 | n=137 | n=269 | n=126 | n=538 | n=262 |
| Baseline | 59.8 (47.66) | 55.8 (52.01) | 56.1 (54.16) | 56.9 (57.15) | 57.8 (51.05) | 56.7 (54.30) |
| Week 26 | 35.1 (55.00) | 35.4 (55.04) | 33.4 (57.87) | 47.6 (53.71) | 34.1 (56.59) | 42.1 (54.11) |
| Change from baseline ^c | 14.6 (30.15) | 13.1 (31.37) | 14.8 (27.78) | 11.7 (25.24) | 14.4 (28.81) | 12.5 (28.17) |
| p-value ^g | <0.001 [†] | <0.001 [†] | <0.001 [†] | 0.103 | <0.001 [†] | <0.001 [†] |
| p-value: baseline ^h | | 0.438 | | 0.971 | | 0.619 |
| p-value: change from baseline ⁱ | | 0.977 | | 0.211 | | 0.407 |
| Belly profile - patient^c | n=272 | n=137 | n=269 | n=126 | n=538 | n=262 |
| Baseline | 3.3 (1.27) | 3.2 (1.47) | 3.2 (1.36) | 3.3 (1.19) | 3.3 (1.32) | 3.3 (1.34) |
| Week 26 | 2.6 (1.43) | 2.8 (1.50) | 2.7 (1.56) | 3.1 (1.43) | 2.7 (1.48) | 3.0 (1.45) |
| Change from baseline ^f | -0.7 (1.25) | -0.3 (1.25) | -0.5 (1.29) | -0.3 (1.03) | -0.6 (1.26) | -0.3 (1.13) |
| p-value ^g | <0.001 [†] | <0.001 [†] | <0.001 [†] | 0.005 [†] | <0.001 [†] | <0.001 [†] |
| p-value: baseline ^h | | 0.328 | | 0.437 | | 0.861 |
| p-value: change from baseline ⁱ | | 0.042* | | 0.075 | | 0.003 [†] |
| Belly profile - physician^c | n=272 | n=137 | n=269 | n=126 | n=538 | n=262 |
| Baseline | 3.1 (1.15) | 3.1 (1.19) | 3.1 (1.22) | 3.1 (1.17) | 3.1 (1.18) | 3.1 (1.18) |
| Week 26 | 2.5 (1.34) | 2.7 (1.34) | 2.6 (1.35) | 2.8 (1.34) | 2.5 (1.34) | 2.8 (1.32) |
| Change from baseline ^f | -0.6 (1.05) | -0.4 (1.13) | -0.6 (1.19) | -0.3 (1.09) | -0.6 (1.12) | -0.3 (1.10) |
| p-value ^g | <0.001 [†] | <0.001 [†] | <0.001 [†] | 0.004 [†] | <0.001 [†] | <0.001 [†] |
| p-value: baseline ^h | | 0.757 | | 0.996 | | 0.844 |
| p-value: change from baseline ⁱ | | 0.036* | | 0.021* | | <0.001 [†] |

ITT, intent-to-treat; PRO, patient-reported outcome; SD, standard deviation.

^a A larger actual value indicates less belly appearance distress.

^b A smaller actual value indicates a better belly size rating (i.e., on target with a “healthy look”).

^c A smaller actual value indicates a smaller belly profile where a 0 is “normal”.

^d Positive change from baseline score indicates improvement (less distress).

^e Change scores underwent a transformation to absolute differences. A positive change from baseline score indicates improvement.

^f A negative change from baseline score indicates improvement (less dysmorphic).

^g For individual studies, within-group change was tested using a paired samples t-test; for combined results, within-group change was tested using a mixed model analysis.

^h Parametric ANCOVA for baseline comparison including relevant covariates (e.g., gender, age) for scores.

ⁱ Ranked ANCOVA for between-treatment comparisons including relevant covariates (e.g., gender, age) for scores.

* p<0.05; † p<0.01.

PRO responder analysis

In December 2009, the FDA released guidance for industry concerning PRO measures for use in medical product development. In a section on interpretation of clinical trial results, the document emphasizes the importance of displaying individual responses using an *a priori responder definition* (FDA 2009). The guidance document suggests appropriate definitions for responders, including anchor-based methods such as patient ratings of meaningful change, as well as distribution-based methods that provide an estimate of the magnitude of treatment changes, such as the between-person standard deviation or standard error (FDA 2009).

The main PRO responder analysis presented here uses an anchor-based method which involves characterizing an individual patient as a responder based on the difference between their body profile at baseline and their baseline judgment of the smallest amount of improvement in belly profile considered to be beneficial. On the basis of the FDA's recommendation, we also report the magnitude of change in the main PRO parameters which is associated with a clinically meaningful reduction in VAT (see next paragraph on Association of PRO with Clinically Meaningful VAT Reduction). In addition, a distribution-based responder criterion was also used (see next paragraph on Responsiveness Unit Analysis) that is well-established in QOL literature and involves converting scores to responsiveness units (Guyatt 1987, Tuley 1991, Testa 1993, Testa 1996, Zou 2005).

PRO responder analysis: Anchor-based criterion

The pre-specified anchor-based criterion for a PRO responder is based on the patient-rated belly profile assessment and involves 3 questions that patients were asked 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 health and well being.

The patient-reported belly profile responder interval is operationally defined as the sample mean difference between “current look” (choice 1) minus the minimally acceptable benefit (choice 3) at baseline.

The responder interval for patient-rated belly profile was 2.298, indicating that the smallest benefit represents an improvement of more than 2 profiles. Therefore, a patient was considered a PRO responder if he/she decreased the profile score by more than 2 profiles. The proportion of PRO “responders” and “non-responders” was compared in each treatment arm using Fisher’s exact test, with a 2-sided alpha level of 0.05. The results of the PRO responder analyses for patient-reported belly profile are presented in **Table 11**.

Table 11. Patient-Reported “Belly Profile” Responder Analyses (ITT Population, LOCF)

| | LIPO-010 | | CTR-1011 | | COMBINED | |
|------------------|-----------|---------|-----------|---------|--------------|---------|
| Responder, n (%) | No | Yes | No | Yes | No | Yes |
| Tesamorelin | 251 (92%) | 21 (8%) | 246 (92%) | 22 (8%) | 495 (92%) | 43 (8%) |
| Placebo | 130 (95%) | 7 (5%) | 122 (97%) | 4 (3%) | 252 (96%) | 10 (4%) |
| p-value | 0.409 | | 0.08 | | 0.033 | |

ITT, intent-to-treat; LOCF, last observation carried forward.

Similarly, the physician-reported belly profile responder analyses were performed as described above. The physician-reported belly profile responder interval was 1.634. Therefore, a patient improving by at least 2 belly profiles or more was considered a PRO responder. The results of the responder analyses for physician-reported belly profile are presented in **Table 12**.

Table 12. Physician-Reported “Belly Profile” Responder Analyses (ITT Population, LOCF)

| Responder, n (%) | LIPO-010 | | CTR-1011 | | COMBINED | |
|------------------|--------------|----------|-------------|------------|--------------|-----------|
| | No | Yes | No | Yes | No | Yes |
| Tesamorelin | 205 (75%) | 67 (25%) | 221 (82.5%) | 47 (17.5%) | 425 (79%) | 113 (21%) |
| Placebo | 117 (85%) | 20 (15%) | 113 (90%) | 13 (10%) | 230 (88%) | 32 (12%) |
| p-value | 0.021 | | 0.072 | | 0.002 | |

ITT, intent-to-treat; LOCF, last observation carried forward.

For “belly appearance distress,” responder intervals were calculated by regressing the change from baseline “belly appearance distress” score onto the change from baseline patient-reported belly profile score. The unstandardized coefficient from the regression parameter estimates the number of raw belly appearance scale units changed for each “one profile” change in the patient-reported belly profile scale. The unstandardized coefficient was then multiplied by the patient-rated belly profile responder interval to obtain the belly appearance responder interval.

The “belly appearance distress” responder interval was -19.266. Thus, patients who improved by about 2 scale units or more were labelled PRO responders and analyzed as described above. The tabular display (with p-values) of the PRO responder analyses for “belly appearance distress” is presented in **Table 13**.

Table 13. “Belly Appearance Distress” Responder Analyses (ITT Population, LOCF)

| Responder, n (%) | LIPO-010 | | CTR-1011 | | COMBINED | |
|------------------|-----------|----------|-----------|----------|--------------|-----------|
| | No | Yes | No | Yes | No | Yes |
| Tesamorelin | 199 (73%) | 73 (27%) | 199 (74%) | 69 (26%) | 399 (74%) | 139 (26%) |
| Placebo | 110 (80%) | 27 (20%) | 105 (83%) | 21 (17%) | 215 (82%) | 47 (18%) |
| p-value | 0.143 | | 0.053 | | 0.013 | |

ITT, intent-to-treat; LOCF, last observation carried forward.

The same procedure was replicated for the belly size scale. The belly size responder interval was -17.072. Therefore, a patient improving by about 1 scale unit or more in

his/her absolute change score was considered a PRO responder. The results of the responder analysis for belly size are presented in **Table 14**.

Table 14. Belly Size Responder Analyses (ITT Population, LOCF)

| Responder, n (%) | LIPO-010 ^a | | CTR-1011 ^b | | COMBINED ^b | |
|------------------|-----------------------|----------|-----------------------|-----------|-----------------------|-----------|
| | No | Yes | No | Yes | No | Yes |
| Tesamorelin | 185 (68%) | 87 (32%) | 150 (56%) | 118 (44%) | 308 (57%) | 230 (43%) |
| Placebo | 97 (71%) | 40 (29%) | 81 (64%) | 45 (36%) | 163 (62%) | 99 (38%) |
| p-value | 0.651 | | 0.126 | | 0.193 | |

ITT, intent-to-treat; LOCF, last observation carried forward.

^a For LIPO-010, the raw change score was used.

^b For CTR-1011 and integrated summary of efficacy PRO, the absolute change score was used.

It should be noted that this responder analysis is conservative because the smallest benefit in patient-reported “belly profile” at baseline was more than 2.0 profiles, which in practice, requires a change of 3 profiles or more from baseline to meet the criteria of a responder. To change 3 profiles, a patient would have needed to identify the baseline current look as at least 3 profiles worse than “normal.” Further, patients in both groups selected a “minimum” profile that was close to “normal,” which maximizes the amount they would have to change to be defined as a responder. In study LIPO-010, 88 of 135 placebo and 201 of 271 tesamorelin patients met that criterion to be eligible to change by three units or more, while in CTR-1011, there were 92 of 126 placebo and 182 of 269 tesamorelin patients. However, despite the conservative responder criteria, for three of the four main belly parameters there was a significantly greater proportion of PRO responders in the tesamorelin group than in the placebo group.

Association of PRO with Clinically Meaningful VAT Reduction

For the patient-rated “belly appearance distress” analysis, patients in the tesamorelin group who experienced an 8% or more VAT decrease (tesamorelin +8% VAT decrease group) were 2.2 times more likely to be a responder than the reference group, which included patients on placebo who did not show an 8% or more decrease in VAT (p<0.001). For the “belly profile” analysis, patients in the tesamorelin +8% VAT decrease group

were 2.9 times more likely to be responders than those in the reference group ($p=0.014$). For belly size evaluation, patients in the tesamorelin +8% VAT decrease group were 1.8 times more likely to be responders compared with those in the reference group ($p=0.004$).

Responsiveness Unit Analysis

PRO Week 26 change scores were converted to responsiveness units, which are effect sizes based on standard deviation of change among stable subjects. This standardizing unit – an effect size – is equivalent to dividing the change score by the standard error of measurement (SEM). The standard deviation used in the calculation is taken from the Phase V Outcomes Information System reference database and represents stable within-subject variation between two parallel test forms. The reliability (r) of the scale is determined from the correlation between those forms. The responsiveness unit is calculated as the change score divided by the SEM, i.e. $SD/\sqrt{1-r}$. Conversion to responsiveness units permits direct comparison of the HRQOL data with the Phase V Outcomes Information System reference database, comprised of 15,000 longitudinal patient assessments collected in randomized, controlled clinical trials. Previous research has shown that between-treatment changes of 0.15 and higher represent clinically meaningful changes ([Guyatt 1987](#), [Tuley 1991](#), [Testa 1993](#), [Testa 1996](#), [Zou 2005](#)).

For “belly appearance distress”, patient-rated “belly profile”, and physician-reported “belly profile” the difference between responsiveness units in the tesamorelin group and the placebo group were larger or equal to the criterion considered clinically important (0.15). The difference between the tesamorelin group and the placebo group was 0.15 for “belly appearance distress”, 0.32 for patient rated “belly profile”, and 0.25 for physician-rated “belly profile”.

Other PRO endpoints

Other PRO endpoints with positive findings include weight concern, current overall appearance, the body appearance distress composite scale, and the HRQOL Global Analogue Scale (GAS). Statistically significant improvements from baseline were shown for the body appearance distress composite scale for both tesamorelin and placebo groups. The improvement from baseline was significantly greater in the tesamorelin as compared with the placebo group ($p=0.008$). Weight concern scale scores significantly improved from baseline in the tesamorelin group (-7.2 units; $p<0.001$), but did not significantly change in the placebo group (-2.5). The difference between change from baseline scores was statistically significant ($p=0.014$). Current overall appearance scale scores improved significantly from baseline in the tesamorelin and placebo groups (+0.8 and +0.4; $p<0.001$), with a significantly greater improvement in the tesamorelin group ($p<0.001$). For the GAS, scores did not significantly change from baseline in the tesamorelin group, but significantly deteriorated in the placebo group (-0.2 units; $p<0.033$). There was a significant difference in change from baseline GAS scores between tesamorelin and placebo groups ($p=0.029$).

In terms of responsiveness units, a clinically meaningful responsiveness unit difference was found for overall current appearance (0.39). The responsiveness unit difference for the body appearance composite scale was close to clinical significance with a value of 0.14. Of the HRQOL endpoints, a clinically meaningful difference was found for the decrease in QOL on the GAS for the placebo group as compared to the tesamorelin group (responsiveness unit difference of 0.17).

Correlations between PRO and VAT

The positive changes in PRO were significantly correlated with reductions in VAT for tesamorelin-treated patients, but not for placebo-treated patients (**Table 15**).

Table 15. Correlation Coefficients Between Percent Change from Baseline in VAT at Week 26 and Body Image and HRQOL (ITT Population)

| | Tesamorelin N=542 | | Placebo N=263 | |
|---|-------------------------|---------|-------------------------|---------|
| | Correlation Coefficient | p-value | Correlation Coefficient | p-value |
| Body Image Parameter^a | | | | |
| Belly size | -0.179 [†] | <0.001 | -0.059 | 0.344 |
| Belly appearance distress | -0.229 [†] | <0.001 | 0.047 | 0.445 |
| Body size | -0.154 [†] | <0.001 | -0.010 | 0.869 |
| Body appearance distress | -0.192 [†] | <0.001 | 0.094 | 0.127 |
| Patient-reported belly profile | 0.341 [†] | <0.001 | 0.016 | 0.796 |
| Physician-reported belly profile | 0.219 [†] | <0.001 | 0.096 | 0.123 |
| Health-Related Quality of Life^b | | | | |
| General perceived health | -0.107* | 0.013 | 0.053 | 0.392 |
| Psychological distress | -0.116 [†] | 0.007 | 0.105 | 0.090 |
| Psychological well-being | -0.132 [†] | 0.002 | 0.069 | 0.264 |
| Mental and emotional health | -0.134 [†] | 0.002 | 0.103 | 0.098 |
| Symptom incidence | -0.100* | 0.021 | -0.010 | 0.874 |
| Symptom distress | -0.130 [†] | 0.003 | 0.039 | 0.533 |
| QOL (itemwise) | -0.139 [†] | 0.001 | 0.091 | 0.143 |
| HRQOL Global analogue scale | -0.084 | 0.051 | -0.044 | 0.482 |

HRQOL, health-related quality of life; ITT, intent-to-treat, OOL, quality of life.

^a Spearman's rank correlation (ρ).

^b Pearson correlation (r).

*p<0.05; † p<0.01;

5.1.4.2 Lipids and biomarkers

Lipids

Changes in lipid parameters at Week 26 are summarized in **Table 16 and Figure 11**.

Triglycerides decreased from baseline to 26 weeks in the tesamorelin group and increased in the placebo group in both studies (p<0.001 for the treatment difference for the combined results). The difference was significant in LIPO-010 main but not in CTR-1011.

The total cholesterol-to-HDL-C ratio also showed the same trends, with decreases in the tesamorelin groups and increases in the placebo groups. Non-HDL-C decreased more in

the tesamorelin group than in the placebo group overall and in LIPO-010 main. Differences were significant ($p \leq 0.001$) between groups for the total cholesterol-to-HDL-C ratio and for non-HDL-C in LIPO-010 main and for the combined results but not in CTR-1011. At Week 26, decreases from baseline in the tesamorelin group were greater in patients who were using lipid-lowering therapy compared with those not using lipid-lowering therapy (means of -45.5 vs -29.1 mg/dL for triglycerides, -7.1 vs -3.1 mg/dL for non-HDL-C, and -0.25 vs -0.13 for the total cholesterol-to-HDL-C ratio).

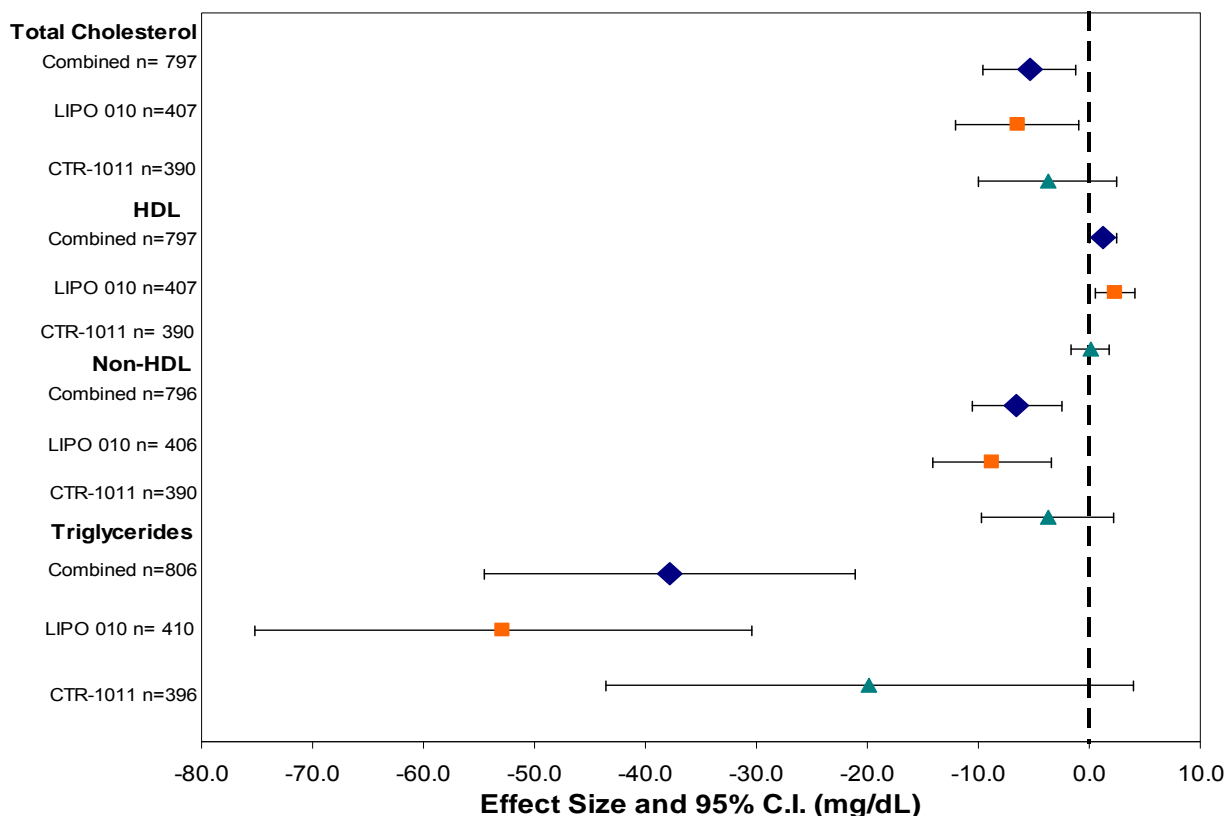
Table 16. Changes from Baseline to Week 26 in Lipid Parameters (ITT Population, LOCF)

| | LIPO-010 | | CTR-1011 | | COMBINED | |
|--------------------------------------|------------------------------------|---------------------|------------------------------------|---------------------|------------------------------------|---------------------|
| | Tesamorelin 2 mg/day (N=273) | Placebo (N=137) | Tesamorelin 2 mg/day (N=270) | Placebo (N=126) | Tesamorelin 2 mg/day (N=543) | Placebo (N=263) |
| Visit, mean (SD) | | | | | | |
| Total Cholesterol, mg/dL | | | | | | |
| Baseline | 197.11 (43.926) | 195.16 (37.891) | 190.50 (43.136) | 189.58 (37.023) | 193.86 (43.624) | 192.47 (37.507) |
| Change to Week 26 | -9.96 (32.837) | -2.53 (25.25) | 1.31 (32.238) | 5.48 (28.554) | -4.41 (32.998) | 1.34 (27.142) |
| p-value ^a | 0.021 | | 0.241 | | 0.011 | |
| Triglycerides, mg/dL | | | | | | |
| Baseline | 251.91 (188.106) | 233.54 (144.949) | 238.67 (261.313) | 222.60 (143.908) | 245.33 (227.357) | 228.30 (144.279) |
| Change to Week 26 | -50.86 (145.077) | 9.04 (118.304) | -22.15 (130.969) | 3.44 (105.955) | -36.58 (138.860) | 6.35 (112.379) |
| p-value ^a | <0.001 | | 0.101 | | <0.001 | |
| HDL-C, mg/dL | | | | | | |
| Baseline | 46.81 (14.799) | 48.03 (14.510) | 43.47 (13.857) | 44.83 (14.947) | 45.16 (14.426) | 46.49 (14.781) |
| Change to Week 26 | 0.81 (8.502) | -1.77 (10.073) | 0.23 (7.849) | -0.02 (10.037) | 0.53 (8.184) | -0.92 (10.074) |
| p-value ^a | 0.011 | | 0.940 | | 0.059 | |
| Total Cholesterol:HDL-C Ratio | | | | | | |
| Baseline | 4.50 (1.345) | 4.30 (1.238) | 4.75 (1.688) | 4.61 (1.609) | 4.62 (1.528) | 4.45 (1.436) |
| Change to Week 26 | -0.31 (0.979) | 0.21 (0.953) | -0.05 (1.009) | 0.15 (0.920) | -0.18 (1.002) | 0.18 (0.936) |
| p-value ^a | <0.001 | | 0.094 | | <0.001 | |
| Non-HDL-C, mg/dL | | | | | | |
| Baseline | 150.02 (41.256) | 147.24 (35.878) | 147.03 (42.583) | 144.75 (35.893) | 148.55 (41.902) | 146.03 (35.838) |
| Change to Week 26 | -10.76 (31.299) | -0.77 (25.147) | 1.08 (30.478) | 5.50 (26.904) | -4.93 (31.431) | 2.27 (26.152) |
| p-value ^a | 0.001 | | 0.216 | | 0.001 | |

HDL-C, high-density lipoprotein cholesterol; ITT, intent-to-treat; LOCF, last observation carried forward; non-HDL-C, non-high-density lipoprotein cholesterol; SD, standard deviation.

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

Figure 11. Effect Size and 95% CI of Changes in Lipid Parameters at Week 26 (ITT Population, LOCF)



CI, confidence interval; HDL, high-density lipoprotein; ITT, intent-to-treat; LOCF, last observation carried forward; non-HDL, non-high-density lipoprotein.

Total cholesterol also decreased in the tesamorelin group and increased in the placebo group in both studies, and the mean change to 26 weeks was statistically significantly different in the combined results ($p=0.012$). Total cholesterol decreased more in tesamorelin-treated patients who used lipid-lowering therapy (-6.4 mg/dL) than in tesamorelin-treated patients who did not use lipid-lowering therapy (-2.8 mg/dL). HDL-C increased in the tesamorelin group and decreased in the placebo group, but the treatment difference was only statistically significant at Week 13 ($p=0.038$). Altogether, these results show that tesamorelin favorably improves the lipid profile, whereas the lipid profile in untreated patients tends to worsen. It may also be worth noting that approximately 10%

more patients used lipid-lowering therapy in LIPO-010 main (50.5%) than in CTR-1011 (40.7%).

Bone and inflammatory markers

Selected biomarkers were measured in LIPO-010 only, and baseline values and changes from baseline are shown in **Table 17**.

Cross-linked N-telopeptides of type I collagen (NTx) are a marker of bone turnover. Over 26 weeks, this marker increased in the tesamorelin group and decreased in the placebo group, but the difference was not significant. Osteocalcin is produced by osteoblasts and is a marker of osteoblast activity, and serum levels are associated with increases in bone mineral density. Osteocalcin has also been shown in mice to increase pancreatic beta-cell proliferation (thus enhancing insulin production), to increase insulin sensitivity, and to reduce VAT ([Lee 2007](#)). Recently, an increase in osteocalcin level has been associated with increased insulin sensitivity and reduced VAT in humans ([Fernandez-Real 2009](#)). In LIPO-010 main, osteocalcin increased in the tesamorelin group and decreased in the placebo group and the difference was significant ($p < 0.001$).

Table 17. Change from Baseline to Week 26 in Biomarkers (LIPO-010 Main, ITT Population)

| | | Tesamorelin (N=273) | | Placebo (N=137) | | p-value ^a |
|-------------------------------------|-------------------|---------------------|----------------------------|-----------------|----------------------------|----------------------|
| | | n | Mean (SD) | n | Mean (SD) | |
| NTx, nmol bone collagen equivalents | Baseline | 213 | 475 (380) | 111 | 563 (458) | 0.068 |
| | Change to Week 26 | | +121 (469) | | -1.76 (476) | 0.118 |
| Osteocalcin, ng/mL | Baseline | 251 | 8.46 (4.28) | 129 | 9.09 (7.44) | 0.298 |
| | Change to Week 26 | | 3.72 (6.82) | | -1.66 (6.11) | <0.001 [‡] |
| CRP, mg/L | Baseline | 272 | 4.63 (9.39) | 135 | 4.36 (6.64) | 0.771 |
| | Change to Week 26 | | -0.39 (11.9) | | +0.37 (7.93) | 0.543 |
| Adiponectin, µg/mL | Baseline | 270 | 5.30 (3.68) | 134 | 5.41 (3.20) | 0.774 |
| | Change to Week 26 | | +0.49 (2.71) [†] | | -0.05 (1.34) | 0.029 |
| tPA antigen, ng/mL | Baseline | 269 | 9.67 (4.05) | 129 | 9.68 (3.73) | 0.988 |
| | Change to Week 26 | | -2.19 (2.54) ^{††} | | -1.64 (2.87) ^{††} | 0.034 |

| | | Tesamorelin (N=273) | | Placebo (N=137) | | p-value ^a |
|----------------------|-------------------|---------------------|---------------|-----------------|--------------|----------------------|
| | | n | Mean (SD) | n | Mean (SD) | |
| PAI-1 antigen, ng/mL | Baseline | 269 | 34.9 (19.8) | 129 | 35.0 (18.4) | 0.953 |
| | Change to Week 26 | | -2.48 (16.9)* | | -0.97 (17.3) | 0.342 |

CRP, C-reactive protein; ITT, intent-to-treat; NTx, cross-linked N-telopeptides of type I collagen; PAI-1, plasminogen activator inhibitor-1;

SD, standard deviation; tPA, tissue-type plasminogen activator.

^a Between group difference (the ANCOVA model is variable at baseline + treatment).

* p<0.05 for within-group comparison between Week 26 and baseline.

† p<0.01 for within-group comparison between Week 26 and baseline.

‡ p≤0.001 for within-group comparison between Week 26 and baseline.

CRP is considered to be an inflammatory marker and levels >3 mg/L are associated with an increased risk of CHD, although the evidence for the value of reducing CRP to reduce CHD risk is not yet clear (Buckley 2009). Lemieux et al (2001) have reported a strong and positive correlation between plasma levels of CRP and body fat mass, waist girth, and visceral fat in a sample of 159 men, aged 22 to 63 years, covering a wide range of adiposity. Elevated levels of CRP are found in HIV-infected patients (Feldman 2003, Samaras 2009). Recent data from the FRAM Study indicate that HIV-infected patients with high CRP (>3 mg/L) had a 2.7-fold higher adjusted odds of death than those with CRP < 1 mg/L (Tien 2010). A small decrease in CRP was observed in the tesamorelin group and a mean increase was observed in the placebo group at Week 26 of treatment, but there was no significant difference between groups.

Adiponectin is a hormone produced and secreted by adipocytes, and recent evidence has shown that it is also secreted by cardiomyocytes (Bik 2009). Low adiponectin level is associated with visceral obesity and predicts diabetes and CVD (Pischon 2004, Duncan 2004). HIV-infected patients with abdominal fat accumulation have been reported to have significantly lower adiponectin levels than those without lipodystrophy (Samaras 2009). Adiponectin levels significantly increased from baseline to Week 26 in the tesamorelin group, and the change was significantly different from the placebo group.

Data from the Atherosclerosis Risk in Communities (ARIC) study showed that increased levels of markers of fibrinolytic function, including tissue plasminogen activator (tPA),

and plasminogen activator inhibitor-1 (PAI-1) were positively associated with the incidence of coronary heart disease (CHD) (Folsom 2001). Treatment with tesamorelin was associated with a significant decrease from baseline to week 26 in tPA antigen ($p=0.034$ vs. placebo). PAI-1 antigen also significantly decreased from baseline in the tesamorelin group, but the difference between groups was not significant. Taken together, these findings suggest that tesamorelin may decrease prothrombotic risk in HIV-infected patients with excess abdominal fat.

5.1.4.3 Other body composition measurements and anthropometrics

Trunk fat decreased significantly more ($p<0.001$) in the tesamorelin group than in the placebo group, respectively, at both Week 13 and Week 26 (-0.82 vs $+0.14$ kg at Week 13, and -0.90 vs $+0.28$ kg at Week 26).

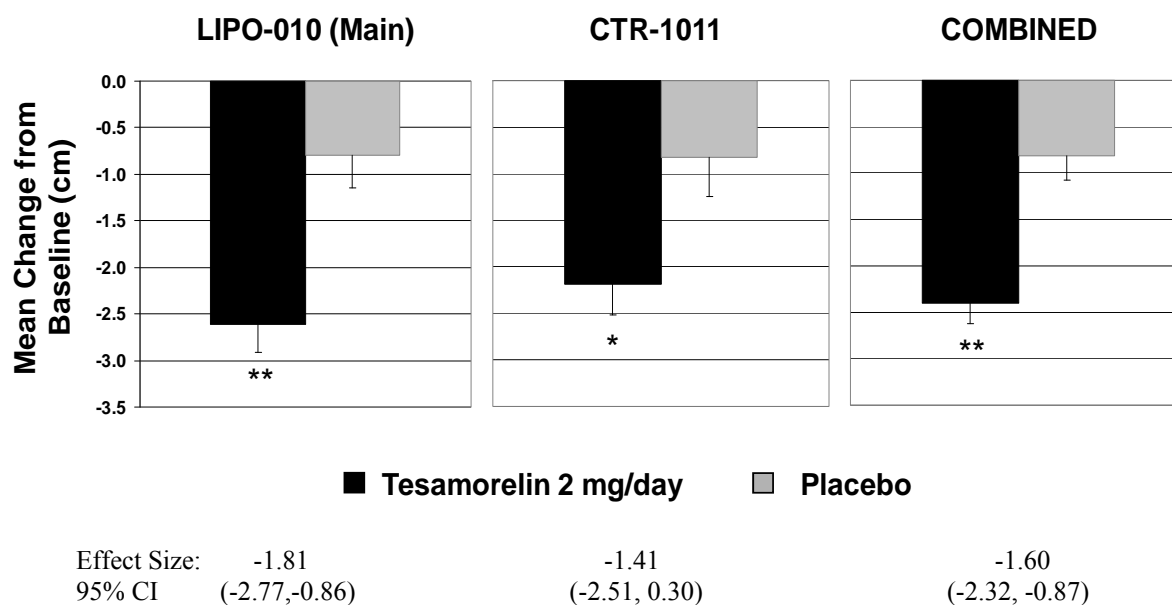
LBM increased from baseline at 13 weeks ($+1.2$ kg) and 26 weeks ($+1.3$) in the tesamorelin group, but decreased at 13 weeks (-0.08 kg) and 26 weeks (-0.14 kg) in the placebo group. Changes were significantly different ($p<0.001$) at both time points. Conversely, total fat decreased in the tesamorelin group and increased in the placebo group at 13 weeks (-0.93 vs $+0.26$ kg, $p<0.001$) and 26 weeks (-0.98 vs $+0.46$ kg, $p<0.001$).

Abdominal SAT changes were not significantly different between the tesamorelin and the placebo groups, but the change from baseline in the VAT/SAT ratio was significantly different ($p<0.001$). Limb fat changes were statistically significantly different between groups at Week 26, but the difference was not considered clinically significant.

Mean WC decreased from baseline in both treatment groups, but the change was significantly greater in the tesamorelin group than in the placebo group ($p<0.001$) (**Figure 12**). Mean hip circumference was generally stable in both groups, with a greater increase in the placebo group. The mean waist-to-hip ratio was significantly different between groups, but the difference was small. A numerically greater mean increase in hip circum-

ference in the placebo group than in the tesamorelin group resulted in a statistically significant treatment difference ($p=0.021$) in LIPO-010 main that was not observed in CTR-1011.

Figure 12. Changes in Waist Circumference at Week 26 (Main, ITT Population)



Data are mean + SEM.

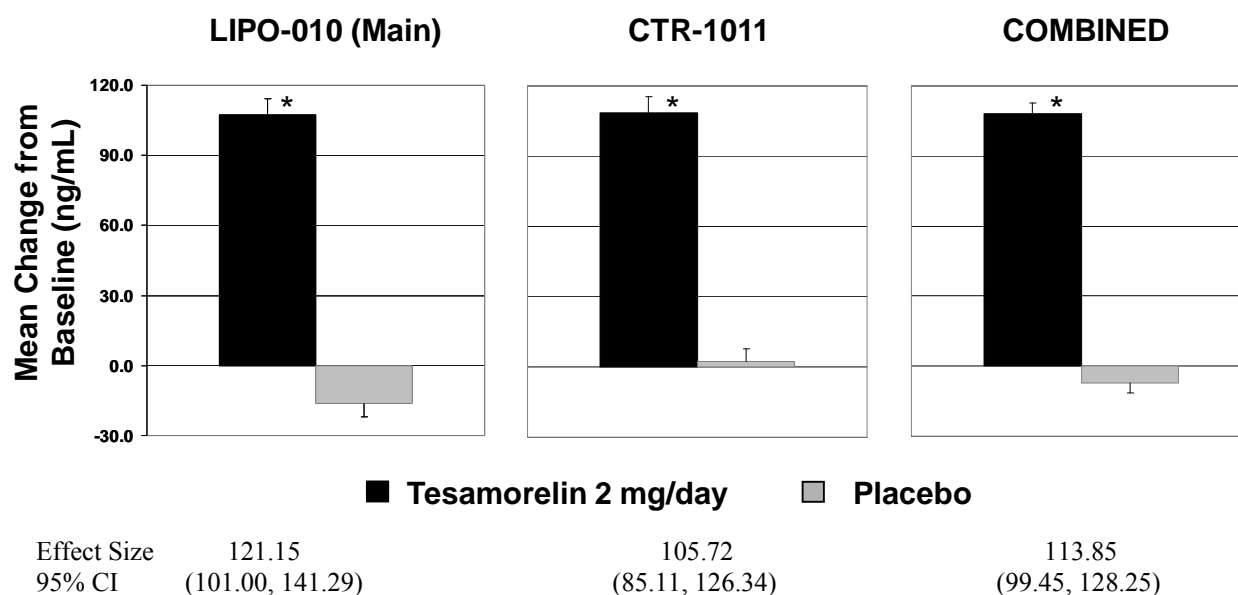
CI, confidence interval; ITT, intent-to-treat; SEM, standard error of the mean.

* $p<0.05$; ** $p<0.001$ 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).

5.1.4.4 IGF-1

Mean IGF-1 levels increased in the tesamorelin group but decreased in the placebo group at 26 weeks (**Figure 13**). The mean changes were significant at Week 13 ($p<0.001$) and Week 26 ($p<0.001$).

Figure 13. Changes in IGF-1 Levels at Week 26 (Main, ITT Population)



Data are mean + SEM.

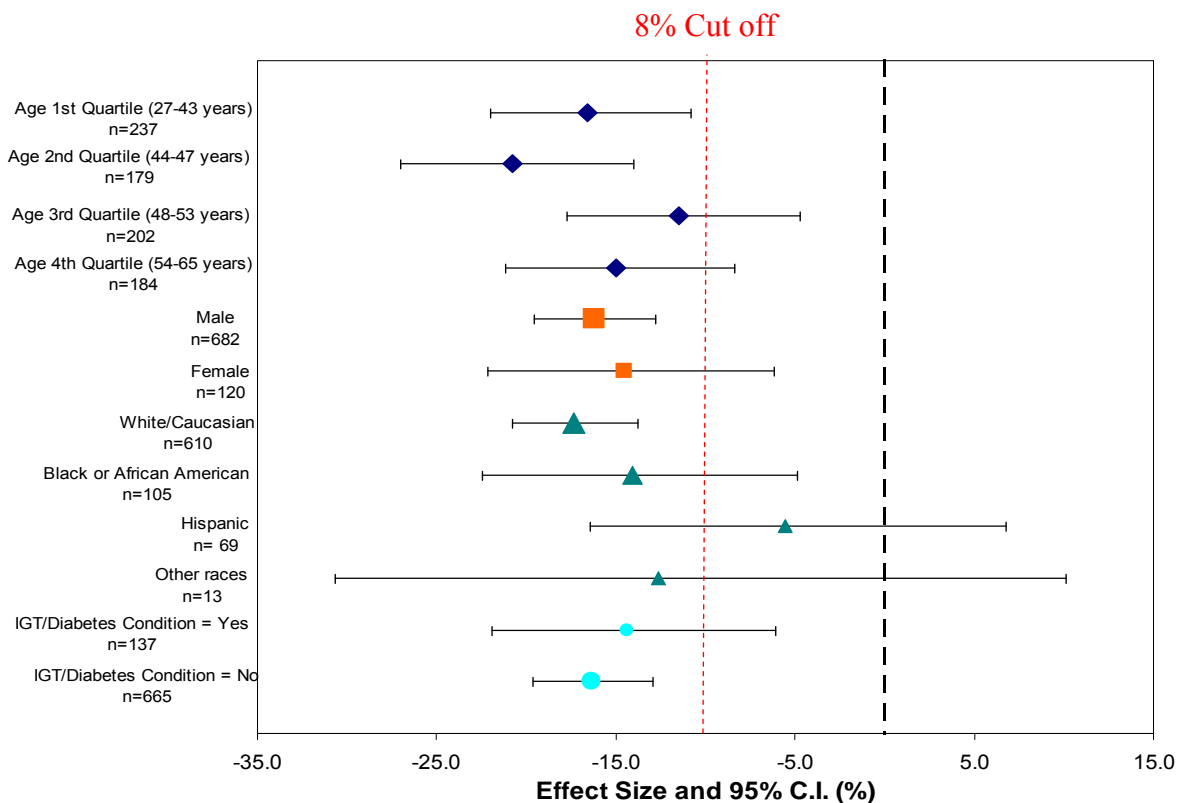
CI, confidence interval; IGF-1, insulin-like growth factor 1; ITT, intent-to-treat; SEM, standard error of the mean.

* $p < 0.001$ 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).

5.1.5 Subgroup analyses by demographics and treatments

In the combined studies, no statistically significant treatment-by-covariate interactions were observed for the percent change from baseline in VAT when age, gender, race, IGT/diabetes, ART regimen (baseline use and changes in therapy), anti-tesamorelin IgG antibody status (present or absent, titer), and testosterone use were included as categorical covariates or when age was included as a continuous covariate. Differences between groups in mean percent change in VAT from baseline were similar across subgroups defined by quartiles of baseline VAT. These results indicate that patients with a smaller VAT at baseline had a similar percent change in VAT as patients with a larger VAT at baseline. No site effect was found, indicating that there was no effect of treatment center on the overall conclusions. The effect size and 95% C.I for the % change in VAT at week 26 per subgroup analyses for the main covariates are shown in **Figure 14**.

Figure 14. Forest Plot of the Percent Change in VAT per Subgroup Analyses (ITT Population, LOCF)



CI, confidence interval; IGT, impaired glucose tolerance, VAT, visceral adipose tissue.

Moreover, in the combined studies, no statistically significant treatment-by-covariate interactions were observed for the change from baseline in trunk fat when gender, race, IGT/diabetes, ART regimen (baseline use and changes in therapy), and testosterone use were included as categorical covariates. However, a statistically significant treatment-by-age quartile interaction was observed for the change from baseline when age was included as a categorical covariate ($p=0.007$). Except for the 50th to 75th percentile of age, the change from baseline in trunk fat was statistically significantly different between groups, with a decrease in the tesamorelin group and an increase in the placebo group.

5.2 Extension Phase Studies (LIPO-010 Extension, CTR-1012)

Patients receiving tesamorelin and completing the main phase of LIPO-010 or study CTR-1011 were re-randomized to receive tesamorelin (tesamorelin-tesamorelin group) or placebo (tesamorelin-placebo group) in the 26-week extension. Patients who received placebo in the main phase were switched to tesamorelin (placebo-tesamorelin group). The groups are referred to as T-T, T-P, and P-T for convenience in the following text.

5.2.1 Patient disposition

As illustrated in **Table 18**, 85% of the patients who received tesamorelin for 52 weeks (T-T group) completed the extension phase as compared to 76% of the patients re-randomized to placebo (T-P), and 81% of the patients switching from placebo to tesamorelin (P-T group). AEs were reported as the primary reason for early study discontinuation by more patients in the P-T group (45%) than in the T-T or T-P groups (16% and 22%, respectively).

Table 18. Patient Disposition (Extension, ITT Population)

| Patient Disposition, n (%) | LIPO-010 | | | CTR-1012 | | | COMBINED | | |
|---|----------------|---------------|---------------------------|---------------|---------------|--------------------------|----------------|----------------|---------------------------|
| | T-T N=154 | T-P N=50 | P-T ^a N=111 | T-T N=92 | T-P N=85 | P-T ^a N=86 | T-T N=246 | T-P N=135 | P-T ^a N=197 |
| Randomized patients, ITT population ^b | 154 (100.0) | 50 (100.0) | 111 (100.0) | 92 (100.0) | 85 (100.0) | 86 (100.0) | 246 (100.0) | 135 (100.0) | 197 (100.0) |
| PP population ^b | 106 (68.8) | 39 (78.0) | 83 (74.8) | 70 (76.1) | 55 (64.7) | 68 (79.1) | 176 (71.5) | 94 (69.6) | 151 (76.6) |
| Patients who completed extension | 129 (83.8) | 40 (80.0) | 87 (78.4) | 80 (87.0) | 63 (74.1) | 72 (83.7) | 209 (85.0) | 103 (76.3) | 159 (80.7) |
| Primary reason for discontinuation ^c | | | | | | | | | |
| Adverse event | 5 (20.0) | 3 (30.0) | 12 (50.0) | 1 (8.3) | 4 (18.2) | 5 (35.7) | 6 (16.2) | 7 (21.9) | 17 (44.7) |
| Lack of compliance with protocol requirements and/or procedures | 7 (28.0) | 1 (10.0) | 2 (8.3) | 1 (8.3) | 3 (13.6) | 1 (7.1) | 8 (21.6) | 4 (12.5) | 3 (7.9) |
| Withdrawal of consent | 12 (48.0) | 4 (40.0) | 6 (25.0) | 8 (66.7) | 11 (50.0) | 7 (50.0) | 20 (54.1) | 15 (46.9) | 13 (34.2) |
| Lost to follow-up | 1 (4.0) | 2 (20.0) | 3 (12.5) | 2 (16.7) | 2 (9.1) | 1 (7.1) | 3 (8.1) | 4 (12.5) | 4 (10.5) |

| Patient Disposition, n (%) | LIPO-010 | | | CTR-1012 | | | COMBINED | | |
|-------------------------------|--------------|-------------|---------------------------|-------------|-------------|--------------------------|--------------|--------------|---------------------------|
| | T-T N=154 | T-P N=50 | P-T ^a N=111 | T-T N=92 | T-P N=85 | P-T ^a N=86 | T-T N=246 | T-P N=135 | P-T ^a N=197 |
| Abnormal laboratory values | 0 | 0 | 1 (4.2) | 0 | 0 | 0 | 0 | 0 | 1 (2.6) |
| Others | 0 | 0 | 0 | 0 | 2 (9.1) | 0 | 0 | 2 (6.3) | 0 |
| p-value ^d | 0.753 | | | 0.438 | | | 0.434 | | |
| p-value ^e | | | | | | | 0.128/0.744 | | |

P-T, placebo-tesamorelin; T-P, tesamorelin-placebo; T-T, tesamorelin-tesamorelin.

Note: Tesamorelin refers to tesamorelin 2 mg/day.

^a Patients who received placebo in the main phase were automatically switched to receive tesamorelin in the extension phase.

^b Percentages are based on the number of randomized patients.

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

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

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

5.2.2 Baseline characteristics

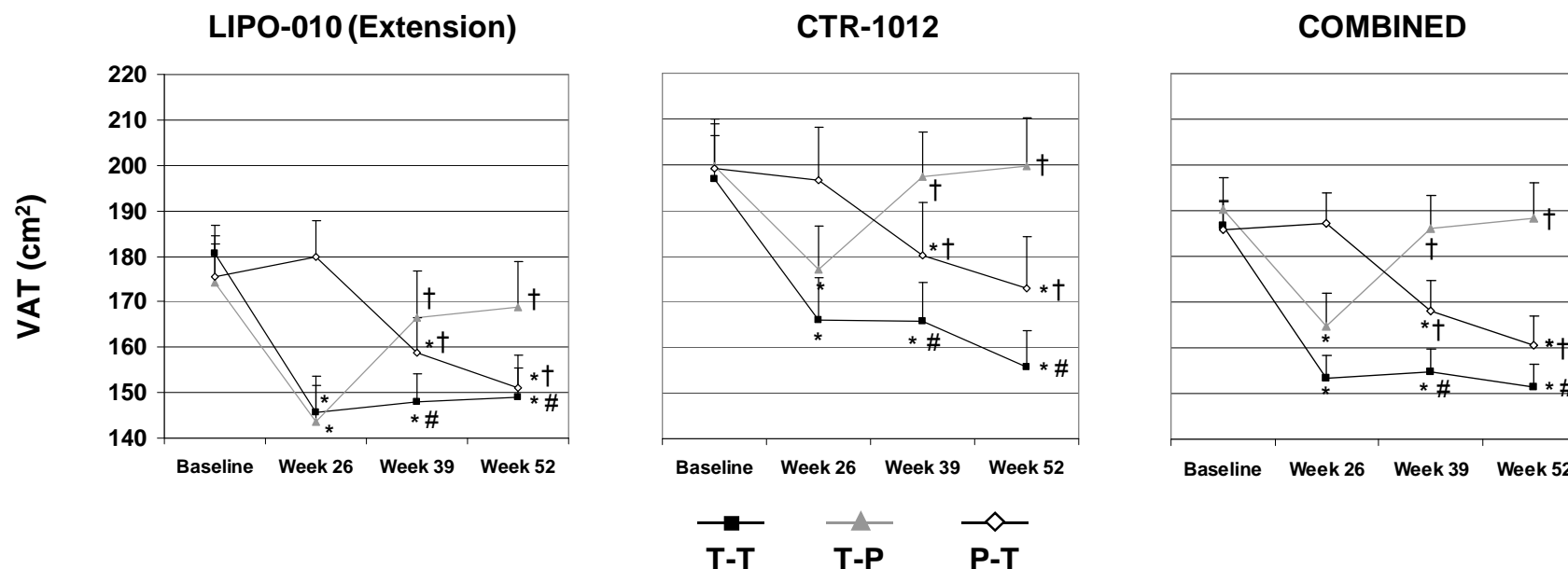
Most baseline characteristics were not significantly different among groups (**Appendix V**). However, statistically significantly higher mean BMI (29.4 kg/m² vs 28.6 kg/m²) and hip circumference (100.9 cm vs 99.1 cm) values were observed in the T-P group vs the T-T group, respectively. No statistical differences in these parameters were observed in the individual studies. Most of the clinical characteristics were not different among groups, but the distribution of viral load was significantly different between the T-T and T-P groups at 26 weeks. Also, a statistically significant difference was observed between the combined T-T and T-P groups and the P-T group for type of ART regimen. In LIPO-010 extension, the duration of ART regimen was significantly shorter in the P-T group than in T-T and T-P groups (means of 53.7 months vs 62.4 and 68.6 months, respectively, p=0.009).

5.2.3 Primary endpoint: change in VAT

In the group that received tesamorelin throughout the 52 weeks (T-T group), the change from baseline to 52 weeks was statistically significant, and the change from Week 26 to Week 52 was -1.29% (non-significant) (**Figure 15**). Seventy-eight percent of patients who were responders at Week 26 (lost $\geq 8\%$ of their baseline VAT) maintained their VAT loss at Week 52.

The difference between the T-T group and the T-P group was significant ($p < 0.001$), which indicated the loss of efficacy associated with tesamorelin discontinuation in the T-P group. The statistically significant mean percent decrease in VAT from Week 26 to Week 52 in the P-T group illustrated the onset of efficacy when tesamorelin was initiated.

Figure 15. VAT Profile over 52 Weeks (Extension, ITT Population)



ITT, intent-to-treat; P-T, placebo-tesamorelin; T-P, tesamorelin-placebo; T-T, tesamorelin-tesamorelin; VAT, visceral adipose tissue.

Data are mean + SEM.

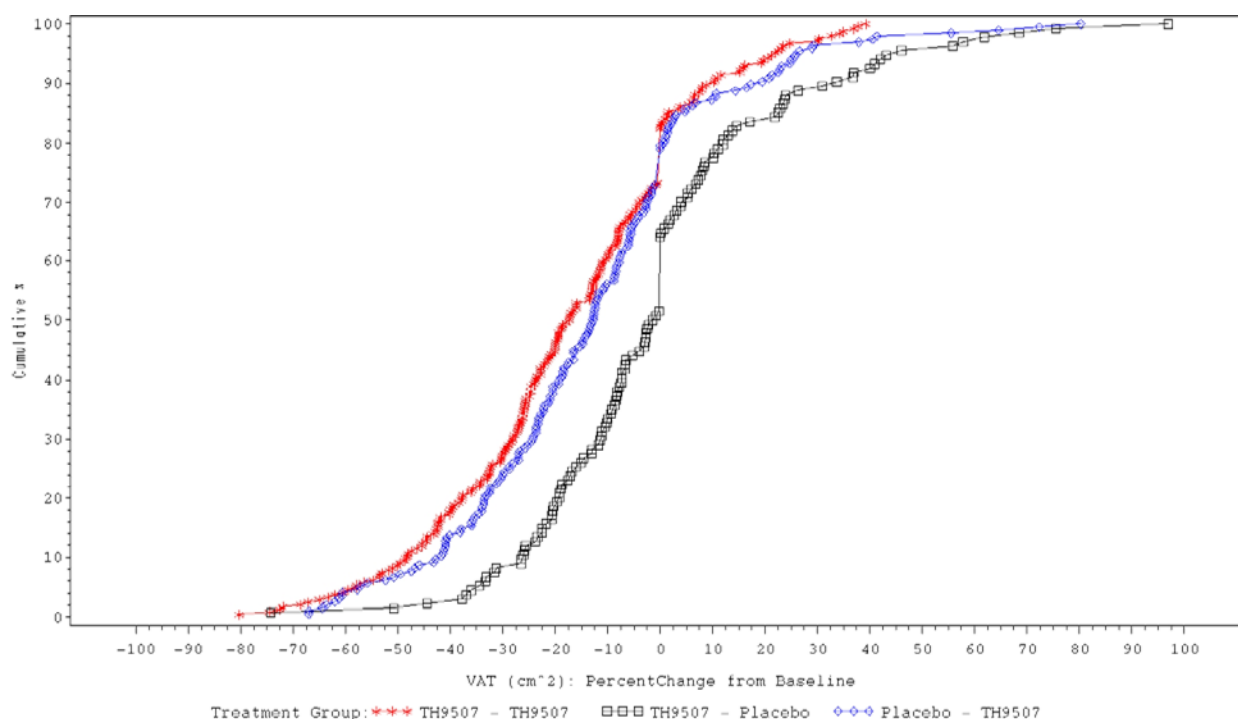
* p<0.01 vs baseline.

† p<0.01 vs Week 26.

p<0.001 for T-T vs T-P comparison within each study (model is $\log [\text{VAT}/\text{baseline}] = \log [\text{baseline VAT}] + \log [\text{VAT Week 26}/\text{baseline}] + \text{treatment group}$; for T-T vs T-P comparisons based on the combined results, the model is $\log [\text{VAT}/\text{baseline}] = \log [\text{baseline VAT}] + \log [\text{VAT Week 26}/\text{baseline}] + \text{treatment group} + \text{study}$; only subjects in the T-T and T-P groups are included in these analyses).

The cumulative distribution function of the percent change in VAT from baseline to Week 52 showed that higher proportions of patients in the T-T and P-T groups than in the T-P group had decreased VAT values at Week 52 (**Figure 16**).

Figure 16. Cumulative Distribution Function of the Percent Change in VAT by Treatment Group at Week 52 (Extension, ITT Population)



5.2.4 Secondary endpoints and other parameters

5.2.4.1 Patient-reported outcomes

Extension phase results for PRO are summarized in **Table 19**. In the T-T group, the “belly appearance distress” score improved significantly from baseline to Week 52 ($p < 0.01$), and a small, insignificant improvement occurred between Week 26 and Week 52. The change from baseline to Week 52 in the T-T group was significantly different from that in the T-P group ($p < 0.001$), indicating a loss of efficacy with tesamorelin discontinuation. Patient-rated and physician-rated “belly profile” scores were significantly

improved at Week 52 compared to baseline in all 3 treatment groups. Changes from baseline to 52 weeks in “belly size” scores were not different between the T-T and T-P groups. The improvement in patient-rated “belly profile” scores observed at Week 26 was sustained at Week 52 in the T-T group, whereas the T-P group tended to lose the improvement, although the changes at Week 52 were still significantly different from baseline. Patient-rated “belly profile” change from baseline scores were significantly different between T-T and T-P. Physician-rated “belly profile” change from baseline scores were not significantly different between the T-T and T-P groups.

Table 19. PRO: Belly Appearance Distress, Belly Size, and Belly Profile at Week 52 (Extension, ITT Population)

| Patient-Reported Outcome, Mean (SD) | LIPO-010 | | | CTR-1012 | | | COMBINED | | |
|---|---------------------------|---------------------------|---------------------------|---------------------------|---------------------------|---------------------------|---------------------------|---------------------------|---------------------------|
| | T-T N=153 | T-P N=50 | P-T N=111 | T-T N=92 | T-P N=85 | P-T N=86 | T-T N=245 | T-P N=135 | P-T N=197 |
| Belly appearance distress ^a | | | | | | | | | |
| Baseline | 21.7 (22.17) | 23.5 (20.77) | 23.3 (25.53) | 23.9 (24.56) | 16.8 (17.63) | 17.2 (19.56) | 22.5 (23.07) | 19.3 (19.06) | 20.6 (23.26) |
| Week 26 | 35.9 (27.46) | 36.8 (21.49) | 30.5 (28.04) | 31.5 (24.41) | 32.2 (27.44) | 25.4 (26.80) | 34.3 (26.38) | 33.9 (25.41) | 28.3 (27.55) |
| Week 52 | 33.8 (25.24) | 28.5 (23.43) | 31.0 (25.50) | 37.1 (26.76) | 26.6 (24.30) | 29.7 (27.25) | 35.1 (25.78) | 27.3 (23.91) | 30.4 (26.22) |
| Change from baseline ^d | 12.2 (26.51) [†] | 5.0 (22.16) | 7.7 (25.63) [†] | 13.2 (33.83) [†] | 9.9 (24.25) [†] | 12.5 (29.52) [†] | 12.6 (29.41) [†] | 8.1 (23.53) [†] | 9.8 (27.43) [†] |
| Change from Week 26 ^d | -2.0 (25.06) | -8.3 (29.41) | 0.5 (25.11) | 4.9 (24.35)* | -5.7 (29.33) | 4.3 (32.42) | 0.6 (23.96) | -6.3 (29.03)* | 2.2 (28.41) |
| p-value ^e | 0.020* | | | 0.005* | | | <0.001 [†] | | |
| Belly size ^b | | | | | | | | | |
| Baseline | 62.1 (43.69) | 61.0 (42.61) | 59.2 (48.49) | 50.8 (56.87) | 58.5 (55.71) | 59.0 (58.90) | 57.9 (49.25) | 59.4 (51.09) | 59.1 (53.14) |
| Week 26 | 37.1 (51.55) | 25.5 (52.12) | 34.5 (54.78) | 31.0 (54.64) | 30.0 (61.33) | 48.0 (56.00) | 35.0 (52.51) | 28.3 (57.93) | 40.5 (55.69) |
| Week 52 | 32.8 (52.76) | 44.5 (44.97) | 25.9 (55.59) | 21.7 (55.50) | 42.1 (55.40) | 30.2 (66.99) | 28.6 (53.88) | 43.0 (51.62) | 27.8 (60.70) |
| Change from baseline ^f | 18.5 (30.72) [†] | 15.5 (28.97) [†] | 18.5 (31.57) [†] | 20.9 (29.71) [†] | 13.5 (24.26) [†] | 14.2 (29.34) [†] | 19.4 (30.31) [†] | 14.3 (26.01) [†] | 16.6 (30.61) [†] |
| Change from Week 26 ^f | 2.0 (30.82) | -4.0 (34.02) | 3.6 (33.68) | -2.7 (32.05) | 1.5 (30.15) | -1.8 (29.32) | 2.4 (31.76) | -2.2 (31.63)* | 2.9 (31.43)* |
| p-value ^e | 0.408 | | | 0.101 | | | 0.075 | | |
| Belly profile, patient-rated ^c | | | | | | | | | |
| Baseline | 3.4 (1.27) | 3.2 (1.39) | 3.2 (1.43) | 3.1 (1.43) | 3.4 (1.30) | 3.3 (1.17) | 3.3 (1.34) | 3.3 (1.34) | 3.3 (1.32) |
| Week 26 | 2.6 (1.40) | 2.4 (1.54) | 2.9 (1.52) | 2.4 (1.58) | 2.8 (1.57) | 3.0 (1.47) | 2.5 (1.47) | 2.7 (1.56) | 2.9 (1.50) |
| Week 52 | 2.4 (1.53) | 2.8 (1.53) | 2.5 (1.51) | 2.2 (1.56) | 2.9 (1.39) | 2.3 (1.51) | 2.3 (1.54) | 2.9 (1.44) | 2.5 (1.51) |
| Change from | -1.0 (1.42) [†] | -0.4 (1.27) | -0.7 (1.44) [†] | -0.9 (1.35) [†] | -0.5 (1.16) [†] | -1.0 (1.30) [†] | -0.9 (1.39) [†] | -0.5 (1.20) [†] | -0.8 (1.38) [†] |

| Patient-Reported Outcome, Mean (SD) | LIPO-010 | | | CTR-1012 | | | COMBINED | | |
|---|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| | T-T N=153 | T-P N=50 | P-T N=111 | T-T N=92 | T-P N=85 | P-T N=86 | T-T N=245 | T-P N=135 | P-T N=197 |
| Change from Week 26 ^b | -0.2 (1.34) | 0.4 (1.19)* | -0.3 (1.24) [†] | -0.2 (1.33) | 0.1 (1.42) | -0.7 (1.24) [†] | -0.2 (1.30) | 0.2 (1.34) | -0.5 (1.25) [†] |
| p-value ^c | 0.0033* | | | 0.018* | | | <0.001 [†] | | |
| Belly profile, physician-rated ^c | | | | | | | | | |
| Baseline | 3.1 (1.15) | 3.1 (1.13) | 3.2 (1.24) | 3.1 (1.26) | 3.2 (1.20) | 3.0 (1.26) | 3.1 (1.19) | 3.2 (1.17) | 3.1 (1.25) |
| Week 26 | 2.4 (1.34) | 2.5 (1.31) | 2.7 (1.39) | 2.3 (1.34) | 2.5 (1.32) | 2.8 (1.45) | 2.3 (1.34) | 2.5 (1.32) | 2.8 (1.41) |
| Week 52 | 2.2 (1.51) | 2.4 (1.44) | 2.4 (1.34) | 2.0 (1.33) | 2.5 (1.33) | 2.2 (1.52) | 2.1 (1.45) | 2.4 (1.37) | 2.3 (1.42) |
| Change from Baseline | -0.9 (1.20) [†] | -0.7 (1.19) [†] | -0.8 (1.10) [†] | -1.0 (1.33) [†] | -0.7 (1.33) [†] | -0.8 (1.27) [†] | -1.0 (1.25) [†] | -0.7 (1.28) [†] | -0.8 (1.17) [†] |
| Change from Week 26 | -0.2 (1.13)* | -0.1 (1.18) | -0.4 (1.15) [†] | -0.2 (1.26) | -0.1 (1.25) | -0.5 (1.48) [†] | -0.2 (1.16)* | -0.1 (1.24) | -0.4 (1.30) [†] |
| p-value ^c | 0.351 | | | 0.043 | | | 0.066 | | |

ITT, intent-to-treat; PRO, patient-reported outcome; P-T, placebo-tesamorelin; SD, standard deviation; T-P, tesamorelin-placebo; T-T, tesamorelin-tesamorelin.

^a A larger actual value indicates less belly appearance distress.

^b A smaller actual value indicates a better belly size rating (i.e., on target with a “healthy look”).

^c A smaller actual value indicates a smaller belly profile where a 0 is “normal”.

^d For individual studies, within group change was tested using a paired samples t-test; For combined results, within-group change was tested using a mixed model analysis. A positive change from baseline score indicates an improvement (i.e., less distress).

^e Ranked ANCOVA for between-treatment comparisons (T-T vs T-P) including relevant covariates (e.g., gender, age) for scores.

^f Change scores underwent a transformation to absolute differences. A positive change from baseline score indicates improvement. For individual studies, within-group change was tested using a paired samples t-test for study LIPO-010 and a one-sample t-test against the value of “0” for study CTR-1012; for combined results, within group change was tested using a mixed model analysis.

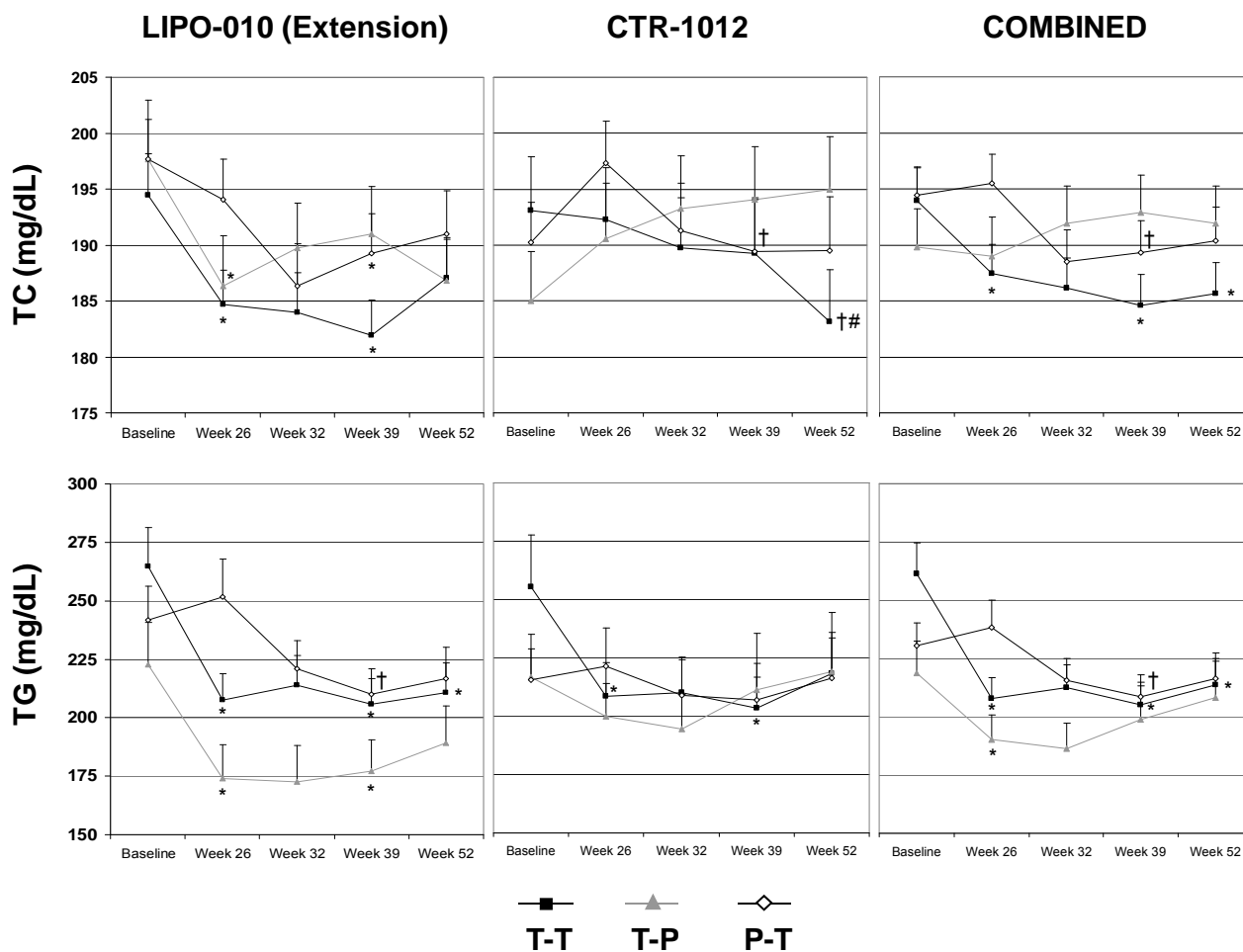
^g For individual studies, within-group change was tested using a paired samples t-test; For combined results, within-group change was tested using a mixed model analysis. A negative change from baseline score indicates improvement (less dysmorphic).

* p<0.05; † p<0.01.

5.2.4.2 Lipids

At Week 52, triglycerides, total cholesterol, and non-HDL-C decreased significantly from baseline in the T-T group (p<0.01 for all), and the mean changes in these parameters were statistically significantly different from the T-P group. Total cholesterol-to-HDL-C slightly decreased from baseline in the T-T group; the mean change, however, was not statistically significantly different from the T-P group (**Figure 17**). Mean HDL-C statistically significantly decreased from baseline in the T-T group, but remained within the normal range. There was no statistically significant difference between the T-T and T-P groups for mean change from baseline to Week 52 in HDL-C.

Figure 17. Total Cholesterol and Triglyceride Levels over 52 Weeks (Extension, ITT Population)



P-T, placebo-tesamorelin; T-P, tesamorelin-placebo; T-T, tesamorelin-tesamorelin.

Data are mean + SEM.

* p<0.01 vs baseline.

† p<0.01 vs Week 26.

p=0.001 for T-T vs T-P comparisons within each study (model includes variable at baseline + variable at Week 26 minus baseline + lipid-lowering therapy + treatment group; for T-T vs T-P comparisons based on the combined results, the model includes variable at baseline + variable at Week 26 minus baseline + lipid-lowering therapy + treatment group + study; only subjects in the T-T and T-P groups are included in these analyses).

5.2.4.3 Other body composition measurements and anthropometrics

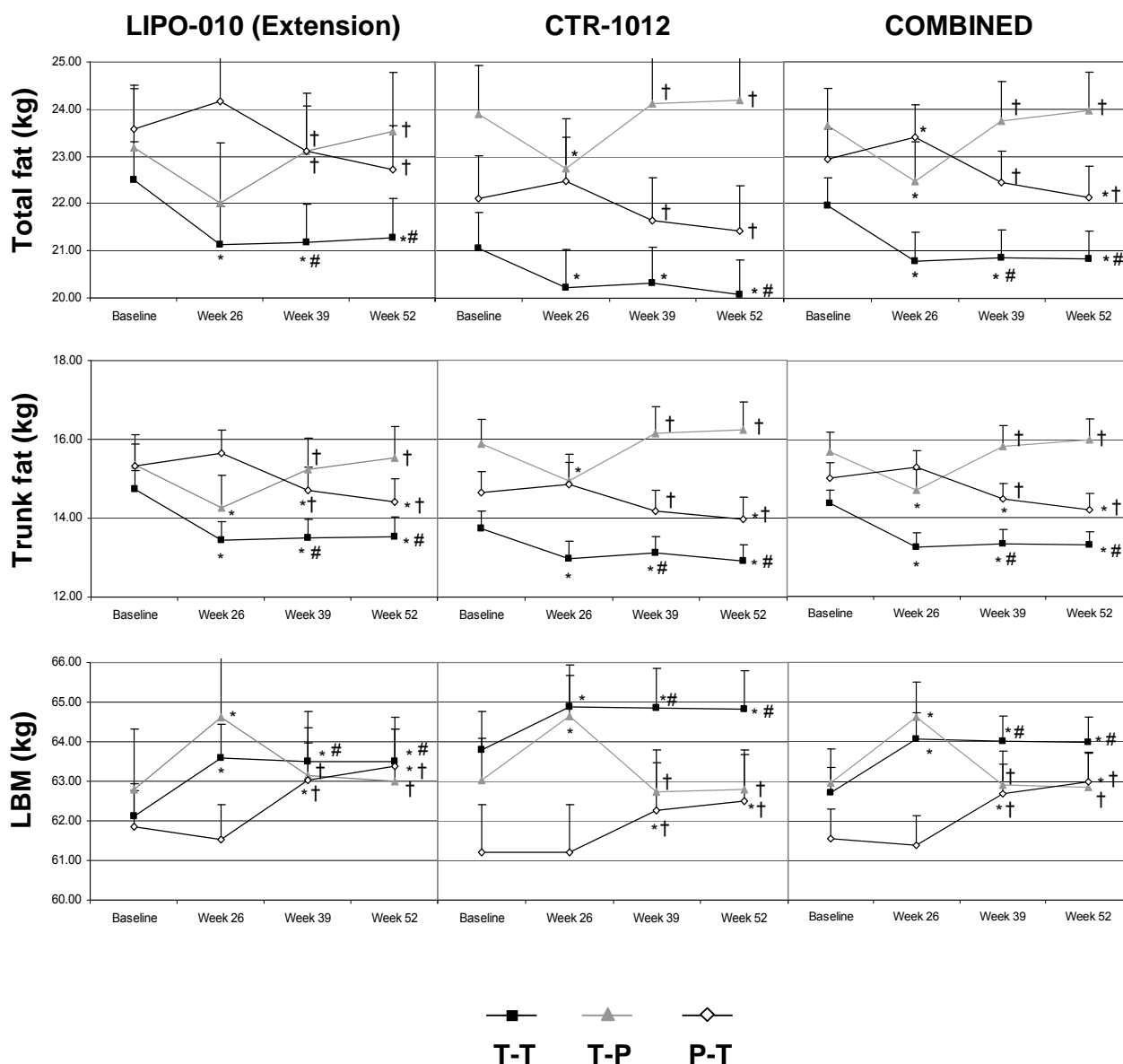
Trunk fat and total fat changed by small but insignificant amounts from Week 26 to Week 52 in the T-T group and decreased significantly from Week 26 to Week 52 in the P-T group ($p<0.01$) (**Figure 18**). The decreases from baseline to Week 52 were significant in the T-T group ($p<0.01$) and statistically significantly different from those observed in the T-P group ($p<0.001$).

The change in LBM from Week 26 to Week 52 was small and statistically insignificant in the T-T group, and there was a significant increase from Week 26 to Week 52 in the P-T group (**Figure 18**). LBM decreased significantly from Week 26 to Week 52 in the T-P group ($p<0.01$). The change from baseline to Week 52 in the T-T group was significantly different from that in the T-P group ($p<0.001$).

The mean change from baseline in abdominal SAT was not significantly different, but the mean change from baseline in the VAT/SAT ratio was significantly different ($p<0.001$) between the T-T and T-P groups. Limb fat did not change significantly within groups. No clinically or statistically significant between-group differences were found.

The mean changes from Week 26 to Week 52 in WC and the waist-to-hip ratio were small and insignificant in the T-T group. WC increased in the T-P group, although the increase was not statistically significant. The waist-to-hip ratio changed significantly from Week 26 to Week 52 in the T-P group ($p<0.01$), indicating a loss of efficacy following discontinuation of tesamorelin. Changes from baseline in both measures were significantly different between the T-T and T-P groups (WC, $p<0.001$; waist-to-hip ratio, $p=0.008$). Hip circumference did not change significantly, and there were no between-group differences for this measurement.

Figure 18. Total Fat, Trunk Fat, and Lean Body Mass over 52 Weeks (Extension, ITT Population)



ITT, intent-to-treat; LBM, lean body mass; P-T, placebo-tesamorelin; T-P, tesamorelin-placebo; T-T, tesamorelin-tesamorelin.

Data are mean + SEM.

* p<0.01 vs baseline.

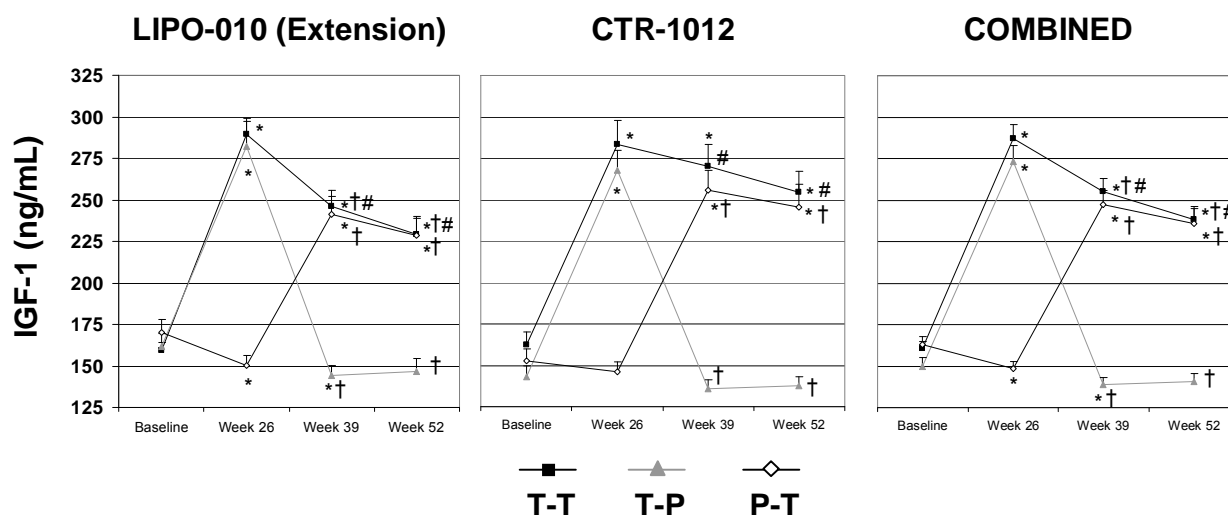
† p<0.01 vs Week 26.

p<0.001 for T-T vs T-P comparison within each study (model includes variable at baseline + variable at Week 26 minus baseline + treatment group; for T-T vs T-P comparisons based on the combined results, the model includes variable at baseline + variable at Week 26 minus baseline + treatment group + study; only subjects in the T-T and T-P groups are included in these analyses).

5.2.4.4 IGF-1

The increase in IGF-1 from baseline to Week 52 was significant in the T-T group ($p < 0.01$) and significantly different from the T-P group ($p < 0.001$) (**Figure 19**). From Week 26 to Week 52, IGF-1 decreased significantly in the T-P group and increased significantly in the P-T group ($p < 0.01$ for each group). These results support the sustained efficacy of tesamorelin and the loss of efficacy associated with discontinuation of tesamorelin.

Figure 19. IGF-1 Levels over 52 Weeks (Extension, ITT Population)



IGF-1, insulin-like growth factor-1; ITT, intent-to-treat; P-T, placebo-tesamorelin; T-P, tesamorelin-placebo; T-T, tesamorelin-tesamorelin.

Data are mean + SEM.

* $p < 0.01$ vs baseline.

† $p < 0.01$ vs Week 26.

$p < 0.001$ for T-T vs T-P comparisons within each study (model includes IGF-1 at baseline + IGF-1 at Week 26 minus baseline + treatment group; for T-T vs T-P comparisons based on the combined results, the model includes IGF-1 at baseline + IGF-1 at Week 26 minus baseline + treatment group + study; only subjects in the T-T and T-P groups are included in these analyses).

5.3 Summary of Efficacy in Phase 2 Study (LIPO-008)

Seventy-nine percent of the patients completed the LIPO-008 study. The main reason for discontinuation was withdrawal of consent.

There were no significant differences among groups in baseline characteristics or ART (**Table 20**). Overall, the average age was 46 years, and the mean weight and BMI were 87 kg and 28 kg/m², respectively. The mean WC was 101.5 cm and the mean waist-to-hip ratio was 1. IGT and diabetes were present in 20% and 5%, respectively, of the entire study group, with no significant differences among groups.

Table 20. Patient Demographics and Disease Characteristics at Baseline in LIPO-008 (ITT Population)

| Characteristic | Tesamorelin 2 mg/day N=21 | Tesamorelin 1 mg/day N=19 | Placebo N=21 |
|---|------------------------------|------------------------------|-----------------|
| Age, years | | | |
| Mean (SD) | 44.6 (7.14) | 46.5 (6.42) | 46.1 (7.39) |
| Median | 43.7 | 46.6 | 46.9 |
| Range | 34–59 | 33–60 | 32–60 |
| Gender, n (%) | | | |
| Male | 18 (85.7) | 18 (94.7) | 18 (85.7) |
| Female | 3 (14.3) | 1 (5.3) | 3 (14.3) |
| Ethnic origin, n (%) | | | |
| White/Caucasian | 17 (81.0) | 15 (78.9) | 18 (85.7) |
| Asian | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Black/African-American | 2 (9.5) | 1 (5.3) | 1 (4.8) |
| Hispanic | 2 (9.5) | 2 (10.5) | 2 (9.5) |
| Other | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Duration of HIV condition, years | | | |
| N | 15 | 15 | 13 |
| Mean (SD) | 11.2 (4.87) | 12.1 (6.30) | 10.6 (5.32) |
| Median | 8.0 | 13.0 | 10.0 |
| Range | 4-19 | 1-21 | 3-19 |
| Viral load, copies/mL | | | |
| N | 4 | 3 | 1 |
| Mean (SD) | 959.5 (735.47) | 3903.7 (3508.03) | 4407.0 |
| Undetectable viral load (<50 copies/mL), n (%) | 13 (61.9) | 10 (52.6) | 15 (71.4) |
| Undetectable viral load (<400 copies/mL), n (%) | 4 (19.0) | 6 (31.6) | 5 (23.8) |

| Characteristic | Tesamorelin 2 mg/day N=21 | Tesamorelin 1 mg/day N=19 | Placebo N=21 |
|---|------------------------------|------------------------------|-----------------|
| CD4 cell count, cells/mm³ | | | |
| Mean (SD) | 577.0 (327.22) | 525.4 (309.10) | 540.9 (252.93) |
| Median | 521.0 | 460.0 | 527.0 |
| Range | 211-1426 | 134-1155 | 150-1000 |
| Duration of ART, months | | | |
| N | 21 | 19 | 20 |
| Mean (SD) | 75.5 (24.40) | 71.8 (34.70) | 77.3 (57.12) |
| Median | 72.0 | 73.0 | 84.0 |
| Range | 36-168 | 24-132 | 4-240 |
| Type of ART regimen, n (%) | | | |
| PI | 4 (19.0) | 8 (42.1) | 11 (52.4) |
| NRTI | 21 (100) | 19 (100) | 21 (100) |
| NNRTI | 15 (71.4) | 12 (63.2) | 11 (52.4) |
| Entry inhibitor | 0 | 2 (10.5) | 0 |

ART, antiretroviral therapy; HIV, human immunodeficiency virus; ITT, intent-to-treat; NNRTI, non-nucleoside reverse transcriptase inhibitors; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; SD, standard deviation.

VAT decreased significantly from baseline at Weeks 6 and 12 in the tesamorelin 2-mg group (-13.7 and -21.5 cm², respectively), but this change was not significantly different from placebo (**Table 21**). VAT decreased by 5%, 4%, and 16% in the placebo, tesamorelin 1-mg, and tesamorelin 2-mg groups, respectively. A strong dose-response relationship was observed at each time point.

Table 21. Actual Change from Baseline to Week 6 and Week 12 in LIPO-008 (ITT Population)

| Visit, Mean (SD) | Tesamorelin 2 mg/day N=21 | Tesamorelin 1 mg/day N=19 | Placebo N=21 | p-value |
|-------------------------------|------------------------------|------------------------------|-------------------|---------------------|
| Baseline VAT, cm ² | 160.242 (53.5000) | 157.826 (56.6141) | 190.540 (75.6608) | 0.2289 ^a |
| Change at Week 6 | -13.657 (15.9810)* | -8.179 (28.3943) | -5.806 (27.4581) | 0.5774 ^b |
| Change at Week 12 | -21.500 (27.9158)* | -11.943 (28.7108) | -12.021 (32.4765) | 0.4465 ^b |
| Change at last observation | -19.097 (26.6236)* | -11.969 (27.7994) | -12.390 (31.3278) | 0.5631 ^b |

ITT, intent-to-treat; SD, standard deviation; VAT, visceral adipose tissue.

* Statistically significant difference from baseline.

^a p-value for continuous data is based on ANOVA model including the treatment term.

^b p-value is based on the ANCOVA model: change from baseline in VAT = baseline and treatment.

Trunk fat decreased from baseline in the tesamorelin 1-mg and 2-mg groups and increased in the placebo group; the difference in changes was significant between the te-

samorelin 2-mg group and the placebo group at both Week 6 and Week 12. Also, LBM increased in the tesamorelin groups and decreased in the placebo group, with a statistically significant difference between the tesamorelin 2-mg and placebo groups at Weeks 6 and 12. The trunk-to-limb fat ratio decreased significantly from baseline in the tesamorelin 1-mg group ($p=0.001$), but not in the tesamorelin 2-mg or placebo groups.

At Week 12, IGF-1 increased by a mean (standard deviation [SD]) of 87.5 (66.9) ng/mL from a mean baseline of 165.3 ng/mL and 122.6 (79.1) ng/mL from a mean baseline of 157.0 ng/mL in the tesamorelin 1-mg and 2-mg groups, respectively. These increases from baseline were statistically significant and significantly different from placebo in both the tesamorelin 1-mg ($p=0.0015$) and the tesamorelin 2-mg ($p<0.0001$) groups. The mean change from baseline to Week 6 was also statistically significant among the 3 treatment groups. Changes from baseline and differences compared with placebo for IGFBP-3 were also significant for both active treatments.

HDL-C increased from baseline in each group, and this change was statistically significant at Week 12 in the tesamorelin 2-mg group ($p=0.042$). The total cholesterol-to-HDL-C ratio decreased from baseline to Week 12 in each tesamorelin group and increased in the placebo group, but none of the treatment differences was statistically significant. The change from baseline in the total cholesterol-to-HDL-C ratio was significant at the last observation ($p=0.008$) in the tesamorelin 2-mg group. Triglycerides decreased in both tesamorelin groups and were significantly decreased from baseline to Week 12 ($p=0.0295$) in the tesamorelin 2-mg group. At Week 12, mean levels of total cholesterol and non-HDL-C were increased in the placebo group and decreased in the tesamorelin 2-mg group.

Changes from baseline in glycemic parameters (FBG, HbA_{1c}, 2-hour postprandial blood glucose, fasting insulin, and the HOMA-IR) were not significantly different from placebo for either 1 mg or 2 mg tesamorelin.

With regard to QOL measurements, significant differences among groups were not observed for the general part of the QOL questionnaire. For the disease-specific part of the questionnaire, significant improvements in abdominal bloating and enlarged abdominal girth were recorded for the tesamorelin 2-mg group and in abdominal pain for the tesamorelin 1-mg group.

5.4 Efficacy Conclusions

5.4.1 Main phase conclusions

Combined results showed that daily SC administration of 2 mg tesamorelin to HIV patients for 26 weeks resulted in a statistically significant mean percent decrease in VAT compared with an increase in the placebo group. In both main phase studies, mean changes in VAT were significantly greater with 2 mg tesamorelin compared with placebo ($p < 0.001$), with decreases of 15.1% (LIPO-010) and 11.1% (CTR-1011) in the tesamorelin groups.

Significant increases in IGF-1 confirmed the PD efficacy of tesamorelin. For multiple secondary and other efficacy endpoints assessing lipids, body composition, anthropometrics, and “belly appearance distress,” combined study results were generally consistent with the results from individual studies and supported the superior efficacy of tesamorelin 2 mg compared with placebo.

The changes in biomarkers with tesamorelin, assessed in the main phase of LIPO-010, also showed a trend toward improvement in metabolic factors, with significant increases in osteocalcin, adiponectin, and tPA antigen levels.

Many endpoints provided important information about the utility of tesamorelin for managing the lipodystrophy side effects of ART. These endpoints include:

- A statistically significant decrease from baseline in mean trunk fat compared with placebo in the individual and the combined main phase studies.
- A greater improvement in mean “belly appearance distress” scores compared with placebo in the individual and the combined main phase studies.
- Statistically significant decreases from baseline in triglycerides (combined and LIPO-010 main results).
- Statistically significant decreases from baseline in mean total cholesterol and non-HDL-C (combined and LIPO-010 main results).
- A statistically significant increase from baseline in mean LBM compared with placebo in the individual and the combined main phase studies.

Differences between tesamorelin- and placebo-treated patients were consistent among subgroups defined by gender, age, race, geographic region, IGT/diabetes, baseline VAT, ART regimen, anti-tesamorelin IgG antibody status and titer, and testosterone use.

5.4.2 Extension phase conclusions

The efficacy of tesamorelin was sustained over 52 weeks, as shown by a significant decrease in VAT from baseline to Week 26 and a small (but insignificant) decrease in VAT from Week 26 to Week 52 in the group that received tesamorelin throughout (T-T group).

Seventy-eight percent of patients in the T-T group who were responders (lost $\geq 8\%$ of their baseline VAT) at Week 26 maintained their VAT loss at Week 52. VAT increased after tesamorelin was discontinued in the T-P group; most of the VAT loss was regained by Week 39 of treatment. A statistically significant mean percent decrease in VAT was observed from Week 26 to Week 52 in the group switched from placebo to tesamorelin (P-T group), demonstrating the onset of efficacy when tesamorelin was initiated.

At Week 52, trunk fat loss and LBM gain were sustained in the T-T group, but improvements in these parameters were lost in the T-P group. As in the main phase, trunk fat, and LBM improved and limb fat was preserved in P-T patients.

Non-HDL-C and total cholesterol decreased in patients who received tesamorelin for 52 weeks, whereas treatment had no significant effect on triglycerides, and the total cholesterol-to-HDL-C ratio. In the P-T group, non-HDL-C decreased.

The primary results were corroborated by sustained improvements in “belly appearance distress” scores over 52 weeks in the group receiving tesamorelin throughout and decreased improvements in the group re-randomized to placebo.

5.4.3 Phase 2 study (LIPO-008) conclusions

After 12 weeks of treatment, tesamorelin 2 mg decreased VAT by 16%, which was comparable with the decrease achieved with pharmacological rhGH (-8.6%) ([Kotler 2004](#)). Trunk fat and VAT were significantly decreased from baseline to Week 12. Both 1 mg and 2 mg tesamorelin significantly increased IGF-1 from baseline to Week 12. Treatment with tesamorelin resulted in a dose-related increase in LBM.

Tesamorelin 2 mg improved the lipid profile, with significant improvements in triglycerides, the total cholesterol-to-HDL-C ratio, and HDL-C at Week 12. Over 12 weeks, tesamorelin 2 mg did not significantly affect glucose control, either among patients who had normal glucose tolerance or among those who had IGT or type 2 diabetes.

6 CLINICAL SAFETY

6.1 Overview of Safety Evaluation

The overall safety of tesamorelin was evaluated in a combined data set of 17 clinical studies (8 Phase 1, 7 Phase 2, and 2 Phase 3 studies). The Phase 3 studies conducted in HIV-infected patients with lipodystrophy included the LIPO-010 study (main and extension) and the CTR-1011 main and CTR-1012 extension phase studies. The overall safety evaluation also included a Phase 2 study conducted in HIV-infected patients with lipodystrophy (LIPO-008) and a diabetic safety study conducted in non-HIV-infected patients (DIABETIC-006). Five additional Phase 2 studies were also conducted in patients without HIV infection.

The safety population was defined as all randomized patients who received ≥ 1 dose of study treatment (tesamorelin or placebo). Missing data were not imputed. For patients who received multiple doses of tesamorelin in the same study, the analysis treatment group was defined as the maximum dose received. Inferential statistical analyses were conducted; however, data analyses were primarily descriptive. Tests of significance (2-sided) were done using a Type I (α) level of 0.05, unless otherwise specified. No adjustments were made for multiple comparisons.

6.2 All Studies

The 17 clinical studies included 1222 patients who received ≥ 1 dose of tesamorelin for 1 day to 26 weeks. With the additional 197 patients who switched from placebo to tesamorelin in the Phase 3 extension studies, 1419 patients received ≥ 1 dose of tesamorelin overall (**Table 22**). The overall mean exposure to 2 mg/day tesamorelin was 21 weeks. A total of 459 patients received placebo.

Table 22. Overall Duration of Exposure to Tesamorelin by Dose (All Studies)

| | Tesamorelin Dose Groups | | | |
|---|-------------------------|------------------------|----------------------|------------------------|
| | ≤1 mg/day, SC N=179 | 2 mg/day, SC N=1150 | 4 mg/day, SC N=68 | 0.2 mg/day, IV N=22 |
| Duration of exposure to tesamorelin, weeks | | | | |
| Mean (SD) | 8.20 (6.778) | 21.34 (17.642) | 1.56 (1.768) | 0.28 (0.030) |
| Median | 6.57 | 24.00 | 0.29 | 0.29 |
| Maximum | 20.3 | 60.4 | 4.0 | 0.3 |
| Patients, n (%) | | | | |
| 0-13 weeks | 179 (100.0) | 1150 (100.0) | 68 (100.0) | 22 (100.0) |
| 14-26 weeks | 30 (16.8) | 675 (58.7) | 0 | 0 |

IV, intravenous; SC, subcutaneous; SD, standard deviation.

Mean age across the treatment groups ranged from 40 to 56 years. The proportion of patients ≥65 years of age was 16% in the tesamorelin groups and 27% in the placebo group.

No clinically meaningful differences in the reasons for premature study discontinuation were observed between the tesamorelin and placebo groups. The primary reasons for discontinuation in the tesamorelin 2-mg and placebo groups were AEs (7.6% and 5.0%, respectively) and withdrawal of consent (6.4% and 7.4%, respectively). Few patients had AEs leading to discontinuation that the investigator considered severe in intensity (2.5% in the tesamorelin group and 2.2% in the placebo group) or related to study treatment (4.9% in the tesamorelin group and 3.1% in the placebo group).

Comparable percentages of patients in the tesamorelin and placebo groups reported ≥1 AE (76% and 72%, respectively) (**Table 23**). In both the tesamorelin and placebo groups, a higher proportion of patients reported AEs during 0-13 weeks (72% and 65%, respectively) compared to 14-26 weeks (52% and 49%, respectively). Most AEs were of mild or moderate severity. No severe AEs occurred in ≥1% of tesamorelin-treated patients. All AEs occurring in ≥5% of tesamorelin-treated patients and more frequently in tesamorelin-treated than placebo patients were injection-site related. AEs known to be related to GH were reported by 18% and 13% of tesamorelin-treated and placebo patients, respectively.

Table 23. AEs Occurring in $\geq 5\%$ of Tesamorelin-Treated Patients and More Frequently in Tesamorelin-Treated than Placebo Patients (Weeks 0-26) by Treatment Assignment (All Studies)

| | Tesamorelin (All Doses) N=1222 | Placebo N=459 |
|---|-----------------------------------|-------------------|
| Patients with ≥ 1 AE, n (%) | 927 (75.9) | 332 (72.3) |
| | Patients, n (%) | |
| General disorders and administration site conditions | 523 (42.8) | 125 (27.2) |
| Injection-site pain | 112 (9.2) | 9 (2.0) |
| Injection-site erythema | 109 (8.9) | 8 (1.7) |
| Injection-site irritation | 107 (8.8) | 5 (1.1) |
| Injection-site pruritus | 66 (5.4) | 3 (0.7) |

AE, adverse event.

The incidence of SAEs was low in both the tesamorelin and placebo groups (3.1% and 4.4%, respectively). No specific event was reported by >2 patients in either group. The incidence of severe SAEs was also low: 2.2% in the tesamorelin group and 3.1% in the placebo group. Only 0.4% of patients in each of the tesamorelin and placebo groups reported SAEs considered to be related to treatment. No SAE considered to be related to treatment was reported by more than 1 patient in either group.

A total of 10 deaths (8 tesamorelin and 2 placebo patients) were reported in 4 studies and are discussed in **Appendix III**. Four deaths (1 placebo and 3 tesamorelin 2-mg) occurred in patients aged 81 to 95 years in the Phase 2 study of elderly patients recovering from hip fracture surgery (HF-004). Two patients (1 tesamorelin 1-mg and 1 tesamorelin 2-mg) died in the Phase 2 study of chronic obstructive pulmonary disease (COPD) patients with wasting (COPD-003). All of these patients had significant medical histories relevant to the events leading to death, and the study investigator in all cases considered the deaths to be unrelated to study treatment. Three men in the HIV Phase 3 studies died (1 while receiving placebo only and 2 while receiving tesamorelin 2 mg); in addition, 1 death occurred 9 months after the last dose of tesamorelin (details in **Section 6.4.5**).

6.3 Phase 2 HIV Study (LIPO-008)

Sixty-one (61) HIV-infected patients received study treatment as follows: 21 received tesamorelin 2 mg/day, 19 received tesamorelin 1 mg/day, and 21 received placebo. Mean exposure was 9.6 weeks to tesamorelin 2 mg/day and 12 weeks to tesamorelin 1 mg/day. Mean age across treatment groups ranged from 45 to 47 years. Most patients were men (89%) and white (82%). Baseline demographics and HIV characteristics were comparable among treatment groups. Most had undetectable viral loads (53 to 71%) and mean duration of ART ranged from 72 to 77 months.

The majority of patients in each treatment group completed the study: 71%, 90%, and 76% of patients in the tesamorelin 2-mg, tesamorelin 1-mg, and placebo groups, respectively. Withdrawal of consent and AEs were the most common reasons for study discontinuation.

The proportion of patients who reported ≥ 1 AE was similar between the tesamorelin 2-mg and 1-mg groups (76% and 79%, respectively) and higher in the placebo group (86%). Most AEs were of mild to moderate severity, and the types of AEs reported were not limited to any particular event. Injection-site pruritus was reported in 1 (4.8%) patient who received tesamorelin 2 mg/day, and injection-site erythema was reported in 2 (10.5%) patients who received tesamorelin 1 mg/day. Neither of these administration-site conditions was reported in the placebo group. Arthralgia was reported in 3 (14.3%), 2 (10.5%), and 3 (14.3%) patients who received tesamorelin 2 mg, tesamorelin 1 mg, and placebo, respectively, and pain in extremity was reported in 2 (9.5%) patients in the tesamorelin 2 mg group and not reported in the other groups. There were no deaths. One patient who received tesamorelin 1 mg/day experienced an SAE (chest pain). The event was considered by the study investigator to be of severe intensity and unrelated to study treatment.

6.4 Phase 3 HIV Studies (LIPO-010, CTR-1011, CTR-1012)

6.4.1 Exposure

Overall, the mean cumulative exposure to tesamorelin was 30.5 weeks. A total of 610 patients completed 26 weeks of treatment with tesamorelin (413 and 197 patients in the main and extension phase studies, respectively) and 209 patients completed 52 weeks of treatment with tesamorelin. Of 740 patients who received at least 1 dose of tesamorelin, 740 (100%) were exposed for 0-13 weeks, 647 (87.4%) were exposed for 14-26 weeks, 400 (54.1%) were exposed for 27-39 weeks, 225 (30.4%) were exposed for 40-52 weeks, and 43 (5.8%) were exposed for ≥ 52 weeks.

During the main phase studies (LIPO-010 main and CTR-1011), 543 patients received tesamorelin 2 mg/day and 263 patients received placebo. The mean number of days on study was comparable between the tesamorelin 2-mg (159.1 days) and placebo (157.4 days) groups (**Table 24**). In the extension phase (LIPO-010 extension and CTR-1012), 246 patients continued to receive tesamorelin (T-T group), 135 who had received tesamorelin in the main phase were re-randomized to placebo (T-P group), and 197 who had received placebo in the main phase were switched to tesamorelin (P-T group). The mean days of exposure were similar among the T-T (163.6 days), T-P (153.7 days), and P-T (159.7 days) groups (**Table 24**).

Table 24. Time on Study by Study and Treatment (Combined, Phase 3 Studies)

| | MAIN | | EXTENSION | | |
|----------------------------|----------------------|------------------|---------------|---------------|---------------|
| | Tesamorelin n=541 | Placebo n=262 | T-T n=244 | T-P n=133 | P-T n=196 |
| Time on study, days | | | | | |
| Mean (SD) | 159.1 (51.54) | 157.4 (54.86) | 163.6 (36.73) | 153.7 (43.91) | 159.7 (40.73) |
| Median | 182.0 | 182.0 | 174.0 | 174.0 | 174.0 |
| Maximum | 217 | 201 | 212 | 211 | 209 |

P-T, placebo-tesamorelin; SD, standard deviation; T-P, tesamorelin-placebo; T-T, tesamorelin-tesamorelin.
Tesamorelin refers to tesamorelin 2 mg/day.

6.4.2 Patient disposition

The proportion of patients who completed the main phase was comparable between the tesamorelin and placebo groups (76.1% and 78.7%, respectively). The proportion of patients who completed the extension phase was 85.0% in the T-T group, 76.3% in the T-P group, and 80.7% in the P-T group. No clinically meaningful differences were observed between treatment groups in the primary reasons for study discontinuation in both the main and extension phases (**Table 25**). In the main phase, the most common reasons for discontinuation in the tesamorelin and placebo groups were AEs (9.6% and 6.8%, respectively) and withdrawal of consent (7.9% and 7.2%, respectively). In the extension phase, AEs leading to study discontinuation were reported in a comparatively smaller proportion of patients in the T-T (2.4%) and T-P (5.2%) groups, while the rate in the P-T group (9.1%) was similar to that observed in tesamorelin-treated patients in the main phase.

Table 25. Primary Reason for Discontinuation (Combined, Phase 3 Studies)

| Patients, n (%) | MAIN | | EXTENSION | | |
|---|----------------------|------------------|--------------|--------------|--------------|
| | Tesamorelin n=413 | Placebo n=207 | T-T n=209 | T-P n=103 | P-T n=159 |
| Adverse event | 52 (9.6) | 18 (6.8) | 6 (2.4) | 7 (5.2) | 18 (9.1) |
| Lack of compliance with protocol requirements and/or procedures | 13 (2.4) | 1 (0.4) | 8 (3.3) | 4 (3.0) | 3 (1.5) |
| Withdrawal of consent | 43 (7.9) | 19 (7.2) | 20 (8.1) | 15 (11.1) | 13 (6.6) |
| Lost to follow-up | 12 (2.2) | 9 (3.4) | 3 (1.2) | 4 (3.0) | 4 (2.0) |
| Other | 10 (1.8) | 9 (3.4) | 1 (0.4) | 2 (1.5) | 0 |

P-T, placebo-tesamorelin; T-P, tesamorelin-placebo; T-T, tesamorelin-tesamorelin.
Tesamorelin refers to tesamorelin 2 mg/day.

6.4.3 Baseline characteristics

Baseline characteristics for the main and extension phase studies are shown in **Table 8** and **Appendix V**. Additionally, the proportions of patients who had FBG values <100 mg/dL (tesamorelin, 64.1%; placebo, 66.5%) or ≤110 mg/dL (tesamorelin, 78.1%; placebo, 82.1%) were not significantly different between groups at baseline.

6.4.4 Adverse events

AEs occurring in $\geq 5\%$ of tesamorelin-treated patients and more frequently in tesamorelin-treated patients than placebo patients are shown in **Table 26** for the main and extension phases. During both time periods, many of the events were injection-site related or AEs known to be related to GH (such as arthralgia).

Table 26. Patients Who Experienced AEs Occurring in $\geq 5\%$ of Tesamorelin-Treated Patients and More Frequently in Tesamorelin-Treated than Placebo Patients (Combined, Phase 3 Studies)

| | MAIN | | EXTENSION | | |
|---|----------------------|-------------------|-------------------|------------------|-------------------|
| | Tesamorelin N=543 | Placebo N=263 | T-T N=246 | T-P N=135 | P-T N=197 |
| Patients with AEs, n (%) | 425 (78.3) | 187 (71.1) | 154 (62.6) | 81 (60.0) | 146 (74.1) |
| General disorders and administration-site conditions | 189 (34.8) | 65 (24.7) | 32 (13.0) | 21 (15.6) | 53 (26.9) |
| Injection-site erythema | 46 (8.5) | 7 (2.7) | 3 (1.2) | 0 | 13 (6.6) |
| Injection-site pruritus | 41 (7.6) | 2 (0.8) | 5 (2.0) | 0 | 16 (8.1) |
| Edema peripheral | 33 (6.1) | 6 (2.3) | 5 (2.0) | 0 | 8 (4.1) |
| Injection-site pain | 22 (4.1) | 8 (3.0) | 0 | 0 | 10 (5.1) |
| Infections and infestations | 144 (26.5) | 78 (29.7) | 69 (28.0) | 30 (22.2) | 50 (25.4) |
| Upper respiratory tract infection | 23 (4.2) | 17 (6.5) | 18 (7.3) | 5 (3.7) | 8 (4.1) |
| Sinusitis | 18 (3.3) | 12 (4.6) | 12 (4.9) | 0 | 10 (5.1) |
| Musculoskeletal and connective tissue disorders | 158 (29.1) | 63 (24.0) | 33 (13.4) | 19 (14.1) | 66 (33.5) |
| Arthralgia | 72 (13.3) | 29 (11.0) | 14 (5.7) | 8 (5.9) | 29 (14.7) |
| Pain in extremity | 33 (6.1) | 12 (4.6) | 8 (3.3) | 1 (0.7) | 15 (7.6) |
| Myalgia | 30 (5.5) | 5 (1.9) | 3 (1.2) | 0 | 7 (3.6) |

AE, adverse event; P-T, placebo-tesamorelin; T-P, tesamorelin-placebo; T-T, tesamorelin-tesamorelin.

AEs occurring in $\geq 5\%$ of tesamorelin-treated patients and more frequently in tesamorelin than in placebo patients in the main phase are also shown for the extension phase. Similarly, AEs $\geq 5\%$ of T-T patients and more frequently in T-T than in T-P patients in the extension phase are also shown for the main phase.

To identify AEs that might occur primarily after extended treatment, the incidence of AEs was summarized and compared for weeks 0-13 and 14-26 in the main phase studies and weeks 27-39 and weeks 40-52 in the extension phase studies. The incidence of AEs

was greater during 0-13 weeks than during 14-26 weeks, greater during 27-39 weeks than during 40-52 weeks, and greater during 0-26 weeks than during 27-52 weeks. No AEs were identified that might occur primarily after extended treatment.

During the main phase studies, 9.6% of tesamorelin-treated patients compared to 6.8% of placebo patients discontinued due to AEs. Comparable percentages of tesamorelin-treated and placebo patients (3.5% and 3.4%, respectively) experienced AEs leading to discontinuation and considered to be of severe intensity. A greater proportion of patients in the tesamorelin vs placebo group (8.8% and 4.6%, respectively) had AEs leading to discontinuation and considered to be related to study treatment.

During the extension phase studies, no AEs were reported in $\geq 1.0\%$ of the patients in the T-T group who discontinued the study prematurely. In the P-T group, 3.0% of patients who discontinued the study due to AE experienced injection-site pruritus. The percentages of patients with AEs leading to discontinuation and considered to be severe in intensity were 1.2%, 1.5%, and 3.0% in the T-T, T-P, and P-T groups, respectively. The percentages of patients with AEs leading to discontinuation and considered to be related to study treatment were 1.2%, 2.2%, and 7.1% in the T-T, T-P, and P-T groups, respectively.

Common AEs leading to discontinuation were thought to be related to the induction of GH secretion and local injection-site reactions. The incidence of GH-related and injection-site-related AEs in patients who discontinued the study prematurely is described in sections 6.4.6 and 6.4.7, respectively.

AEs were analyzed by subpopulations of age, gender, race, viral load, hepatitis, anti-tesamorelin IgG antibodies, IGF-1 SDS category, IGT/diabetes, ART regimen, lipid-lowering treatment, concomitant medications, and duration of HIV drug exposure. In general, these analyses indicated no clinically notable differences in the overall incidence of AEs.

6.4.5 Deaths and SAEs

Three deaths occurred during the main and extension phase studies: 1 in the placebo group (1/398; 0.25%) and 2 among tesamorelin-treated patients (2/740; 0.27%) (**Table 27**). The treating physician did not consider any of these deaths to be related to study treatment. Two patients (1 tesamorelin and 1 placebo) had cardiovascular-related AEs that led to death. The third patient, who received tesamorelin, suffered from post-surgical procedure complications of hemorrhage and asphyxiation after tonsillectomy and removal of polyps that led to death. One additional patient died 9 months after the last dose of tesamorelin 2 mg, which he received for 3 months and 5 days. This patient was diagnosed with metastatic lung adenocarcinoma 5 months after the last dose. This event was considered by the treating physician to be related to study treatment. The patient had a history of lymphadenopathy and basal cell carcinoma (**Table 27**; **See Appendix III, Case DE-1**).

Table 27. Deaths (Phase 3 Studies)

| Study | Age/Gender/ Race | Treatment Group | Preferred Term | Duration of Tesamorelin Exposure | Relationship to Study Treatment | Risk Factors |
|---------------------------------|---------------------|--------------------|---|--|---------------------------------------|---|
| CTR-1011 (Main) | 50/Male/White | Placebo | Arrhythmia | NA | Unrelated | Marfan's syndrome, aortic aneurysm, HTN, previous MI with sinus tachycardia |
| LIPO-010 (Extension) | 54/Male/White | T-T | Arteriosclerosis coronary artery | 7 months and 2 days | Unrelated | Angioplasty, CAD, substance abuse (alcohol), atorvastatin calcium |
| LIPO-010 (Extension) | 50/Male/Black | P-T | Post-procedure hemorrhage; asphyxiation | 3 months and 23 days | Unrelated | HTN, angioedema, COPD |

CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; HTN, hypertension; MI, myocardial infarction; NA, not applicable; P-T, placebo-tesamorelin; T-T, tesamorelin-tesamorelin.
Tesamorelin refers to tesamorelin 2 mg/day.

SAEs that occurred in the main and extension phase studies are shown in **Appendix VI**. The incidence of SAEs did not differ between treatment groups across the clinical stud-

ies. No specific SAE was reported by ≥ 2 patients in any treatment group, except sepsis. During the main phase studies, comparable proportions of patients in the tesamorelin and placebo groups reported SAEs (3.7% and 4.2%, respectively) and severe SAEs (2.4% and 3.0%, respectively) (**Table 28**). Sepsis was reported by 2 patients in the tesamorelin group (0.4%). SAEs considered to be related to study treatment occurred in 0.9% and 0.8% of patients in the tesamorelin and placebo groups, respectively. During the extension phase studies, the proportion of patients who experienced SAEs in the T-T, T-P, and P-T groups were 2.8%, 2.2%, and 3.0%, respectively. The incidence of severe SAEs was higher in the T-P and P-T groups (1.5% and 2.5%, respectively) than in the T-T group (0.8%). No specific SAE was reported by ≥ 2 patients in any treatment group. SAEs considered to be related to treatment occurred in 0.4%, 0%, and 1.0% of the T-T, T-P, and P-T groups, respectively.

Table 28. SAEs (Combined, Phase 3 Studies)

| | MAIN | | EXTENSION | | |
|---|----------------------|------------------|--------------|--------------|--------------|
| | 0-26 Weeks | | 27-52 Weeks | | |
| | Tesamorelin N=543 | Placebo N=263 | T-T N=246 | T-P N=135 | P-T N=197 |
| Patients with SAEs, n (%) | 20 (3.7) | 11 (4.2) | 7 (2.8) | 3 (2.2) | 6 (3.0) |
| Patients with ≥ 1 SAE of severe intensity, n (%) | 13 (2.4) | 8 (3.0) | 2 (0.8) | 2 (1.5) | 5 (2.5) |
| Patients with ≥ 1 SAE considered related to study treatment, n (%) | 6 (1.1) | 2 (0.8) | 1 (0.4) | 0 | 2 (1.0) |

P-T, placebo-tesamorelin; SAE, serious adverse event; T-T, tesamorelin-tesamorelin; T-P, tesamorelin-placebo. Tesamorelin refers to tesamorelin 2 mg/day.

Eleven patients (9 tesamorelin and 2 placebo) reported SAEs that were considered to be related to study treatment (**Table 29**). Of the 9 who received tesamorelin, 6 experienced the event in the main phase and 3 experienced the event in the extension phase. All events were moderate or severe in intensity.

Table 29. Patients Who Experienced SAEs Considered Related to Study Treatment (Combined, Phase 3 Studies)

| Study | Age/Gender/Race | Treatment | Preferred Term | Severity | Outcome |
|--------------------|--|-------------------|----------------------------|----------|------------------------|
| 0-26 Weeks | | | | | |
| CTR-1011 | 40/Male/White | Placebo | Hodgkin's disease | Severe | Not resolved |
| | | | Hypersensitivity | Moderate | Resolved |
| | 57/Female/Hispanic or Latino | Placebo | Electrocardiogram abnormal | Moderate | Not resolved |
| | 49/Female/American Indian or Alaska Native | Tesamorelin | Sepsis | Moderate | Resolved |
| | 44/Male/ Hispanic or Latino | Tesamorelin | Electrocardiogram abnormal | Severe | Resolved |
| LIPO-010 (main) | 62/Male/White | Tesamorelin | Mobility decreased | Severe | Resolved |
| | 30/Female/ Black/African American | Tesamorelin | Cardiac failure congestive | Severe | Resolved with sequelae |
| | 45/Male/ Black/African American | Tesamorelin | Diarrhea | Severe | Resolved |
| | | | | | Resolved with sequelae |
| | 29/Female/White | Tesamorelin | Neuropathy peripheral | Moderate | |
| 27-52 Weeks | | | | | |
| CTR-1012 | | Tesamorelin (P-T) | Hodgkin's disease | Severe | Not resolved |
| | 38/Male/ Hispanic or Latino | Tesamorelin (P-T) | Dyspnea | Moderate | Resolved |
| | 49/Male/White | Tesamorelin (T-T) | Chorioretinopathy | Moderate | Resolved |
| | 41/Male/White | | | | |

SAE, serious adverse event.

Tesamorelin refers to tesamorelin 2 mg/day.

6.4.6 GH-related adverse events

The incidence of GH-related AEs was 25.6% and 13.7% in the tesamorelin and placebo groups, respectively, during the main phase studies, and 11.4%, 7.4%, and 23.4% in the T-T, T-P, and P-T groups, respectively, during the extension phase studies (**Table 30**). Among patients who discontinued the study prematurely, a greater proportion of tesamorelin-treated than placebo patients reported GH-related AEs (4.2% and 1.5%, respectively). In the extension phase, GH-related AEs were reported by 0%, 0.7%, and 2.5% of T-T, T-P, and P-T patients, respectively, who discontinued the study.

Table 30. Patients Who Experienced AEs Known to Be Related to GH Occurring in ≥1% of Tesamorelin-Treated Patients and More Frequently in Tesamorelin-Treated than Placebo Patients (Combined, Phase 3 Studies)

| | MAIN | | EXTENSION | | |
|---|----------------------|------------------|------------------|-----------------|------------------|
| | Tesamorelin N=543 | Placebo N=263 | T-T N=246 | T-P N=135 | P-T N=197 |
| Patients with AEs, n (%) | 139 (25.6) | 36 (13.7) | 28 (11.4) | 10 (7.4) | 46 (23.4) |
| General disorders and administration-site conditions | 37 (6.8) | 6 (2.3) | 5 (2.0) | 0 | 10 (5.1) |
| Edema peripheral | 33 (6.1) | 6 (2.3) | 5 (2.0) | 0 | 8 (4.1) |
| Musculoskeletal and connective tissue disorders | 75 (13.8) | 20 (7.6) | 14 (5.7) | 2 (1.5) | 26 (13.2) |
| Pain in extremity | 33 (6.1) | 12 (4.6) | 8 (3.3) | 1 (0.7) | 15 (7.6) |
| Myalgia | 30 (5.5) | 5 (1.9) | 3 (1.2) | 0 | 7 (3.6) |
| Joint stiffness | 8 (1.5) | 2 (0.8) | 2 (0.8) | 0 | 4 (2.0) |
| Musculoskeletal stiffness | 9 (1.7) | 1 (0.4) | 2 (0.8) | 0 | 6 (3.0) |
| Joint swelling | 6 (1.1) | 0 | 1 (0.4) | 1 (0.7) | 1 (0.5) |
| Nervous system disorders | 52 (9.6) | 10 (3.8) | 12 (4.9) | 6 (4.4) | 19 (9.6) |
| Paresthesia | 26 (4.8) | 6 (2.3) | 4 (1.6) | 2 (1.5) | 8 (4.1) |
| Hypoesthesia | 23 (4.2) | 4 (1.5) | 4 (1.6) | 1 (0.7) | 6 (3.0) |
| Neuropathy peripheral | 6 (1.1) | 3 (1.1) | 4 (1.6) | 2 (1.5) | 2 (1.0) |
| Carpal tunnel syndrome | 8 (1.5) | 0 | 2 (0.8) | 0 | 4 (2.0) |

AE, adverse event; GH, growth hormone; P-T, placebo-tesamorelin; T-T, tesamorelin-tesamorelin; T-P, tesamorelin-placebo. AEs occurring in ≥1% of tesamorelin-treated patients and more frequently in tesamorelin than placebo patients in the main phase are also shown for the extension phase. Similarly, AEs occurring in ≥1% of T-T patients and more frequently in T-T than T-P patients in the extension phase are also shown for the main phase.

6.4.7 Injection-site reactions

During the main phase, injection-site reactions (**Table 31**) were reported more frequently in tesamorelin-treated than placebo patients (25% and 14%, respectively). Injection-site pruritus occurred more frequently in women than men (17% of 78 women vs 6% of 465 men). Among patients who discontinued the study prematurely, a greater proportion of tesamorelin-treated than placebo patients reported injection-site-related AEs (4.6% and 1.5%, respectively). During the extension phase, incidence of injection-site reactions was similar between the T-T and T-P groups (6.1% and 4.4%, respectively), but higher (17.8%) in the P-T group. Injection-site-related AEs were reported by 0.4%, 0%, and 4.1% of T-T, T-P, and P-T patients, respectively, who discontinued the study.

Table 31. Patients Who Experienced Injection-Site AEs Occurring in $\geq 1\%$ of Tesamorelin-Treated Patients and More Frequently in Tesamorelin-Treated than Placebo Patients (Combined, Phase 3 Studies)

| | MAIN | | EXTENSION | | |
|---------------------------------|----------------------|------------------|-----------------|----------------|------------------|
| | Tesamorelin N=543 | Placebo N=263 | T-T N=246 | T-P N=135 | P-T N=197 |
| Patients with AEs, n (%) | 133 (24.5) | 38 (14.4) | 15 (6.1) | 6 (4.4) | 35 (17.8) |
| Injection-site bruising | 40 (7.4) | 27 (10.3) | 1 (0.4) | 5 (3.7) | 6 (3.0) |
| Injection-site erythema | 46 (8.5) | 7 (2.7) | 3 (1.2) | 0 | 13 (6.6) |
| Injection-site pruritus | 41 (7.6) | 2 (0.8) | 5 (2.0) | 0 | 16 (8.1) |
| Injection-site pain | 22 (4.1) | 8 (3.0) | 0 | 0 | 10 (5.1) |
| Injection-site irritation | 16 (2.9) | 3 (1.1) | 2 (0.8) | 0 | 7 (3.6) |
| Injection-site hemorrhage | 9 (1.7) | 1 (0.4) | 2 (0.8) | 0 | 1 (0.5) |
| Injection-site urticaria | 9 (1.7) | 1 (0.4) | 0 | 0 | 3 (1.5) |
| Injection-site reaction | 7 (1.3) | 2 (0.8) | 2 (0.8) | 0 | 2 (1.0) |
| Injection-site swelling | 8 (1.5) | 1 (0.4) | 1 (0.4) | 0 | 3 (1.5) |
| Injection-site rash | 6 (1.1) | 0 | 1 (0.4) | 0 | 0 |

AE, adverse event; P-T, placebo-tesamorelin; T-P, tesamorelin-placebo; T-T, tesamorelin-tesamorelin.

Tesamorelin refers to tesamorelin 2 mg/day.

AEs occurring in $\geq 1\%$ of tesamorelin-treated patients and more frequently in tesamorelin than in placebo patients in the main phase are also shown for the extension phase. Similarly, AEs occurring in $\geq 1\%$ of T-T patients and more frequently in T-T than in T-P patients in the extension phase are also shown for the main phase.

6.4.8 Other safety parameters

Routine safety laboratory tests were assessed as: (1) mean changes from baseline, (2) newly occurring or notably worsening abnormalities, and (3) shifts from baseline low or normal to high. Newly occurring or notable worsening abnormalities are presented for blood chemistry parameters in **Table 32** and for hematology parameters in **Table 33**.

Blood chemistry

No clinically meaningful mean changes from baseline in alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin were observed in any treatment group during the main and extension phase studies.

After 26 weeks of treatment:

(1) the increase from baseline in creatine kinase levels was 20.1 U/L in the tesamorelin group and 88.6 U/L in the placebo group,

(2) a greater proportion of patients in the tesamorelin group compared to the placebo group had a newly occurring or notable worsening in creatine kinase levels (13.1% vs 9.1%, respectively) (**Table 32**) and

(3) a greater proportion of patients in the tesamorelin group compared to the placebo group shifted from low or normal levels at baseline to high levels (22.5% vs 12.5%, respectively).

After 52 weeks of treatment:

(1) the increase from baseline in creatine kinase levels was 60.2 U/L in the T-T group, 22.0 U/L in the T-P group, and 27.6 U/L in the P-T group.

(2) a greater proportion of patients in the T-T group compared to the T-P group had a newly occurring or notable worsening in creatine kinase levels (15.0% vs 8.1%, respectively) and

(3) the percentages of patients with shifts from low or normal levels at baseline to high levels were generally similar among treatment groups. At Week 52, the percentage of patients with ALT shifts was higher in the P-T group (20.0%) compared to the T-T (10.2 %) and T-P (9.4%) groups, and the percentage of patients with shifts in alkaline phosphatase was higher in the T-T group (9.0%) compared to the T-P (2.3%) and P-T (6.4%) groups. Also, at Week 52 the percentage of patients with creatine kinase shifts was higher in the T-T group (21.2%) and P-T (28.3%) groups compared to the T-P (12.5%) group.

No clinically significant changes in the levels of pituitary hormones other than GH, such as thyroid-stimulating hormone, luteinizing hormone, and prolactin, occurred in patients who received tesamorelin.

Table 32. Newly Occurring or Notable Worsening Blood Chemistry Abnormalities of Interest by Treatment Assignment and Time on Study (Combined, Phase 3 Studies)

| Parameter | Criteria for Notable Changes/ Abnormalities | MAIN | | | EXTENSION | | | |
|----------------------------|--|---------|-------------------------------|---------------------------|-----------|-----------------------|-----------------------|-----------------------|
| | | Visit | Tesamorelin N=543 n (%) | Placebo N=263 n (%) | Visit | T-T N=246 n (%) | T-P N=135 n (%) | P-T N=197 n (%) |
| Alkaline phosphatase (U/L) | >1.5 × ULN | Week 13 | 1 (0.2) | 4 (1.5) | Week 39 | 2 (0.8) | 0 | 1 (0.5) |
| | | Week 26 | 5 (0.9) | 4 (1.5) | Week 52 | 5 (2.0) | 2 (1.5) | 1 (0.5) |
| ALT (U/L) | >3 × ULN | Week 13 | 7 (1.3) | 1 (0.4) | Week 39 | 1 (0.4) | 1 (0.7) | 0 |
| | | Week 26 | 5 (0.9) | 0 | Week 52 | 3 (1.2) | 0 | 1 (0.5) |
| | >10 × ULN | Week 13 | 0 | 0 | Week 39 | 0 | 0 | 0 |
| | | Week 26 | 0 | 0 | Week 52 | 0 | 0 | 0 |
| | | Week 13 | 0 | 0 | Week 39 | 0 | 0 | 0 |
| | | Week 26 | 0 | 0 | Week 52 | 0 | 0 | 0 |
| AST (U/L) | >3 × ULN | Week 13 | 5 (0.9) | 1 (0.4) | Week 39 | 1 (0.4) | 1 (0.7) | 0 |
| | | Week 26 | 1 (0.2) | 2 (0.8) | Week 52 | 2 (0.8) | 0 | 1 (0.5) |
| | >10 × ULN | Week 13 | 0 | 0 | Week 39 | 0 | 0 | 0 |
| | | Week 26 | 0 | 0 | Week 52 | 0 | 0 | 1 (0.5) |
| | | Week 13 | 0 | 0 | Week 39 | 0 | 0 | 0 |
| | | Week 26 | 0 | 0 | Week 52 | 0 | 0 | 0 |
| Total bilirubin (mg/dL) | >1.2 × ULN | Week 13 | 74 (13.6) | 39 (14.8) | Week 39 | 30 (12.2) | 15 (11.1) | 33 (16.8) |
| | | Week 26 | 60 (11.0) | 40 (15.2) | Week 52 | 20 (8.1) | 17 (12.6) | 27 (13.7) |
| Creatine kinase (U/L) | >200 U/L and >20% increase from screening | Week 13 | 82 (15.1) | 23 (8.7) | Week 39 | 45 (18.3) | 19 (14.1) | 29 (14.7) |
| | | Week 26 | 71 (13.1) | 24 (9.1) | Week 52 | 37 (15.0) | 11 (8.1) | 28 (14.2) |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; P-T, placebo-tesamorelin; T-P, tesamorelin-placebo; T-T, tesamorelin-tesamorelin; ULN, upper limit of normal.

Hematology

No clinically meaningful mean changes from baseline in erythrocytes or eosinophils were observed in any treatment group during the main and extension phase studies.

Only two hematology parameters, absolute erythrocyte and absolute eosinophil levels, were identified where there was a ≥2% difference between treatment groups in the pro-

portion of patients with newly occurring or notable worsening abnormalities. The incidence of newly occurring or notable worsening in erythrocyte values was higher in tesamorelin-treated than placebo patients (12.5% and 8.0%, respectively) in the main phase at Week 26 and also higher in T-T than T-P patients (17.9% and 11.9%, respectively) in the extension phase at Week 52 (**Table 33**). A similar pattern was observed for eosinophil values, however, the incidence and differences between treatment groups were notably less.

At Week 26, 4.2% of tesamorelin-treated and 2.0% of placebo-treated patients had shifts from low or normal eosinophil levels at baseline to high levels. At Week 52, 6.2% of T-T patients and 3.3% of T-P patients had shifts from low or normal eosinophil levels at baseline to high levels.

Table 33. Newly Occurring or Notable Worsening Hematology Abnormalities of Interest by Treatment Assignment and Time on Study (Combined, Phase 3 Studies)

| Parameter | Criteria for Notable Changes/ Abnormalities | MAIN | | | EXTENSION | | | |
|---------------------------------------|---|---------|-------------------------------|---------------------------|-----------|-----------------------|-----------------------|-----------------------|
| | | Visit | Tesamorelin N=543 n (%) | Placebo N=263 n (%) | Visit | T-T N=246 n (%) | T-P N=135 n (%) | P-T N=197 n (%) |
| Erythrocytes, x10 ¹² /L | ≥10% change from screening | Week 13 | 68 (12.5) | 18 (6.8) | Week 39 | 43 (17.5) | 18 (13.3) | 27 (13.7) |
| | | Week 26 | 68 (12.5) | 21 (8.0) | Week 52 | 44 (17.9) | 16 (11.9) | 28 (14.2) |
| Eosinophils, x10 ⁹ /L | >1.1 × ULN | Week 13 | 24 (4.4) | 4 (1.5) | Week 39 | 7 (2.8) | 2 (1.5) | 16 (8.1) |
| | | Week 26 | 13 (2.4) | 6 (2.3) | Week 52 | 12 (4.9) | 3 (2.2) | 10 (5.1) |

Tesamorelin refers to 2mg/day. P-T, placebo-tesamorelin; T-P, tesamorelin-placebo; T-T, tesamorelin-tesamorelin; ULN, upper limit of normal.

Urinalysis

No clinically meaningful mean changes from baseline, or differences between treatment groups, were observed.

6.5 Safety Topics of Special Interest

6.5.1 IGF-1

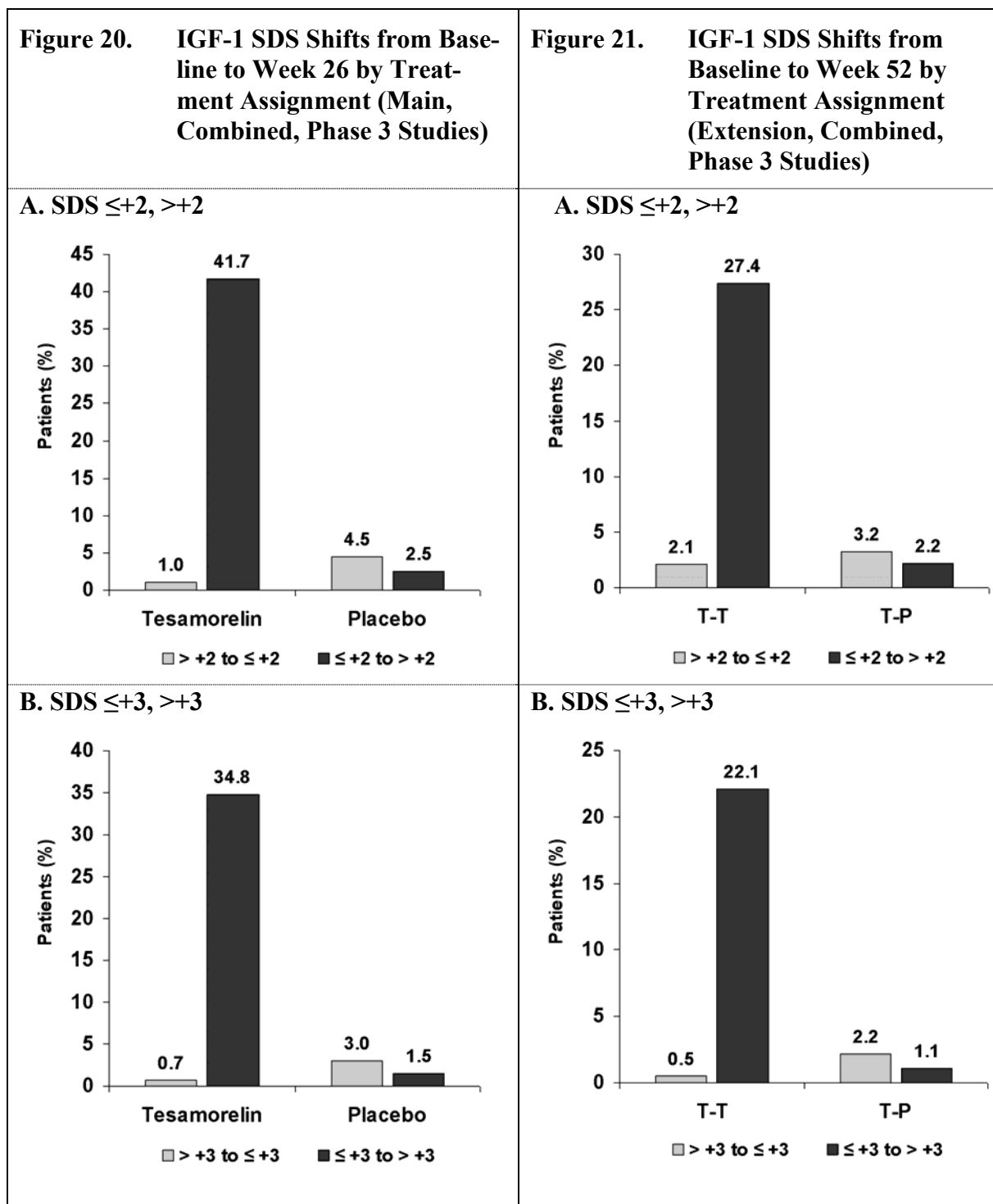
There has been a theoretical concern that high circulating IGF-1 levels for a prolonged period of exposure may be associated with the occurrence of cancer. Data in the literature are controversial, and no link has been established between IGF-1 levels and the occurrence of cancer ([Cutting 1999](#), [Colao 2000](#), [Colao 2000a](#), [Serel 2000](#), [Kurek 2000](#), [Jernstrom 1999](#), [Renehan 2000](#)). GH or GH secretagogue administration would be expected to increase IGF-1 levels, which occurred in the Phase 3 studies. IGF-1 and IGFBP-3 increased in the tesamorelin groups, but not in the placebo groups, in both the Phase 3 studies and in the HIV Phase 2 study. In the Phase 3 studies, IGF-1 levels rose during the first 13 weeks of treatment with tesamorelin and remained relatively stable through 52 weeks of treatment in the T-T group. When tesamorelin treatment was discontinued after 26 weeks in the T-P group, IGF-1 and IGFBP-3 values returned to normal ranges of baseline values.

In tesamorelin-treated patients, mean IGF-1 levels increased by 84% from baseline to Week 26, to a mean level of 261.6 ng/mL (a change from baseline of 107.9 ± 111.6 ng/mL) (normal range for adults aged 17-41 years is 236-333 ng/mL in males and 176-368 ng/mL in females; Esoterix Laboratory). IGF-1 levels remained relatively stable in the T-T group in the extension phase, with a mean level of 238.4 ng/mL at Week 52. Mean IGFBP-3 levels also increased in tesamorelin-treated patients, from a mean level of 2.8 mg/L at baseline to 3.4 mg/L at Week 26. After 52 weeks, mean IGFBP-3 level was 3.2 mg/L in the T-T group. Higher IGFBP-3 levels have been suggested to be protective against cancer risk ([Chan 2002](#)) and represent a proposed mechanism for the lack of increased risk of cancer in GH-treated patients ([Cohen 2000](#), [Cohen 2001](#), [Ali 2003](#)).

For the purposes of safety assessment, IGF-1 levels were expressed as IGF-1 SDS. The SDS describes how far the observation is from above or below the mean value of a popu-

lation of similar age and gender (represented by a SDS score of 0). At baseline (before the first dose of study treatment), the percentage of patients with an IGF-1 SDS $>+2$ and $>+3$ was 6.2% and 1.5%, respectively, in tesamorelin-treated patients and 6.1% and 3.8%, respectively, in placebo patients. At Week 26, the percentage of patients with an IGF-1 SDS $>+2$ and $>+3$ was 47.4% and 35.6%, respectively, in tesamorelin-treated patients and 5.0% and 2.5%, respectively, in placebo patients. At Week 26, a greater proportion of tesamorelin-treated than placebo patients shifted from baseline IGF-1 SDS $\leq+2$ to $>+2$ (41.7% vs 2.5%) (**Figure 20A**). Also, a greater proportion of tesamorelin-treated than placebo patients shifted from baseline IGF-1 SDS $\leq+3$ to $>+3$ at Week 26 (34.8% vs 1.5%) (**Figure 20B**).

At Week 52, the percentage of patients with an IGF-1 SDS $>+2$ and $>+3$ was 33.7% and 22.6%, respectively, in T-T patients and 5.4% and 1.1%, respectively, in T-P patients. Compared to the proportion of patients in the tesamorelin group who shifted from baseline IGF-1 SDS $\leq+2$ to $>+2$ at Week 26 (41.7%), a smaller proportion of patients in the T-T group shifted from baseline IGF-1 SDS $\leq+2$ to $>+2$ (27.4%) at Week 52 (**Figures 20A and 21A**). The same was observed at Week 52 in the T-T group for shifts from baseline IGF-1 SDS $\leq+3$ to $>+3$ (22.1%) compared to those in the tesamorelin group at Week 26 (34.8%) (**Figures 20B and 21B**). The decrease in percentage of T-T patients who shifted into the IGF-1 SDS $>+2$ or $>+3$ categories at Week 52 (as compared to the percentage of tesamorelin patients who shifted at Week 26) was not due to patient drop-outs as similar results were observed when the same analyses were conducted on study completers.



IGF-1, insulin-like growth factor-1; SDS, standard deviation score.

In both the main and extension phase studies, no notable or clinically significant differences were observed in tesamorelin-treated patients when AE incidence was examined by IGF-1 SDS ($\leq +2$ vs $> +2$, and $\leq +3$ vs $> +3$). GH-related AEs examined by IGF-1 SDS occurred in a greater percentage of patients in the IGF-1 SDS $> +2$ and $> +3$ categories compared with the $\leq +2$ category [peripheral edema (7.2% and 8.6% vs 3.7%, respectively), myalgia (6.1% and 5.7% vs 4%), pain in extremity (5.0% and 6.2% vs 4%), arthralgia (14.4% and 14.8% vs 8.8%), and paraesthesia (5.0% and 4.3% vs 3.4%)].

In the Phase 3 studies, patients in the tesamorelin group with IGF-1 SDS $> +2$ and SDS $> +3$ were examined by anti-tesamorelin IgG antibody status and titer (presented in **Section 7.1**).

It is of note that IGF-1 levels $> +2$ and $> +3$ SDS have been reported in patients treated with higher doses of GH for up to 4 years without evidence of increased AEs or elevations in cancer incidence, including in pre-pubertal GH-deficient patients ([Cohen 2002](#)), pubertal GH-deficient patients ([Mauras 2000](#)), pre-pubertal idiopathic short stature patients ([Cohen 2007](#), [Cohen 2010](#)), as well as in IGF-deficient patients treated with rhIGF-1 ([Midyett 2010](#)).

6.5.2 Cancer

In the Phase 3 HIV studies, 15 patients were diagnosed with cancer: 5 were treated with tesamorelin (5/543; 0.92%) and 3 with placebo (3/263; 1.14%) in the main phase, and 7 (7/740; 0.95%) received tesamorelin during the main or extension phases. All cancer events were considered by the treating physician to be unrelated to treatment, except in 1 tesamorelin patient and 1 placebo patient, who each had Hodgkin's disease. The cancer AEs are shown by treatment group in **Table 34**. As seen, the incidence is not different between the tesamorelin and placebo groups.

Exposure to tesamorelin prior to the cancer AE did not exceed 6 months. Of the 5 tesamorelin-treated patients who were diagnosed with cancer in the main phase, 2 had an IGF-1 SDS >+2 at their last visit. Of the 7 patients who were diagnosed with cancer in the extension phase, 3 (1 T-T, 1 T-P, and 1 P-T) had an IGF-1 SDS >+2 at their last visit. In summary, based on data from the Phase 3 studies, there was no evidence of a causal relationship among tesamorelin, increased IGF-1 levels and SDS, and any type of reported cancers.

Table 34. Patients Who Experienced Cancer AEs in Phase 3 Studies

| | Treatment | Adverse Event | Exposure to Tesamorelin Before Event | Outcome |
|------------------------|-------------|------------------------------------|--------------------------------------|--------------|
| Main Phase | | | | |
| | Placebo | Breast cancer in situ (SAE) | NA | Not resolved |
| | Placebo | Hodgkin's disease (SAE) | NA | Not resolved |
| | Placebo | Basal cell carcinoma (non-serious) | NA | Resolved |
| | Tesamorelin | Rectal cancer (SAE) | 5 mo | Resolved |
| | Tesamorelin | Basal cell carcinoma (SAE) | 1 mo, 13 d | Resolved |
| | Tesamorelin | Lung neoplasm (non-serious) | 3 mo, 15 d | Not resolved |
| | Tesamorelin | Basal cell carcinoma (Non-serious) | 3 mo, 21 d | Resolved |
| | Tesamorelin | Neoplasm prostate (non-serious) | 5 mo, 24 d | Resolved |
| Extension Phase | | | | |
| | T-P | Basal cell carcinoma (Non-serious) | 6 mo | Not resolved |
| | T-P | Anal cancer (SAE) | 6 mo, 5 d | Resolved |
| | T-T | Basal cell carcinoma (Non-serious) | 11 mo, 6 d | Resolved |
| | P-T | Basal cell carcinoma (Non-serious) | 5 mo, 7 d | Resolved |
| | P-T | Kaposi's sarcoma (Non-serious) | 1 mo, 3 d | Not resolved |
| | P-T | Hodgkin's disease (SAE) | 2 mo, 22 d | Not resolved |
| | P-T | Lung neoplasm (Non-serious) | 5 mo, 23 d | Not resolved |

AEs, adverse events; d, days; mo, month(s); NA, not applicable; P-T, placebo-tesamorelin; T-P, tesamorelin-placebo; SAE, serious adverse event; T-T, tesamorelin-tesamorelin.

Tesamorelin refers to 2 mg/day.

Post-treatment cancers occurring >30 days after the last dose:

- A. A patient on tesamorelin in the main phase was diagnosed with lung adenocarcinoma metastatic 5 months after the last dose and died 9 months after the last dose. The patient had received tesamorelin for 6 months and 1 day. This event was considered by the treating physician to be related to treatment. The patient had a history of lymphadenopathy and basal cell carcinoma.
- B. A patient on placebo in the extension study (T-P) was diagnosed with Hodgkin's disease 2.5 months after the last dose. This event was considered by the treating physician to be related to treatment.

6.5.3 Glucose tolerance

6.5.3.1 Phase 2 Non-HIV diabetes safety study (DIABETIC-006)

To assess the potential safety concerns associated with increases in GH, such as hyperglycemia, insulin resistance, and diabetes, tesamorelin was administered SC daily for 12 weeks to patients with type 2 diabetes (mean age 61±7 years). This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Eligible patients, stratified by insulin usage, were randomized to tesamorelin 2 mg/day (N=19), tesamorelin 1 mg/day (N=18), or placebo (N=16). The percentages of patients who completed the study were 79%, 78%, and 69%, respectively.

Tesamorelin was generally well tolerated at both doses. AEs were reported in 50% of the placebo, 39% of the 1 mg tesamorelin group, and 58% of the 2 mg tesamorelin group. There were no SAEs or deaths. None of the 37 tesamorelin-treated patients discontinued the study due to an AE; 1 patient in the placebo group discontinued due to urinary retention.

IGF-1 levels increased in both tesamorelin groups but decreased in the placebo group. After 12 weeks of treatment with tesamorelin 1-mg, IGF-1 levels increased by an average of 32.4%; at baseline, the mean level was 102.3 (SD 39.3) ng/mL and increased by 33.2 (SD 36.7) ng/mL by Week 12. In the tesamorelin 2-mg group, IGF-1 levels increased by an average of 60%; at baseline, the mean level was 110.6 (SD 31.4) ng/mL and increased by 66.0 (SD 63.7) by Week 12. In contrast, mean IGF-1 levels in the placebo group decreased by 3.7 ng/mL at Week 12, from a baseline value of 131.3 (SD 49.4) ng/mL.

No clinically meaningful difference was observed between the tesamorelin and placebo groups for mean changes from baseline in blood chemistry, hematology, and urinalysis values.

Tesamorelin did not interfere with the relative insulin response⁴ or with glycemic parameters. A statistically significant treatment difference ($p=0.024$) was only observed at Week 8 in FBG level, which increased in the tesamorelin 2-mg and placebo groups and decreased in the tesamorelin 1-mg group; however, a treatment difference was not observed at Week 12, nor at the follow-up visit at Week 14 (**Table 35**). No significant differences were found among treatment groups for the relative insulin response at baseline or in changes from baseline. The mean relative insulin response increased slightly in all groups at all time points. Mean HbA_{1c} generally decreased in the placebo and the tesamorelin 1-mg groups at Weeks 4, 8, and 12, whereas little change from baseline was observed in the tesamorelin 2-mg group. Mean change from baseline in HbA_{1c} was significantly different among treatment groups at Week 12 ($p=0.015$). In general, insulin users had higher HbA_{1c} values at baseline compared with non-insulin users. In non-insulin users, HbA_{1c} tended to decrease from baseline in all groups. In insulin users, increases in HbA_{1c} of more than 0.5% (absolute values) were observed in 1 patient receiving tesamorelin 1 mg/day and in 2 patients receiving tesamorelin 2 mg/day.

⁴ Defined as response after OGTT: Relative insulin response = $\frac{\Delta \text{Insulin (30 min - 0 min)}}{\Delta \text{Glucose (30 min - 0 min)}}$

Table 35. Changes from Baseline in FBG (mg/dL) (DIABETIC-006)

| | | Tesamorelin 2 mg/day N=19 | Tesamorelin 1 mg/day N=18 | Placebo N=16 |
|----------------------------------|-----------|------------------------------|------------------------------|-----------------|
| Baseline | N | 19 | 18 | 16 |
| | Mean (SD) | 138.62 (25.65) | 156.47 (42.62) | 123.46 (44.62) |
| | Min; Max | 81.94; 199.84 | 107.91; 242.80 | 57.96; 233.80 |
| Change at Week 1 | N | 19 | 16 | 16 |
| | Mean (SD) | 15.93 (43.52) | 15.12 (50.42) | 3.11 (26.95) |
| | Min; Max | -33.97; 161.87 | -61.96; 122.90 | -40.97; 57.96 |
| Change at Week 4 ^a | N | 16 | 16 | 14 |
| | Mean (SD) | 18.41 (24.23) | 3.49 (36.79) | 7.27 (61.63) |
| | Min; Max | 0.00; 38.47 | -49.95; 79.94 | -109.91; 147.89 |
| Change at Week 8 ^b | N | 15 | 14 | 11 |
| | Mean (SD) | 15.71 (22.57) | -9.70 (25.13) | 5.81 (55.98) |
| | Min; Max | -16.99; 47.97 | -38.97; 41.96 | -114.91; 126.90 |
| Change at Week 12 | N | 15 | 13 | 10 |
| | Mean (SD) | 2.59 (42.98) | -13.00 (27.52) | -11.00 (38.47) |
| | Min; Max | -77.94; 111.91 | -69.95; 30.98 | -101.92; 50.96 |
| Change at Week 14 | N | 16 | 16 | 14 |
| | Mean (SD) | -1.31 (28.49) | 9.18 (93.06) | 9.99 (63.22) |
| | Min; Max | -63.95; 52.96 | -75.94; 331.72 | -136.89; 125.89 |

FBG, fasting blood glucose; SD, standard deviation.

Data were reported in standard international units and converted to conventional units by multiplying by 18.

^a p=0.016 (Wilcoxon sign rank test [2 mg/day tesamorelin group]); p=0.040 (Wilcoxon sign rank test [2 mg/day tesamorelin group]).

^b p=0.024 for treatment, insulin use, and center group difference (ANOVA).

6.5.3.2 Phase 3 studies

Given the results of the diabetes safety study (DIABETIC-006), which showed that tesamorelin could be safely used in patients with type 2 diabetes, HIV-infected patients with IGT and some patients with diet-controlled diabetes were included in the Phase 3 studies. In the Phase 3 studies, patients were randomized into the Main studies in a 2:1 (active:placebo) ratio and into the Extension studies in a 3:1 (active:placebo) ratio. At baseline in the Phase 3 studies, 38.9% and 38.1% of tesamorelin and placebo patients, respectively, had IGT while 7.4% and 8.1%, respectively, had diet-controlled diabetes (based on FBG and 2-hour OGTT glucose criteria of 2006 and 2010 American Diabetes Association [ADA] definition).

Inferential statistics

In the main phase studies, mean changes from baseline in FBG, 2-hour OGTT glucose, insulin, and HOMA-IR were not significantly different between the tesamorelin and placebo groups at Week 26 (**Table 36**). The mean change from baseline in HbA_{1c} was statistically significantly different between the tesamorelin and placebo groups (0.14% vs 0.02%, respectively; p=0.0004), however, the mean change was slight and HbA_{1c} remained in a normal range in the tesamorelin group (5.26% at baseline and 5.39% at Week 26). After 52 weeks, the mean change from baseline in all glucose parameters did not differ significantly between the two groups (**Table 37**).

Table 36. Glucose Parameters (Combined, Main Phase)

| | BASELINE | | Δ WEEK 26 | |
|----------------------------|----------------|----------------|--------------|--------------|
| | Tesamorelin | Placebo | Tesamorelin | Placebo |
| | Mean (SD) | | Mean (SD) | |
| FBG, mg/dL | 98.21 (14.38) | 98.10 (15.96) | 2.65 (15.89) | 0.70 (16.58) |
| 2-hour OGTT Glucose, mg/dL | 112.73 (36.90) | 113.90 (40.09) | 3.20 (37.63) | 3.38 (42.61) |
| Insulin, μIU/mL | 22.15 (29.31) | 19.81 (20.39) | 0.03 (29.29) | 1.43 (21.93) |
| HOMA-IR | 5.53 (8.30) | 4.69 (4.23) | -0.02 (8.50) | 0.44 (7.09) |
| HbA _{1c} , % | 5.26 (0.50) | 5.28 (0.48) | 0.14 (0.4) | 0.02 (0.4)* |

HbA_{1c}, glycosylated hemoglobin; SD, standard deviation

*p=0.0004.

Table 37. Glucose Parameters (Combined, Extension Phase)

| | BASELINE | | Δ WEEK 52 | |
|----------------------------|----------------|----------------|---------------|---------------|
| | T-T | T-P | T-T | T-P |
| | Mean (SD) | | Mean (SD) | |
| FBG, mg/dL | 97.11 (13.09) | 102.23 (16.86) | 1.87 (14.48) | -2.02 (28.24) |
| 2-hour OGTT Glucose, mg/dL | 111.58 (33.60) | 112.44 (39.88) | 1.09 (39.27) | 1.03 (33.73) |
| Insulin, μIU/mL | 19.46 (20.22) | 25.91 (31.38) | -0.41 (19.52) | -6.88 (30.60) |

| | | | | |
|-----------------------|-------------|--------------|--------------|---------------|
| HOMA-IR | 4.78 (5.74) | 7.26 (10.95) | -0.04 (5.59) | -2.46 (11.12) |
| HbA _{1c} , % | 5.23 (0.50) | 5.27 (0.47) | 0.07 (0.4) | 0.08 (0.5) |

HbA_{1c}, glycosylated hemoglobin; SD, standard deviation; T-P, tesamorelin-placebo; T-T, tesamorelin-tesamorelin.
 Tesamorelin refers to tesamorelin 2 mg/day.

In the main phase, 1.7% (9/543) of tesamorelin patients compared to 0.4% (1/263) of placebo patients experienced a glucose-related AE (hyperglycemia, glucose tolerance impaired, impaired fasting blood glucose, insulin resistance, type 2 diabetes, blood glucose increased, and glucose tolerance test abnormal). Among those patients continuing on long-term treatment with tesamorelin in the extension phase, 0.5% (2/246) of T-T patients compared with 1.5% (2/135) of T-P patients experienced a glucose-related AE.

Over the course of the Phase 3 studies, 2 patients in the tesamorelin group were discontinued due to increases in FBG levels, as documented by their treating physician. Of note, these two patients started the study with baseline FBG values >126 mg/dL.

In the main phase studies, 1 (0.2%) tesamorelin-treated patient started and received glyburide for 1 week. In the extension phase studies, 3 (1.2%) T-T patients and 1 (0.5%) P-T patients started metformin. All but one of these patients had FBG values >126 mg/dL when the treating physician decided to start the anti-diabetic medication.

Descriptive statistics

Shifts in FBG

Following the FDA's recommendations at the pre-NDA meeting (September 19, 2008), shifts from baseline to Week 26 and from Week 26 to Week 52 were evaluated. Results were presented for 3 subgroups according to FBG at baseline: 1) <100 mg/dL (normal); 2) 100-126 mg/dL (IGT) or 3) ≥126-150 mg/dL with diet-controlled diabetes. For the first 2 categories of FBG at baseline or Week 26 (<100 mg/dL and 100-126 mg/dL), the following shift codes were used:

- post-visit FBG ≥ 126 mg/dL at least once.
- post-visit FBG between 100-126 mg/dL at least twice, but never >126 mg/dL.
- post-visit FBG <100 mg/dL at all visits OR 100-126 mg/dL at 1 visit and other visits <100 mg/dL.

For the third category of FBG at baseline or Week 26 (≥ 126 -150 mg/dL), the following shift codes were used:

- >150 mg/dL OR addition of anti-diabetic agent OR discontinued due to glucose intolerance.
- 126-150 mg/dL at least twice, but never >150 mg/dL.
- <126 mg/dL at all visits OR 126-150 mg/dL at 1 visit and other visits <126 mg/dL.

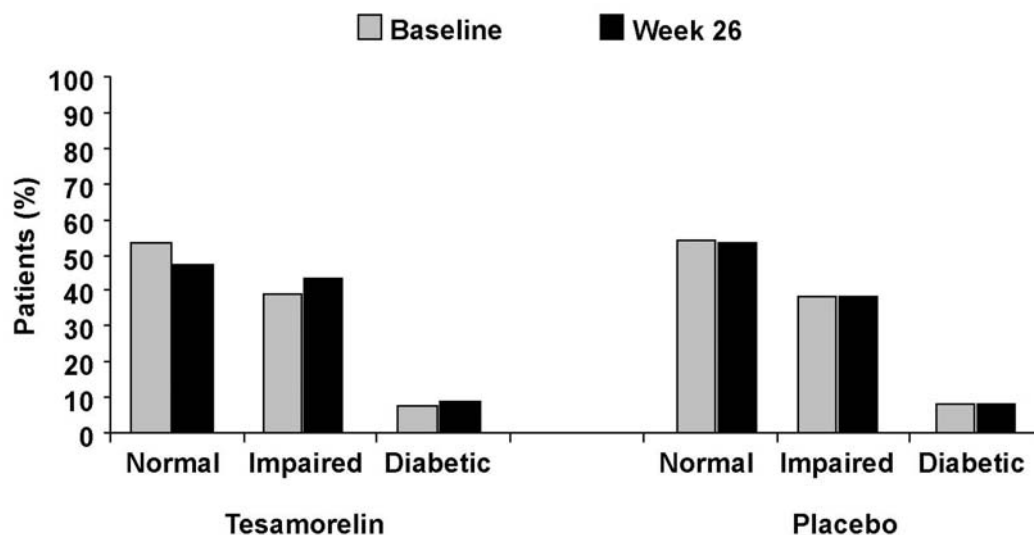
These analyses, which were descriptive in nature, captured the variability in FBG across time for each defined glucose category. Primarily, in both the main and extension phase studies, more fluctuations occurred in tesamorelin than placebo-treated patients, and more tesamorelin-treated patients experienced shifts from <100 mg/dL to 100-126 mg/dL and shifts from 100-126 mg/dL to ≥ 126 mg/dL.

At baseline, 10 tesamorelin-treated patients and 9 placebo patients had FBG values classified as diet-controlled diabetes (≥ 126 -150 mg/dL). Of these patients, 5 in the tesamorelin group and 1 in the placebo group had FBG shifts to >150 mg/dL during the main phase. At Week 26, 9 T-T patients and 7 T-P patients were classified as having diet-controlled diabetes. Of these patients, 2 in the T-T group and 1 in the T-P group had FBG shifts to >150 mg/dL during the extension phase.

Patients with IGT or Diabetes (based on FBG and 2-hour OGTT glucose criteria of 2006 and 2010 ADA Definition)

The proportion of patients with IGT or diabetes was similar between the tesamorelin and placebo groups at baseline in the main phase studies, both individually and when combined (**Figure 22**). Over 52 weeks, the proportion of patients with IGT or diabetes was generally comparable between the T-T and T-P groups at baseline, Week 26, and Week 52. However, when looking at data from 0-26 weeks, there appeared to be an increase of 4.7% in the proportion of patients with IGT in the tesamorelin group (**Figure 23**). This observed increase appeared to be transient because long-term data in patients completing 52 weeks showed stabilization over time in the percentage of patients with IGT as reflected in the T-T group: 41% at baseline, 42% at Week 26, and 42% at Week 52 (**Figure 23**). The same was observed in the percentage of patients in the T-T group who met the diabetes definition (≥ 126 -150 mg/dL): 3% at baseline, 7% at Week 26, and 5% at Week 52.

Figure 22. Patients with Normal, IGT^a, or Diabetes^b at Baseline and Week 26 Based on FBG and 2-Hr OGTT (Main, Combined, Phase 3 Studies)

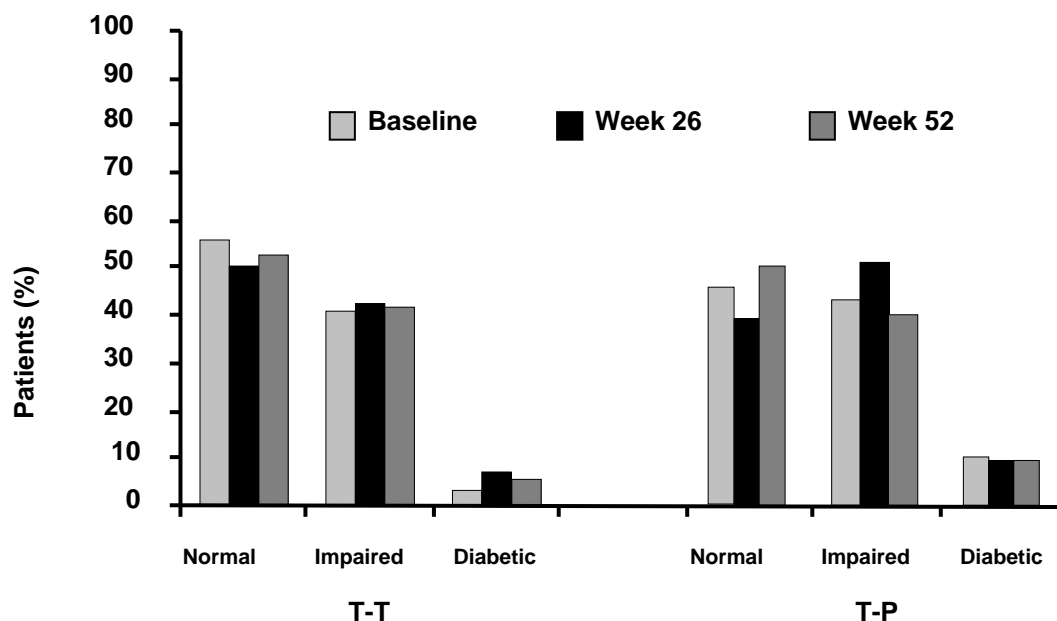


FBG, fasting blood glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test.
[2006 and 2010 ADA Definition](#)

^aIGT=140 mg/dL \leq 2-hour OGTT \leq 199 mg/dL AND/OR 100 mg/dL \leq FBG \leq 125 mg/dL

^bDiabetes=2-hour OGTT \geq 200 mg/dL AND/OR FBG \geq 126 mg/dL

Figure 23. Patients with Normal, IGT^a, or Diabetes^b at Baseline, Week 26, and Week 52 Based on FBG and 2-Hr OGTT (Extension, Combined, Phase 3 Studies)



FBG, fasting blood glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; T-P, tesamorelin-placebo; T-T, tesamorelin-tesamorelin.

[2006 and 2010 ADA Definition](#)

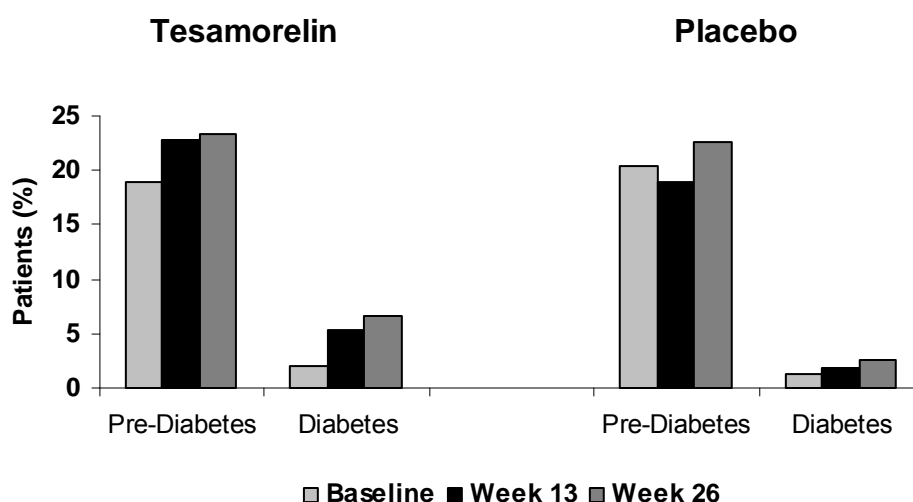
^aIGT=140 mg/dL ≤ 2-hour OGTT ≤ 199 mg/dL AND/OR 100 mg/dL ≤ FBG ≤ 125 mg/dL.

^bDiabetes=2-hour OGTT ≥ 200 mg/dL AND/OR FBG ≥ 126 mg/dL.

Patients with Pre-Diabetes and Diabetes Based on HbA_{1c} Levels (2010 ADA Definition)

At baseline comparable proportions of patients in the tesamorelin and placebo groups were classified as normal (79.0% and 78.4%, respectively), pre-diabetic (18.9% and 20.4%, respectively), and diabetic (2.1% and 1.2%, respectively). The proportion of patients with pre-diabetes was relatively stable in the tesamorelin and placebo groups in the first 26 weeks of treatment. The proportion of patients with diabetes increased in both treatment groups, with a greater increase observed across baseline, Week 13, and Week 26 in the tesamorelin group (2.1, 5.4, and 6.6%, respectively) compared to the placebo group (1.2, 1.9, and 2.5%, respectively) (**Figure 24**).

Figure 24. Patients with Pre-Diabetes^a and Diabetes^b at Baseline, Week 13, and Week 26 Based on HbA_{1c} Levels (Main, Combined, Phase 3)



2010 ADA Definition

^aPre-Diabetes= $5.7\% \leq \text{HbA}_{1c} < 6.5\%$, ^bDiabetes= $\text{HbA}_{1c} \geq 6.5\%$

HbA_{1c} Individual Patient Trends Based on 2010 ADA

In line with the 2010 ADA diagnostic criteria for diabetes and the recommendation to control $\text{HbA}_{1c} < 7\%$ to reduce microvascular complications of diabetes, individual patient trends were analyzed in patients with at least 1 HbA_{1c} post-baseline value $\geq 6.5\%$, as well as in patients with at least 1 HbA_{1c} post-baseline value $\geq 7\%$ (**Table 38**).

During the first 26 weeks of treatment, in patients with baseline $\text{HbA}_{1c} \geq 6.5\%$, the percentage of patients with at least one post-baseline HbA_{1c} value $\geq 6.5\%$ was comparable between the tesamorelin and placebo groups (2.10% vs 1.18%, respectively). However, in patients with a baseline $\text{HbA}_{1c} < 6.5\%$, a slightly larger percentage of patients had at least one post-baseline HbA_{1c} value $\geq 6.5\%$ in the tesamorelin group compared to the placebo group (5.34% vs 2.35%). Overall, only 2.3% of patients in the tesamorelin group had at least one HbA_{1c} value $\geq 7\%$ regardless of the baseline value.

In the subsequent 26 weeks, HbA_{1c} stabilized in the T-T group as shown by comparable percentages of patients in the T-T and T-P groups with at least one post-baseline value $\geq 6.5\%$ or $\geq 7\%$. There was also substantially less of a tendency for a Week 26 HbA_{1c} $< 6.5\%$ to increase to $\geq 6.5\%$ compared to that in the first 26 weeks of treatment. Overall, only 1.63% of patients in the T-T group had at least one HbA_{1c} value $\geq 7\%$ regardless of the baseline value.

Table 38. Patients with At Least One Post Baseline HbA_{1c} Value $\geq 6.5\%$ or $\geq 7\%$ by Baseline HbA_{1c} ($\geq 6.5\%$, $< 6.5\%$) (Combined, Phase 3)

| | Main phase | | Extension phase* | |
|---|----------------------|------------------|------------------|--------------|
| | Tesamorelin N=524 | Placebo N=255 | T-T N=246 | T-P N=135 |
| Baseline HbA _{1c} $\geq 6.5\%$ | | | | |
| At Least One post-BL Value $\geq 6.5\%$ | 11 (2.10%) | 3 (1.18%) | 12 (4.88%) | 7 (5.19%) |
| At Least One post-BL Value $\geq 7\%$ | 5 (0.9%) | 0 (0%) | 4 (1.63%) | 2 (1.48%) |
| Baseline HbA _{1c} $< 6.5\%$ | | | | |
| At Least One post-BL Value $\geq 6.5\%$ | 28 (5.34%) | 6 (2.35%) | 3 (1.22%) | 2 (1.48%) |
| At Least One post-BL Value $\geq 7\%$ | 7 (1.34%) | 0 (0%) | 0 (0%) | 1 (0.74%) |

* Baseline in the Extension phase refers to Week 26 values.

BL=Baseline

Shifts in HbA_{1c} Categories for Study Completers

Shifts in HbA_{1c} categories were also analyzed for study completers, who were defined as patients with HbA_{1c} values at every visit as per protocol. Results are presented in **Table 39**.

Among patients who were normal at baseline, slightly more tesamorelin than placebo patients shifted to the pre-diabetes category (53/317 [16.7%] and 20/156 [12.8%], respectively), and very few tesamorelin and no placebo patients shifted to the diabetes category

(1.3% and 0%, respectively). Among patients who were considered pre-diabetic at baseline, more tesamorelin than placebo patients shifted to the diabetes category (17/65 [26.2%] vs 4/35 [11.4%]).

Table 39. Shifts from Baseline in Normal, Pre-Diabetes, and Diabetes Categories at Week 26 Based on HbA_{1c} Levels, Study Completers (Main, Combined, Phase 3)

| Baseline | Tesamorelin (N=389) | | | Placebo (N=194) | | |
|--------------|--------------------------|--------------|-----------|-----------------|--------------|----------|
| | Post-Baseline Evaluation | | | | | |
| | Patients (%) | | | | | |
| | Normal | Pre-Diabetes | Diabetes | Normal | Pre-Diabetes | Diabetes |
| Normal | 260 (82.0) | 53 (16.7) | 4 (1.3) | 136 (87.2) | 20 (12.8) | 0 (0.0) |
| Pre-Diabetes | 13 (20.0) | 35 (53.8) | 17 (26.2) | 11 (31.4) | 20 (57.1) | 4 (11.4) |
| Diabetes | 0 (0.0) | 2 (28.6) | 5 (71.4) | 0 (0.0) | 2 (66.7) | 1 (33.3) |

2010 ADA Definition

Normal= HbA_{1c} <5.7%, Pre-Diabetes= 5.7% ≤ HbA_{1c} <6.5%, Diabetes HbA_{1c} ≥6.5%

In patients who continued study treatment for an additional 26 weeks, HbA_{1c} shifted downward with a substantially smaller proportion of patients experiencing shifts in HbA_{1c} categories in both the T-T and T-P groups at Week 52 (**Table 40**). Among patients who were normal at baseline, at Week 52 a greater proportion in the T-T than T-P group shifted to the pre-diabetes category (25/150 [16.7%] and 7/67 [10.4%], respectively) and only one patient in each of the T-T and T-P groups (0.7% and 1.5%, respectively) shifted to the diabetes category. Among patients who were pre-diabetes at baseline, only one patient in each of the T-T and T-P groups shifted to the diabetes category at Week 52 (1/22 [4.5%] and 1/13 [7.7%], respectively).

We also observed examples in which there was an improvement in HbA_{1c} category. For those who were defined at baseline as pre-diabetes, 4 (18.2%) T-T patients and 6 (46.2%) T-P patients shifted back to normal. Also, of the 3 T-T patients with diabetes at baseline,

2 (66.7%) patients shifted back to a pre-diabetes condition, while the 1 T-P patient with diabetes at baseline remained in the same category at Week 52.

Table 40. Shifts from Baseline (Week 0) in Normal, Pre-Diabetes, and Diabetes Categories at Week 52 Based on HbA_{1c} Levels, Study Completers (Main, Combined, Phase 3)

| Baseline | T-T (N=175) | | | T-P (N=81) | | |
|--------------|--------------------------|--------------|----------|------------|--------------|-----------|
| | Post-Baseline Evaluation | | | | | |
| | Patients (%) | | | | | |
| | Normal | Pre-Diabetes | Diabetes | Normal | Pre-Diabetes | Diabetes |
| Normal | 124 (82.7) | 25 (16.7) | 1 (0.7) | 59 (88.1) | 7 (10.4) | 1 (1.5) |
| Pre-Diabetes | 4 (18.2) | 17 (77.3) | 1 (4.5) | 6 (46.2) | 6 (46.2) | 1 (7.7) |
| Diabetes | 0 (0.0) | 2 (66.7) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 1 (100.0) |

2010 ADA Definition

Normal= HbA_{1c} <5.7%, Pre-Diabetes= 5.7% ≤ HbA_{1c} <6.5%, Diabetes HbA_{1c} ≥6.5%

In recognition that tesamorelin may increase glucose into the diabetes range in a small number of patients, risk management guidelines for glucose monitoring using HbA_{1c} or FBG are proposed.

6.5.4 Hypersensitivity reactions

The clinical definition of hypersensitivity reaction was developed in accordance with the FDA (see **Section 3.1**). Hypersensitivity reaction usually presents as an extended erythematous and pruritic rash on the abdomen where tesamorelin is injected, sometimes extending to other body parts such as the chest, axillae, arms, and back, or is associated with redness of other body parts including the face, chest, and hands. Occasionally, large hives occur at the injection site, sometimes extending beyond the injection site and/or observed at previous injection sites. Sometimes hives are associated with systemic symptoms.

Using the clinical definition of hypersensitivity reaction developed with the FDA, a retrospective analysis was conducted for the Phase 1 and 2 studies, in which patients were exposed to different doses of tesamorelin, from 0.1 mg qd to 2 mg bid, for durations between 7 days and 3 months. A hypersensitivity reaction was identified in 4 of 491 (0.8%) patients exposed to tesamorelin in those Phase 1 and 2 studies. One patient discontinued prematurely due to hypersensitivity and the other 3 patients completed treatment without a worsening of symptoms. None of these hypersensitivity reactions were considered serious.

In the HIV Phase 3 studies, 28 patients (21 men and 7 women) had hypersensitivity reactions (27/740 [3.6%] in the tesamorelin group and 1 in the placebo group) (**Table 41**). The incidence of hypersensitivity reactions appeared to be higher during the first 26 weeks of tesamorelin treatment and occurred between 8 and 26 weeks of treatment with tesamorelin. Of note, 5 patients had hypersensitivity reaction less than 1 week after starting treatment: 4 patients after receiving the first dose of tesamorelin and 1 P-T patient 4 days after receiving tesamorelin.

Most of the hypersensitivity reactions in tesamorelin-treated patients were characterized by extended skin reactions, were preceded by signs and symptoms, such as injection site erythema and injection site rash (16/27; 59.3%), and were associated with systemic reactions (11/27; 40.7%). The systemic reactions included nausea, palpitation/tachycardia, light-headedness/dizziness, hot flush/flushing, sweating, dyspnea, headache, fuzzy/abnormal vision, weakness, and tongue edema.

Table 41. Incidence of Hypersensitivity Reaction in All Patients Exposed to Tesamorelin in Phase 3 Trials (Combined, Phase 3 Studies)

| | Patients with Hypersensitivity Reactions, n | Patients Exposed to Tesamorelin, n | Planned Duration of Exposure to Tesamorelin, weeks | Incidence, % |
|------------------|---|------------------------------------|--|--------------|
| Main | 16 | 543 | 26 | 2.9 |
| Extension | | | | |
| P-T | 8 | 197 | 26 | 4.1 |

| | | | | |
|-----|---|-----|----|-----|
| T-T | 3 | 246 | 52 | 1.2 |
|-----|---|-----|----|-----|

P-T, placebo-tesamorelin; T-T, tesamorelin-tesamorelin.

Of the 27 reactions in tesamorelin-treated patients, 21 were reported spontaneously and 6 were identified during a retrospective review of all reported rashes and urticaria events. Tesamorelin treatment was rapidly discontinued, as per protocol, in all 21 patients who reported hypersensitivity spontaneously, and all symptoms resolved either spontaneously, with antihistamines, or with topical corticosteroid. During the main phase studies, 12/543 (2.2%) tesamorelin-treated patients discontinued due to a hypersensitivity reaction. In the extension phase studies, 3/246 (1.2%) patients in the T-T group, 0 in the T-P group, and 6/197 (3.0%) patients in the P-T group discontinued due to hypersensitivity reaction.

Hypersensitivity reactions were reviewed for potential anaphylaxis according to the NIAID/FANN proposed definition. Two patients were identified as having some signs and symptoms of possible anaphylaxis according to the criteria. One patient was identified in the retrospective review. This patient initially experienced injection-site erythema, injection-site pruritus, injection-site swelling, and urticaria starting on the first day of tesamorelin administration. The patient also reported swollen tongue 3 weeks after starting tesamorelin. This event increased in severity, along with continued injection-site reactions, 108 days after starting tesamorelin; the patient was then discontinued from study treatment (see case narrative in **Appendix IV**).

The second patient initially experienced injection site redness and itching 1 month after starting tesamorelin and continued thereafter. Three months after the treatment, the patient experienced nausea, tachycardia, shortness of breath and sweating 3 minutes after injection of the study drug. Twenty-three days later, the patient experienced similar reactions, but less intense. It is important to note that those symptoms resolved very quickly (in 1-3 minutes) following administration of Benadryl. The patient was promptly discontinued from study treatment (see case narrative in **Appendix IV**).

None of the hypersensitivity reactions were considered to be anaphylaxis, defined as a systemic life threatening allergic reaction. The patients who reported systemic symptoms noted that the symptoms rapidly resolved either spontaneously or simply with an antihistamine or topical corticosteroid application. None of the patients were treated with epinephrine, bronchodilators or systemic corticosteroids nor needed any emergency medical care. None of the hypersensitivity reactions were considered as SAE or resulted in a serious outcome.

There is a certain pattern in the profile of those patients that may be more likely to develop a hypersensitivity reaction, as these reactions appear to occur more frequently in patients who had previous hypersensitivity medical history and manifested prior associated signs and symptoms (e.g. rash, injection site erythema, pruritus). Women also more frequently reported reactions than men, which was not unexpected as women report higher adverse events to vaccination and other interventions in general. ([Thomas 2009](#), [Wysowski 2005](#))

Twenty-three (23) of the 27 tesamorelin-treated patients who experienced hypersensitivity reactions tested positive for anti-tesamorelin IgG antibodies at least once during the study. After stopping tesamorelin treatment, anti-tesamorelin IgG antibody titers decreased over time in the 16 patients that were followed for antibody assessments every 6-7 weeks for up to 6 months. At the end of the follow-up period, 9 patients were anti-tesamorelin IgG antibody-negative and 7 patients were still anti-tesamorelin IgG antibody-positive (5 patients with titer of 25 [minimal required dilution (MRD) of the anti-tesamorelin IgG assay] and 2 patients with low titers).

6.6 Safety Conclusions

The clinical development program of tesamorelin has not raised any clinically significant safety concerns. As would be expected, the most commonly observed AEs, in patients in the overall program and in HIV-infected patients with excess abdominal fat, were injec-

tion-site related (including injection-site erythema and pruritus) and reactions believed to be related to GH secretion (peripheral edema, arthralgia, pain in extremity, and myalgia). Most of the AEs reported were considered by the investigator to be of mild or moderate severity. No important differences in AE profile were observed in subgroups defined by concomitant medications, type of ART, type of lipid-lowering medication, or baseline demographic and clinical characteristics. In addition, other safety parameters, such as IGF-1 SDS, glucose parameters, and anti-tesamorelin IgG antibodies, were carefully assessed during the HIV Phase 3 program; no important differences were observed in the AE profiles of these subgroups as well.

During the first 26 weeks of the HIV Phase 3 studies, the incidence of SAEs was not different between the tesamorelin and placebo groups, and did not increase with extended treatment up to 52 weeks. In both the main and extension phase studies, no specific SAE was reported by ≥ 2 patients in any treatment group, except sepsis. There were 3 deaths in the HIV Phase 3 studies (1 of 398 [0.25%] placebo patients and 2 of 740 [0.27%] tesamorelin-treated patients), and all were considered by the treating physician to be unrelated to study treatment.

The administration of GH or a GH secretagogue is expected to increase IGF-1, which is a clinical surrogate marker for GH biological activity. In HIV-infected patients, IGF-1 levels rose rapidly during the first 2 weeks of tesamorelin treatment and remained relatively stable throughout 52 weeks. Higher IGF-1 SDS scores were associated with an increase in a few GH-related AEs, but did not affect overall AE profile, nor was there any evidence of a causal relationship with the occurrence of cancers.

The effect of tesamorelin administration on glycemic parameters was a theoretical safety concern because of well known diabetogenic effect of GH. In the Phase 3 studies, no clinically significant differences were observed over 52 weeks between tesamorelin 2 mg and placebo for changes from baseline in FBG, insulin, HOMA-IR, and HbA_{1c}. With regard to FBG shifts and changes in glucose categories, as well as shifts in HbA_{1c} category-

ries, greater differences from baseline occurred in the tesamorelin group. Nevertheless, there was some reversal of these effects after the first 26 weeks. Overall, the data suggest no major safety concerns with regard to glucose homeostasis and that any glycemic changes can be managed in clinical practice.

Using a definition developed with the FDA, the incidence of hypersensitivity reactions is low, with 2.9% during the first 26 weeks and 1.2% in the T-T group during the extension phases. Overall, there is a certain pattern in the profile of those patients that may be more likely to develop a hypersensitivity reaction. None of the hypersensitivity reactions were considered to be anaphylaxis, defined a systemic life threatening allergic reaction. The patients who reported systemic symptoms noted that the symptoms rapidly resolved either spontaneously or simply with an antihistamine or topical corticosteroid application. None of the patients were treated with epinephrine, bronchodilators or systemic corticosteroids nor needed any emergency medical care. None of the hypersensitivity reactions were considered as SAE or resulted in a serious outcome.

In conclusion, the safety data suggest that tesamorelin 2 mg administered SC daily in HIV-infected patients is well tolerated. The key safety observations with tesamorelin, such as increased IGF-1 SDS, slight differences in glucose parameters, hypersensitivity reactions, and the presence of antibodies can be readily managed in clinical practice (See **Section 6.5.1**).

7 IMMUNOGENICITY

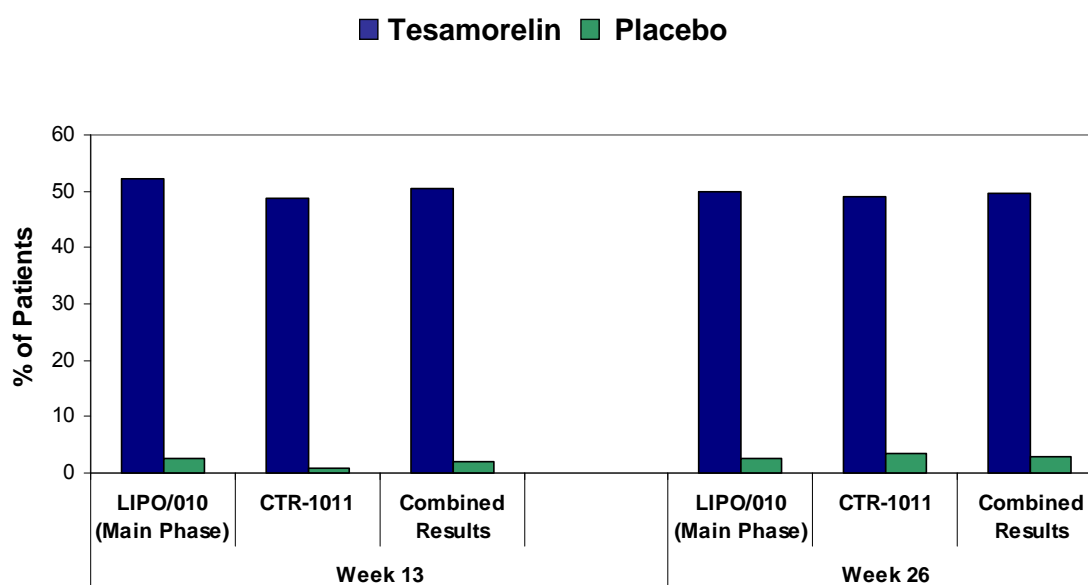
7.1 Antibodies: Prevalence, Impact on Safety, and Reversibility

Antibody formation, a common response to peptide therapeutics when administered subcutaneously ([Schnabel 2006](#)), could potentially lead to undesirable clinical effects, such as a decrease in drug efficacy or an increase in SAEs. Previous studies have established a

precedent for the development of antibodies to hGRF analogues such as tesamorelin. In a study by [Chen et al \(1993\)](#), GHRH (1-29) was administered to GH-deficient children. The majority of the patients developed GHRH antibodies. As part of the tesamorelin Phase 3 program, extensive monitoring was conducted to detect the development of anti-tesamorelin IgG antibodies or *in-vitro* NAb (against tesamorelin or endogenous GRF).

In the HIV Phase 3 main phase studies, anti-tesamorelin IgG antibodies were detected in approximately half the tesamorelin-treated patients at Weeks 13 and 26 (**Figure 25**).

Figure 25. Prevalence of Anti-Tesamorelin IgG Antibodies at Weeks 13 and 26 (Main, Phase 3 Studies)



Most patients with anti-tesamorelin IgG antibodies had low titers (<400), and only 9.3% of tesamorelin-treated patients had high titers (≥ 400) at Week 26 (**Table 42**).

Table 42. IgG Antibody Status and Titers by Study and Treatment Assignment from Baseline to Week 52 (Combined, Phase 3 Studies)

| Antibody Status/Titers, n (%) | MAIN | | EXTENSION | | |
|-------------------------------|----------------------|------------------|--------------|--------------|--------------|
| | Tesamorelin N=543 | Placebo N=263 | T-T N=246 | T-P N=135 | P-T N=197 |
| Baseline | | | | | |
| Absent | 511 (97.9) | 246 (97.2) | 239 (98.8) | 126 (96.9) | 187 (96.9) |
| Present | 11 (2.1) | 7 (2.8) | 3 (1.2) | 4 (3.1) | 6 (3.1) |
| 0-50 ^a (low) | 9 (1.7) | 5 (2.0) | 3 (1.2) | 3 (2.3) | 4 (2.1) |
| 100-200 (low) | 1 (0.2) | 1 (0.4) | 0 | 0 | 1 (0.5) |
| ≥400 (high) | 1 (0.2) | 1 (0.4) | 0 | 1 (0.8) | 1 (0.5) |
| Week 26 | | | | | |
| Absent | 206 (50.5) | 196 (97.0) | 131 (54.8) | 59 (44.4) | 186 (96.9) |
| Present | 202 (49.5) | 6 (3.0) | 108 (45.2) | 74 (55.6) | 6 (3.1) |
| 0-50 ^a (low) | 99 (24.3) | 5 (2.5) | 59 (24.7) | 32 (24.1) | 5 (2.6) |
| 100-200 (low) | 65 (15.9) | 1 (0.5) | 30 (12.6) | 30 (22.6) | 1 (0.5) |
| ≥400 (high) | 38 (9.3) | 0 | 19 (7.9) | 12 (9.0) | 0 |
| Week 52 | | | | | |
| Absent | -- | -- | 103 (52.6) | 76 (81.7) | 58 (39.2) |
| Present | -- | -- | 93 (47.4) | 17 (18.3) | 90 (60.8) |
| 0-50 ^a (low) | -- | -- | 64 (32.7) | 10 (10.9) | 48 (32.4) |
| 100-200 (low) | -- | -- | 19 (9.7) | 5 (5.4) | 25 (16.9) |
| ≥400 (high) | -- | -- | 10 (5.1) | 1 (1.1) | 17 (11.5) |

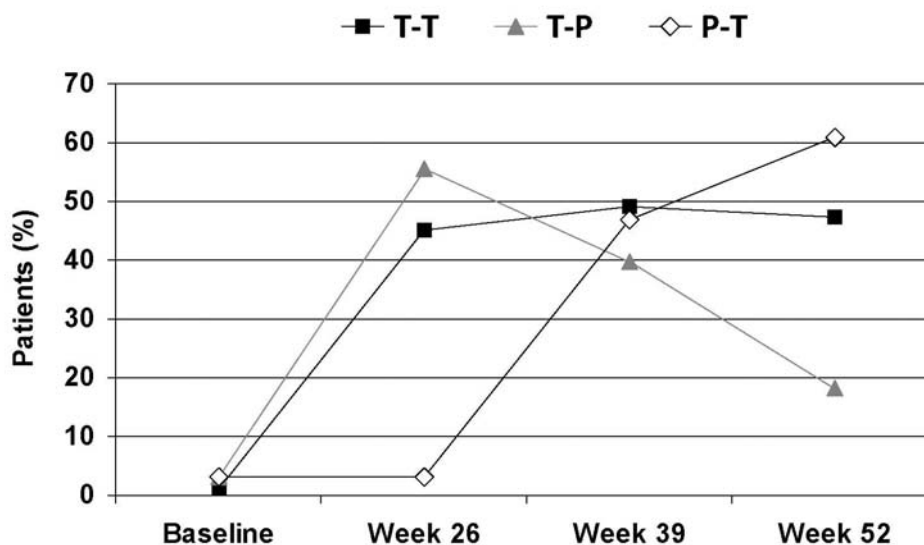
IgG, immunoglobulin G; P-T, placebo-tesamorelin; T-P, tesamorelin-placebo; T-T, tesamorelin-tesamorelin.

Tesamorelin refers to tesamorelin 2 mg/day.

^a 0-50 excludes 0 value.

In the T-T group, the percentage of patients with anti-tesamorelin IgG antibodies remained essentially unchanged throughout the extension (**Figure 26**), and the percentage of patients with high titers did not increase. As was observed in tesamorelin-treated patients in the main phase, the presence of anti-tesamorelin IgG antibodies increased in the P-T group. However, anti-tesamorelin IgG antibodies decreased in the T-P group, indicating the reversibility of antibody presence.

Figure 26. Prevalence of Anti-Tesamorelin IgG Antibodies Over 52 Weeks (Extension, Combined, Phase 3 Studies)



IgG, immunoglobulin G; P-T, placebo-tesamorelin; T-P, tesamorelin-placebo; T-T, tesamorelin-tesamorelin.

In addition, all patients receiving treatment (tesamorelin or placebo) in the extension phase and who were positive for anti-tesamorelin IgG antibodies at the completion (Week 52 or early termination [ET] visit) of study CTR-1012 (n=102) were contacted for follow-up visits to assess anti-tesamorelin IgG antibody status until disappearance of antibodies was confirmed. As of April 7, 2010, 59 of these 102 patients returned for follow-up visits, and 1 of the 59 is still positive.

An analysis of AEs according to anti-tesamorelin IgG antibody status categories was performed. During the main phase studies, no significant differences in AEs were found between patients who were positive or negative for anti-tesamorelin IgG antibodies, with the exception of injection-site pruritus (10.0% vs 4.9%, respectively). During the extensions, no significant differences in AEs were found between patients who were positive or negative for anti-tesamorelin IgG antibodies, with the exception of upper respiratory tract infection (11.1% vs 3.0%, respectively).

In the tesamorelin group at Week 26, similar percentages of patients with and without anti-tesamorelin IgG antibodies had IGF-1 SDS $>+2$ and SDS $>+3$. Similar percentages of patients with anti-tesamorelin IgG antibody titers of 0-50 (0 was excluded), 100-200, and ≥ 400 had IGF-1 SDS $>+2$ (41.8%, 49.2%, and 47.4%, respectively) and IGF-1 SDS $>+3$ (30.6%, 38.5%, and 36.8%, respectively).

In the extension at Week 52, similar percentages of T-T patients with and without anti-tesamorelin IgG antibodies had IGF-1 SDS $>+2$ and SDS $>+3$. Similarly, no pattern was observed between the percentage of patients per titer category and IGF-1 SDS scores: titers of 0 = 36.6%, 0-50 (0 was excluded) = 27%, 100-200 = 36.8% and ≥ 400 = 40.0%. A similar scenario was observed for the SDS $>+3$ category: titers of 0 = 24.8%, 0-50 (0 was excluded) = 17.5%, 100-200 = 26.3% and ≥ 400 = 30.0%.

A subgroup analysis showed no apparent differences in anti-tesamorelin IgG antibody status between individuals above and below the median age of 47 years in the main phase studies and the extensions. A greater proportion of women than men were anti-tesamorelin IgG antibody-positive at Week 26 (78% vs 45%). Titers also tended to be higher in women, but generally speaking, women tend to produce stronger immune responses compared to men ([Verthelyi 2001](#)). At Week 52, the percentage of women positive for anti-tesamorelin IgG antibodies in the T-T group was 57%, compared with 46% in men. From Week 26 to Week 52, the prevalence of anti-tesamorelin IgG antibodies tended to stay the same in men but decreased in women. However, the small number of women in the study relative to the number of men prevents meaningful interpretation of these differences.

Approximately 60% of anti-tesamorelin IgG antibody-positive patients had cross-reactive antibodies with hGRF.

The presence of *in vitro* detected neutralizing antibodies (NABs) against endogenous hGRF was assessed in all anti-tesamorelin IgG antibody-positive patients treated with tesamorelin for 52 weeks (or at ET during the extension phase). Five percent of the patients were found to be hGRF NAB-positive, all with titers of 25 (MRD for the NAb assay). No impact on IGF-1 levels was observed when comparing the change in IGF-1 level at Week 52/ET among the anti-tesamorelin IgG antibody-negative, anti-tesamorelin IgG antibody-positive/hGRF NAB-negative, and anti-tesamorelin IgG antibody-positive/hGRF NAB-positive patients.

Neutralizing antibody activity against hGRF was also measured at Week 52/ET from anti-tesamorelin IgG antibody-positive patients in the T-P group. Only 2 patients were hGRF NAB-positive up to 52 weeks (1 completer with a titer of 25 and 1 who had discontinued early with a titer of 200). These results indicate the reversibility of the presence of hGRF NABs.

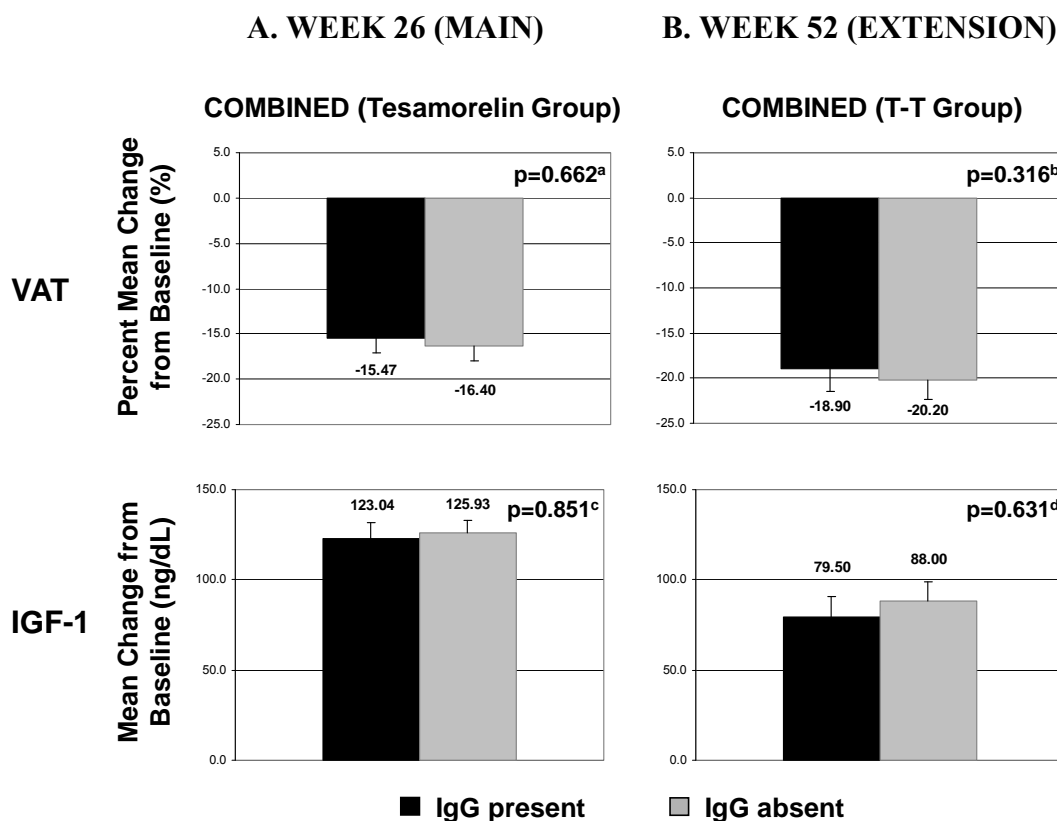
7.2 Impact of Antibodies on Efficacy and Interaction with Other Variables

The presence and titer of anti-tesamorelin IgG antibodies had no statistically significant effect on the change from baseline in VAT or IGF-1 in the main phase (**Figure 27A**). No treatment-by-covariate interactions were found for the change in VAT or IGF-1 when anti-tesamorelin IgG antibody status, titer level, and titer category were included as categorical covariates.

The presence of anti-tesamorelin IgG antibodies on VAT responders at 26 weeks was also assessed. The subjects were classified per VAT responders (VAT loss of $\geq 8\%$ from baseline) and VAT non-responders (VAT loss of $< 8\%$ from baseline). The results demonstrate that the presence of anti-tesamorelin IgG antibodies has no impact on the proportions of VAT responders.

In the extension phase studies, in the T-T group, the changes from baseline in VAT and IGF-1 were similar and not statistically significantly different between subgroups by anti-tesamorelin IgG antibody status or titer categories (**Figure 27B**).

Figure 27. Impact of Anti-Tesamorelin IgG Antibodies on VAT and IGF-1 in Tesamorelin-Treated Patients (Combined, ITT Population)



IGF-1, insulin-like growth factor-1; IgG, immunoglobulin G; ITT, intent-to-treat; VAT, visceral adipose tissue.

^a Model: $\text{Ln}(\text{VAT}/\text{baseline}) = \log(\text{baseline VAT}) + \text{study} + \text{antibodies}$.

^b Model based on the T-T and P-T groups: $\text{Ln}(\text{VAT}/\text{baseline}) = \text{Ln}(\text{baseline VAT}) + \text{treatment} + \text{study} + \text{antibodies} + \text{treatment} * \text{antibodies}$.

^c Model: $\text{IGF-1 at Week 26} - \text{IGF-1 at baseline} = \text{IGF-1 at baseline} + \text{study} + \text{antibodies}$.

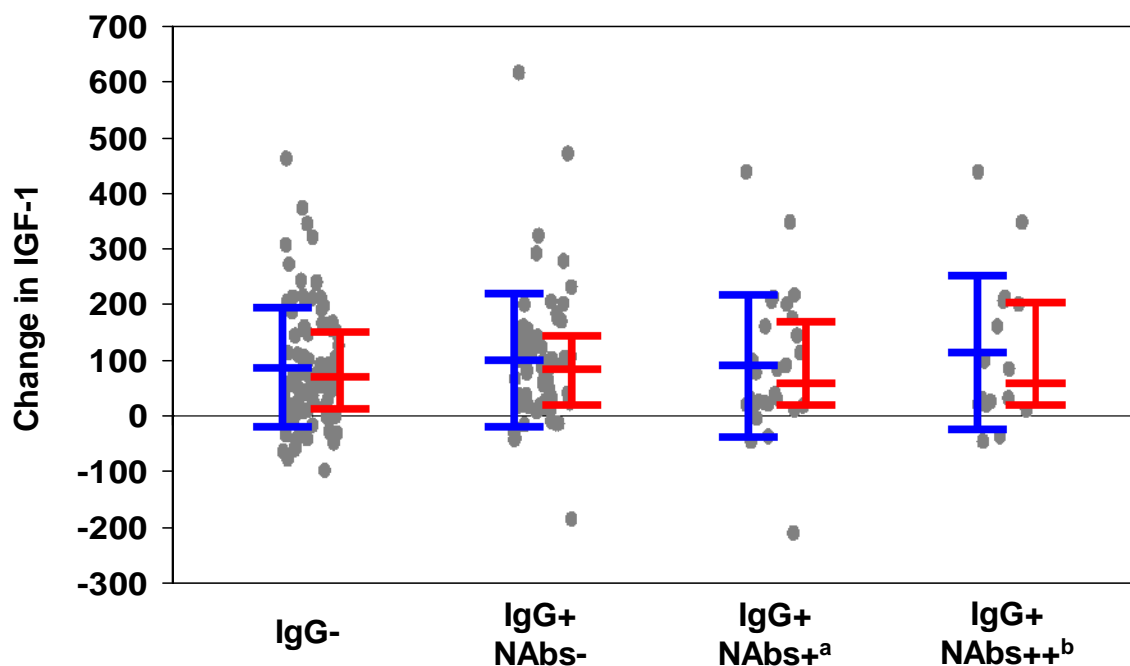
^d Model based on the T-T and P-T groups: $\text{IGF-1 at Week 52} - \text{IGF-1 at baseline} = \text{IGF-1 at baseline} + \text{treatment} + \text{study} + \text{antibodies} + \text{treatment} * \text{antibodies}$.

To assess the impact of *in vitro* detected tesamorelin NAbs on efficacy, Week 52/ET samples from anti-tesamorelin IgG antibody-positive patients in the T-T group were

tested for neutralizing activity. Ten percent of patients were tesamorelin NAb-positive (2 with titers ≥ 400 , 2 with titers of 100, 7 with titers of 50, and 13 with titers of 25). No effect was observed when comparing changes from baseline in VAT and IGF-1 among the anti-tesamorelin IgG antibody-negative, anti-tesamorelin IgG antibody-positive/tesamorelin NAb-negative, and anti-tesamorelin IgG antibody-positive/tesamorelin NAb-positive patients (**Figures 28 and 29**).

The potential impact of tesamorelin NAb on VAT responders was also assessed. The patients were classified per VAT responders (VAT loss of $\geq 8\%$ from baseline) and VAT non-responders (VAT loss of $< 8\%$ from baseline). The results demonstrate that the presence of *in vitro* detected tesamorelin NAb has no impact on the proportions of VAT responders.

Figure 28. Percent Change in IGF-1 at Week 52 (or ET) per tesamorelin NAb Categories (T-T)



ET, early termination; IGF-1, insulin-like growth factor-1; IgG, immunoglobulin G; NAbs, neutralizing antibodies; T-T, tesamorelin to tesamorelin.

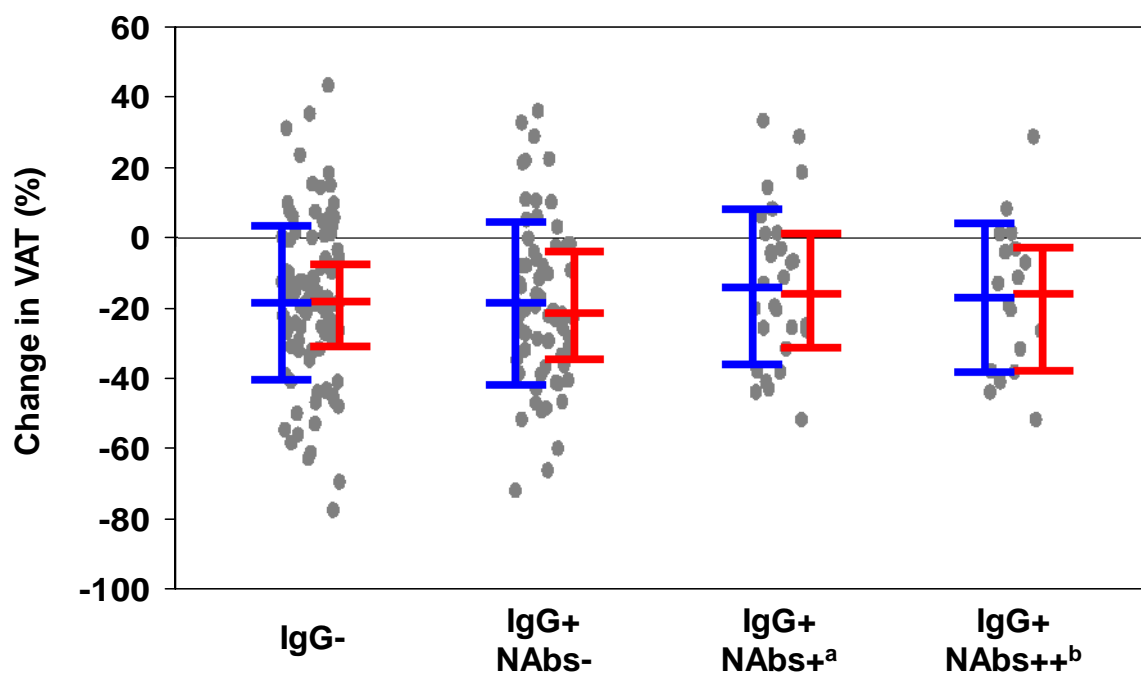
Blue: Mean- 1 SD, Mean, Mean+ 1 SD.

Red: 25th percentile, Median, 75th percentile.

^a NAbs potentially positive.

^b NAbs positive.

Figure 29. Percent Change in VAT at Week 52 (or ET) per tesamorelin NAbs Categories (T-T)



ET, early termination; IgG, immunoglobulin G; NAbs, neutralizing antibodies; VAT, visceral adipose tissue; T-T, tesamorelin to tesamorelin.

Blue: Mean- 1 SD, Mean, Mean+ 1 SD.

Red: 25th percentile, Median, 75th percentile.

^a NAbs potentially positive.

^b NAbs positive.

7.3 Immunogenicity Conclusions

Anti-tesamorelin IgG antibodies were detected in approximately half of tesamorelin-treated patients in the HIV Phase 3 studies at 26 weeks, but most had low titers and the proportion of patients with these antibodies did not increase with continued tesamorelin treatment up to 52 weeks. Among patients who were re-randomized to placebo during the

extensions, the percentage of patients with anti-tesamorelin IgG antibodies decreased from 56% to 18%, indicating the reversibility of this effect.

In the patients with anti-tesamorelin IgG antibodies treated with tesamorelin for 52 weeks, 5% and 10% were found to be hGRF NAb-positive and tesamorelin NAb-positive, respectively.

In anti-tesamorelin IgG antibody-positive patients, the presence or absence of hGRF NABs or tesamorelin NABs had no apparent effect on AE profiles or IGF-1 or VAT results. These observations suggest that the presence of these antibodies has no clinically significant effects on GH release.

8 RISK MANAGEMENT

8.1 Background

During the initial 26 weeks, the percentage of subjects with AEs or SAEs were comparable between tesamorelin (*EGRIFTA*[™]) and placebo groups; the most frequently reported AEs in tesamorelin patients were mainly related to injection sites reactions (erythema and pruritus) or those known to be related to GH (peripheral edema, arthralgia, pain in extremity, and myalgia). Most AEs were considered by investigators to be mild to moderate in severity and unrelated to study treatment. In the extension phase studies, no differences in AEs or SAEs were observed in patients who received tesamorelin for 52 weeks compared with 26 weeks.

However, there were key safety observations with tesamorelin, such as increased IGF-1 SDS, slight changes in measures of glucose homeostasis and hypersensitivity reactions each of which can be readily managed in clinical practice. In order to aid the clinician, we are proposing guidelines to manage the theoretical risk of malignancy associated with elevated IGF-1 SDS levels, as well as the potential changes in glucose parameters and occurrence of hypersensitivity reactions. These guidelines will be mentioned in the Full

Prescribing Information (FPI) and Medication Guide, as well as in other educational materials provided to patients, physicians and pharmacists – as described further in Section 8.1.4, the Risk Evaluation and Mitigation Strategy (REMS).

8.1.1 IGF-1 SDS and Long-Term Safety Observational Study

High IGF-1 levels have been linked in some epidemiological studies to an increased risk of developing certain cancers ([Ma 1999](#), [Chan 1998](#), [Hankinson 1998](#)) there is a theoretical increased risk of malignancy for patients who are treated with tesamorelin and who achieve very high IGF-1 levels. It should be noted, however, that in adult patients treated with rhGH over many years, there has never been any evidence of such an increase in cancer incidence ([Hatrick 2002](#), [Svensson 2004](#)).

Consistent with recommendations for rhGH, patients with active neoplasia should not be treated with tesamorelin. For patients with a history of neoplasia, treatment with tesamorelin should be carefully considered, given an assessment of risk-benefit and patients monitored for recurrence.

HIV positive patients that are treated with tesamorelin should be monitored for IGF-1 levels at least annually. In phase-3 studies with tesamorelin there were increases in the percentage of patients moving into the >2 and >3 IGF-1 SDS categories. However, no increase in risk for any particular malignancy was observed in tesamorelin-treated patients during these clinical trials. Given the theoretical risk of elevated IGF-1 levels, treatment discontinuation is recommended if the IGF-1 SDS is ≥ 3 after 52 weeks of tesamorelin treatment. These recommendations will be further discussed and refined through convening an independent panel of experts that will review the available data on clinical outcomes, cancer incidence, and IGF-1 levels, on an ongoing basis. Recommendations of the panel and available data will be summarized and submitted to FDA on a regular basis.

Furthermore, a long-term safety observational study that will follow both tesamorelin treated patients and an untreated HIV group, will be implemented to gather additional data on any potential for increased cancer risk in the clinical setting.

8.1.2 Glucose Homeostasis

Given the potential effects on glucose homeostasis, it is recommended that HIV-positive patients with a past medical history of diabetes mellitus or patients presenting with a FBG ≥ 126 mg/dL or HbA_{1c} $\geq 6.5\%$ should not receive tesamorelin therapy.

Once patients are deemed eligible to receive tesamorelin treatment, FBG or HbA_{1c} will be measured after 26 weeks of administration. If the FBG remains below 126 mg/dL or HbA_{1c} remains below 6.5 %, and treatment is continued, these measures will be repeated at a minimum of every 26 weeks. If FBG is > 150 mg/dL or HbA_{1c} is $> 7\%$, tesamorelin should be discontinued. If the FBG is between 126-150 mg/dL or HbA_{1c} is 6.5-6.9 % after 26 weeks of treatment, the patient should have a follow-up FBG or HbA_{1c} assessment after receiving tesamorelin for an additional 13 weeks. At this 39 week assessment, if the FBG remains above 126 mg/dL or the HbA_{1c} remains above 6.5%, then it is recommended to discontinue tesamorelin treatment.

8.1.3 Hypersensitivity Reactions

Only approximately 3% of patients who received tesamorelin developed hypersensitivity reactions which were generally mild to moderate in severity. These reactions generally resolved rapidly following drug discontinuation, with only the need for supportive treatment (eg, antihistamines).

In cases of suspected hypersensitivity reactions, patients will be advised to seek prompt medical attention and treatment with tesamorelin should be discontinued immediately.

8.1.4 Limited Distribution Network

To encourage the appropriate *EGRIFTA*[™] prescribing in the indicated patient population (HIV patients with lipodystrophy and excess abdominal fat), *EGRIFTA*[™] will be exclusively dispensed through a targeted network of contracted pharmacies in the United

States. Only Contracted Network Pharmacies will be able to purchase *EGRIFTA*[™] from EMD Serono. EMD Serono will have the ability to track each box of *EGRIFTA*[™] to the Contracted Network Pharmacies via unique box serial number.

8.1.5 Risk Evaluation and Mitigation Strategy (REMS)

To help ensure the safe and effective use of tesamorelin, Theratechnologies Inc./EMD Serono Inc. have developed a Risk Evaluation and Mitigation Strategy (REMS) that includes a prescriber education and communication plan as well as a patient medication guide.

8.1.5.1 Objectives

The goal of the *EGRIFTA*[™] Risk Evaluation and Mitigation Strategy (REMS) is to assure proper implementation of two elements in practice that can favourably impact benefit-risk for the intended population:

- Educate HIV prescribers and HIV patients on the safe and effective use of *EGRIFTA*[™] in HIV patients, by providing *EGRIFTA*[™] educational materials and information.
- Encourage appropriate *EGRIFTA*[™] prescribing in the indicated patient population.

This educational material will include the above-mentioned recommendations from sections 8.1.1, 8.1.2 and 8.1.3 for the safe use of *EGRIFTA*[™].

8.1.5.2 Design and Components

The design of this plan was based on guidance provided in the FDA Amendments Act of 2007 ([Risk Evaluation and Mitigation Strategies, www.fda.gov](http://www.fda.gov)) and the FDA document “Guidance for Industry Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments and Proposed REMS Modifications” (September 2009).

The REMS medication guide will be included with the full prescribing information (FPI) for tesamorelin. Each carton of tesamorelin, which contains a 1-month supply of the drug,

will include the revised FPI plus medication guide, ensuring that each patient receives a copy of the guide. Additional guides will be available at the tesamorelin website or by calling Theratechnologies Inc./EMD Serono Inc. at a toll-free number. The website will offer non-promotional information on the REMS only, and the name of the website will be chosen to avoid the perception of drug promotion.

The communication plan supporting the implementation of REMS is designed to educate health care professionals who prescribe antiretrovirals about the key risks and benefits involved with the use of tesamorelin. Physicians and pharmacists will be provided with the FPI and medication guide. In addition, a Dear Health Care Professional Letter will be distributed to prescribers, and a Dear Pharmacist Letter will be distributed to pharmacists and to directors of pharmacies at managed care organizations.

8.1.5.3 Assessment

A REMS assessment plan has been developed to examine the extent to which the medication guide and communication plan meets REMS goals and whether these goals require modification. Distribution of REMS materials will be analyzed to ensure that the entire target list of prescribers and pharmacists receives the appropriate level of information. Knowledge, attitude, and behaviour (KAB) surveys will also be collected from patients and prescribers to test their receipt and understanding of tesamorelin educational materials. These surveys are designed to assess the extent to which the materials convey the most important information that prescribers and patients need to know to assure the safe use of tesamorelin. These assessments will be completed at 18 months, 3 years and 7 years following implementation.

9 BENEFIT-RISK ASSESSMENT

Patients who suffer from HIV-associated lipodystrophy experience disfiguring body composition changes including excessive accumulation of fat in the visceral compartment, breasts, and the upper back (lipohypertrophy) and/or noticeable loss of subcutaneous fat in the trunk, face and extremities (lipoatrophy). In addition to the accumulation of fat, lipohypertrophy is associated with a negative self image, worsening of a number of metabolic parameters including triglycerides, cholesterol, and glucose; and a resultant potential impact on long-term cardiovascular health outcomes.

Currently, there are no approved therapies or guidelines for the treatment of this syndrome. There exist some options, although none of them has predictably satisfactory results. One option has been to switch one or more components of the ART, although this does not necessarily improve body composition and may not be an appropriate therapeutic approach from a virological or immunological safety standpoint. Alternative recommendations have been hypocaloric diet and exercise, or agents such as metformin. However, metformin may actually increase lipoatrophy and some diet and exercise regimens may also further reduce subcutaneous adipose tissue (SAT), which is clinically undesirable in this patient population.

Due to very limited treatment options, some patients have been known to delay the initiation of ART or to discontinue ART altogether, putting themselves at increased risk for mortality, opportunistic infections, and other complications.

Tesamorelin, if approved, would represent a major advance in the treatment of HIV-associated lipohypertrophy. Tesamorelin has a positive impact on the main feature of the condition: increased visceral adipose tissue (reducing it by 13% for the 2 studies combined, $p < 0.001$ vs placebo) and waist circumference (reducing it by 2.4 cm for the 2 studies combined, $p < 0.001$ vs placebo). An increasing number of studies, in both HIV and

non-HIV populations, indicate that increased waist circumference and/or excess abdominal fat correlate with increased cardiovascular risks.

This new treatment also has a positive impact on other body composition measures, specifically by increasing lean body mass and decreasing trunk fat. Unlike other experimental options, tesamorelin has only a small, not clinically significant, impact on SAT. This result is an important secondary benefit for patients who are suffering from concurrent lipoatrophy. The mixed form of lipodystrophy, lipoatrophy and lipohypertrophy, represented the majority of patients who were enrolled in the Phase III trials of tesamorelin.

Tesamorelin also improved many of the lipid parameters associated with increased VAT and waist circumference. Although not all these benefits are of equal magnitude, taken as an aggregate they suggest a positive metabolic profile for tesamorelin.

Perhaps the benefit of greatest importance, is the impact of the drug on the patient's quality of life, which is reflected in reported changes in self image and improved relationships with other people. Patients feel more "normal" and this improvement is a source of measured benefit for the treating physician.

The decision to continue or stop treatment should include an assessment of all three areas discussed above physical, psychological and metabolic-in the context of the individual patient's risk. The possible risks associated with tesamorelin treatment were clearly identified in the safety section of this document, and include:

- GH related AEs, including increase in IGF-1 levels, and injection site AEs
- worsening of glucose homeostasis in a small number of patients
- hypersensitivity reactions
- presence of antibodies

In summary, tesamorelin's benefit risk can be tabulated as follows:

| Favorable Effects | Unfavorable Effects ¹ |
|--|--|
| <ul style="list-style-type: none"> ▪ Reduces Visceral Adipose Tissue ▪ Decreases waist circumference and trunk fat ▪ Improves Patient Reported Outcomes: Belly Appearance Distress and Belly Profile ▪ Preserves Health Related Quality of Life ▪ Improves lipid parameters ▪ Preserves abdominal and limb fat ▪ VAT decrease correlates well with waist circumference and Patient Reported Outcomes (allowing identification of response as early as 13 weeks) | <ul style="list-style-type: none"> ▪ GH related and injection site AEs ▪ Altered glucose homeostasis in a small number of patients² ▪ Hypersensitivity reactions |

¹ See Risk Management Plan

² Percentage varies based on using FBG/2hr OGTT or HbA_{1c} definition: (2-4% diabetic by week 26, 0-1% by week 52)

A **Risk Management Plan** has been developed to provide resources to physicians that will help them identify any emerging risks and to either manage them or to discontinue treatment. This plan is comprised of several elements:

1) Risk Evaluation and Mitigation Strategy (REMS):

The Medication Guide will include the following information:

- ongoing monitoring of FBG or HbA_{1c}, ensuring early identification of a limited number of patients experiencing changes in glucose homeostasis
- discontinuing tesamorelin treatment in case of hypersensitivity reactions
- ongoing monitoring for IGF-1 levels to ensure that patients will not be treated for a long period of time with IGF-1 levels above 3 SDS
- description of the appropriate indicated patient population

2) Long-term Observational Safety Study:

To ensure a long-term understanding of the product's benefit/risk profile, the Sponsor will implement a long-term observational safety study that will follow both patients

treated with tesamorelin and an untreated HIV- positive control group, not receiving, to gather additional data on cancer risk in this clinical setting.

3) Network of Contracted Pharmacies:

To encourage the appropriate prescribing of tesamorelin in the indicated patient population (HIV- positive patients with lipohypertrophy as defined by excess abdominal fat), tesamorelin will be exclusively dispensed through a targeted network of contracted pharmacies in the United States. Only Contracted Network Pharmacies will be able to purchase tesamorelin from EMD Serono. EMD Serono will have the ability to track each box of tesamorelin to the Contracted Network Pharmacy via a unique serial number on each box.

Conclusion:

Tesamorelin has the potential to offer patients and physicians the means to combat excess visceral fat accumulation, a significant side effect of ART, not only offering improved body composition, but improved QOL and reduction in the risk of other health consequences associated with lipohypertrophy.

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11 APPENDICES

11.1 Appendix I: Patient-Reported Outcomes Methodology

Patient-reported outcomes (PRO) related to body image distortion and its consequences were secondary endpoints in the Phase 3 studies. PRO data were collected using well-defined and reliable scales and indices appropriate for the population studied, including measures of body dysmorphia and health-related quality of life (HRQOL) from the Phase V Technologies, Inc. Outcomes Information System ([Turner 2010, FDA Drug Master File 22780](#)).

11.1.1 Body image impact conceptual framework

The core conceptual model comprises 2 main constructs—Body Image and Health Status. More specific components are associated with each construct. The schema shown in **(Figure 30)** represents the Body Image Construct. The Image Perception component represents the individual's perception regarding each body characteristic represented in the module, e.g. face, belly, arms, and legs. Image Distress characterizes the degree to which the individual's perception of each characteristic is more or less distressing. Theory suggests that individuals internalize a set of body conformation standards. Distress is hypothesized to be directly associated with the degree of discrepancy between the individual's self-perception and the standard. Image Comparison involves an individual's judgment regarding an explicitly represented set of body characteristic standards. The correspondance between Image Perception and Image Comparison provides an indication of the degree of distortion an individual manifests regarding Body Image. Specific body characteristics are selected for each construct, depending upon the particular research question and disease condition. For example, the belly might be the focus for obesity or lipodystrophy while the breasts might be the focus for breast cancer treatment.

Figure 30. Body Image Construct

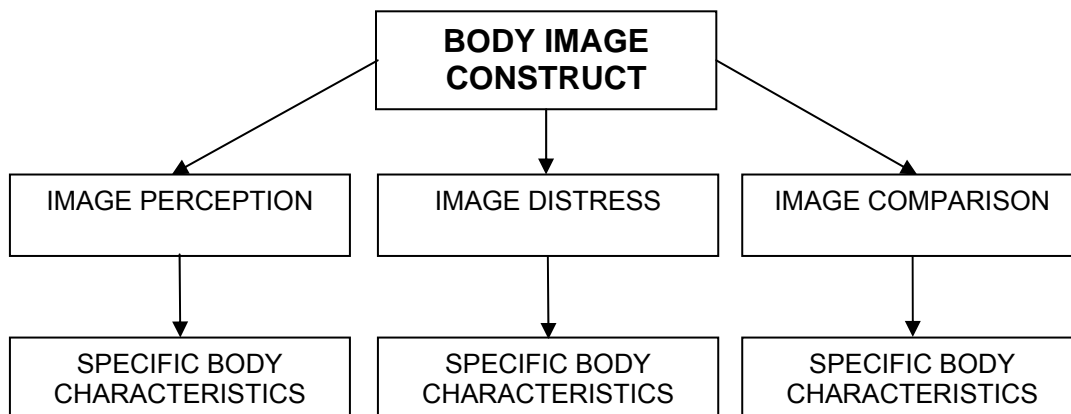


Figure 31. Health Status Construct

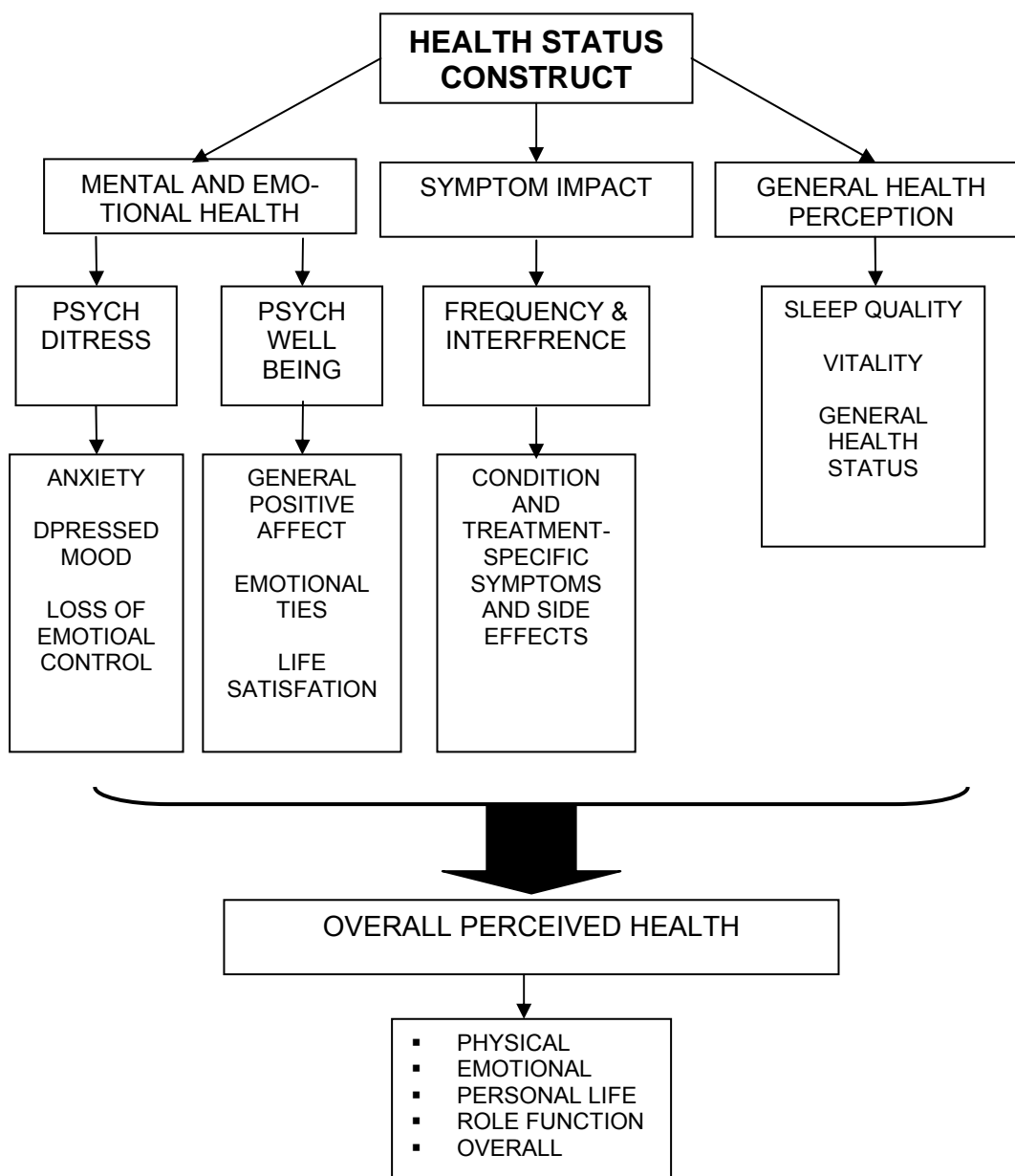


Figure 31 represents the Health Status Construct, which is composed of both objective health status and subjective health perception components. “Objective” refers to the respondent’s self-judgment about status and functioning, rather than that of an observer, or a healthcare provider. Three specific and one summary component are hypothesized to be most affected by variation in the Body Image Construct. Mental and Emotional Health encompass both Psychological Distress and Psychological Well Being. While deterioration in body image is hypothesized to increase distress, effective intervention may improve overall well-being. As Body Image Distress increases, individuals are hypothesized to experience elevated Anxiety, Depressed Mood, and Loss of Emotional Control. Conversely, as Body Image Distress decreases, General Positive Affect, Emotional Ties, and Life Satisfaction should be enhanced. The General Health Perception component encompasses Vitality, and General Health including bodily pain and sleep disturbance. The Symptom Impact component comprises a set of condition and treatment-specific symptoms and side effects about which 2 assessments are made—how frequent was symptom occurrence, and how much it interfered with the individual’s functioning. The Overall Perceived Health component provides a summary gestalt from the respondent’s perspective and incorporates judgments about physical and emotional as well as personal and role functioning and an overall integrative assessment.

Conceptually, as the Body Image construct changes, whether by condition or disease-produced deterioration, altered perceptual ability, or effective (or ineffective) intervention, the impact will be manifested by changes in the Health Status construct. Individual differences reflect objective differences in functional status, subjective differences reflected in perception, and variation in responsiveness to treatment or intervention.

11.1.2 Body image impact measurement model

The Body Image Impact module (BIIM) was developed to serve as a link between clinical endpoints and patient-reported outcomes. The scales are primarily descriptive and are

focused on individual body characteristics as the unit of measurement. Those components that are multiple single-item scales were developed from a classical psychometric perspective.

Body image distress: Body image distress scale

The Body Image Distress Scale provides an assessment of the distress associated with the respondent's perception of each body characteristic. Using "current appearance" evaluation from the Body Size Scale as the frame of reference, respondents indicate the degree of distress associated with each body characteristic evaluated. The score associated with each response option are shown below, but did not appear on the actual questionnaire.

The question is phrased as follows:

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

- a. The amount of flesh on my face
- b. The amount of flesh on the back of my neck or between my shoulder blades
- c. The size of my legs
- d. The size of my belly
- e. The size of my breasts
- f. The size of my buttocks
- g. The size of my arms

The structured responses are scored as follows:

Respondent Selects Phrase

| | |
|-------------------------------------|------|
| 1. Extremely upsetting and Distress | 0 |
| 2. Very Upsetting and Distressing | 12.5 |
| 3. Quite Upsetting and Distressing | 25 |
| 4. A little Upsetting | 37.5 |
| 5. No feeling either way | 50 |
| 6. A little encouraging | 67.5 |
| 7. Quite encouraging | 75 |
| 8. Very Encouraging | 87.5 |
| 9. Extremely Encouraging | 100 |

Body image comparison: Respondent-reported body profile scales

The Body Profile Scales measure the respondent's self-evaluation against standardized silhouettes for belly and dorso-cervical (hump) body characteristics. Sets of 6 profile silhouettes (see below) were created from clinic-based photographs to represent progressive development from Normal to Moderate-to-Severe lipodystrophy-related abdominal adipose tissue and dorso-cervical adipose "hump". The respondent selects from the set the one that represents his or her self-evaluation for each of 3 scenarios:

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 health and well being?***

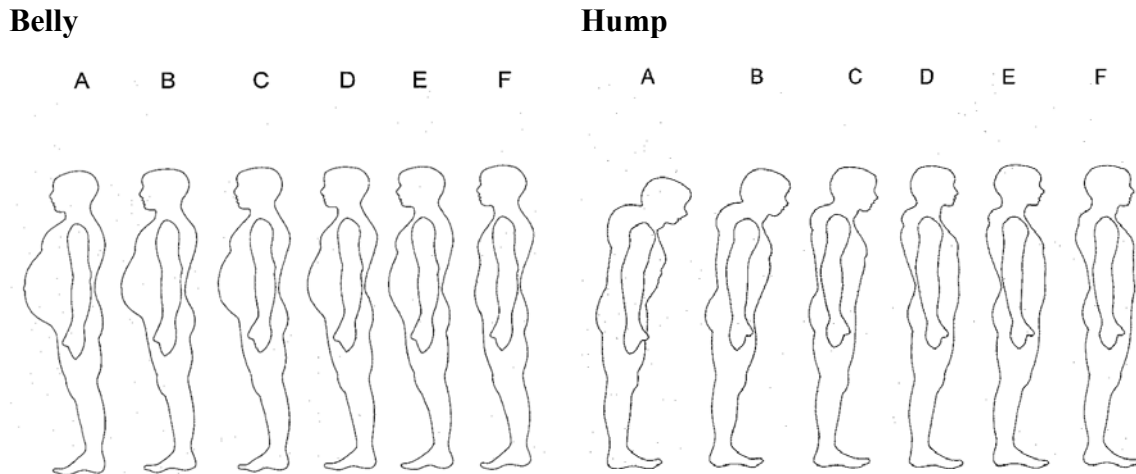
Each profile is given an ordinal score from 5 (most extreme) to 0 (ideal). Two Body Profile scores are calculated as the difference between the current evaluation and (1) the ideal profile, and (2) the smallest meaningful improvement profile.

The Body Profile Scale can be administered to an independent observer. The instructions are modified to:

1. Select the picture that *most closely* resembles how you think (Name) looks today?
2. Select the picture that *most closely* resembles how you would most like (Name) to look?
3. Select the picture that *most closely* resembles the smallest amount of improvement that you would consider beneficial to (Name)'s health and well being?

The independent observer can be a health care provider, relative, or significant other. The Profile Scale scoring remains the same.

Set of Six Belly and Dorso-cervical Hump Profiles:



Body image perception: Body size scale

The Body Size Scale was developed to assess individual perception of specific body characteristics. The scale was designed to provide characteristic-specific evaluations as well as a composite perceptual discord score. The Body Size Scale consists of 7 related questions that address specific body characteristic. The stem compares the respondent's "current appearance" to his or her self-defined "healthy look."

The Body Size Scale introduction is phrased as follows.

The following statements are about your appearance. Think about how you would look if you were "healthy". Now consider your "current appearance". Compared to your "healthy look", please comment about how you feel regarding the following areas of you body.

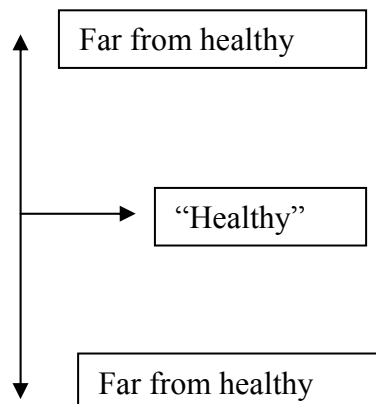
- a. The amount of flesh on my face
- b. The amount of flesh on the back of my neck or between my shoulder blades
- c. The size of my legs
- d. The size of my belly
- e. The size of my breasts
- f. The size of my buttocks
- g. The size of my arms

Responses are selected when prompted by:

Compared to my “healthy look”, my current amount or size is....

Respondent Selects Phrase

1. A great deal less/very smaller or thinner
2. A lot less/much smaller or thinner
3. Somewhat less, smaller or thinner
4. A little less, smaller or thinner
5. About right
6. A little more or bigger
7. Somewhat more or bigger
8. A lot more or much bigger
9. A great deal more or very much bigger



The perceived distance from “healthy look” is scored bi-directionally to reflect body size discrepancies in either direction from “About Right”. The score is shown beside each response option, but did not appear on the actual questionnaire.

Response

Initial Score

| | |
|--|------|
| 1. A great deal less/very smaller or thinner | -100 |
| 2. A lot less/much smaller or thinner | -75 |
| 3. Somewhat less, smaller or thinner | -50 |
| 4. A little less, smaller or thinner | -25 |
| 5. About right | 0 |
| 6. A little more or bigger | +25 |
| 7. Somewhat more or bigger | +50 |
| 8. A lot more or much bigger | +75 |
| 9. A great deal more or very much bigger | +100 |

Each individual body characteristics is the primary unit of measurement. The bi-directional scoring allows respondents to judge their characteristic as either “bigger” or “smaller” than their “healthy look”, providing standardization across repeated assessments. The bi-directional scoring also provides an integrative composite score, calculated as the sum of the absolute distances.

11.1.3 Weight assessment and overall appearance

The BIIM was developed for a number of body image applications, for some of which “weight” is an integral part. For lipodystrophy, however, actual weight is less an issue. This section contains two questions regarding weight: weight evaluation (under- to over-weight), weight concern, and overall appearance. The scores for each response option are shown below, but did not appear on the actual questionnaire.

Weight Assessment is phrased as follows:

Thinking about your weight today, do you consider yourself to be:

The response categories are:

- | | |
|----------------------------------|------|
| 1. Very Underweight | -100 |
| 2. Somewhat Underweight | -50 |
| 3. My Weight Is Just About Right | 0 |
| 4. Somewhat Overweight | 50 |
| 5. Very Overweight | 100 |

The Weight Concern item is phrased as follows:

Thinking about your weight now and your weight before you started the study drugs you are currently taking, how concerned are you about your weight now?

- | | |
|------------------------------------|-----|
| 1. Extremely Concerned | 100 |
| 2. Very Worried | 75 |
| 3. Somewhat Worried and Concerned | 50 |
| 4. A Little Concerned | 25 |
| 5. Not Concerned or Worried At All | 0 |

The Overall Appearance item is phrased as follows:

Thinking about all aspects of your current appearance, do you find your current appearance to be?

- | | |
|--|---|
| 1. Extremely Upsetting and Distressing | 0 |
| 2. Very Upsetting and Distressing | 2 |
| 3. Quite Upsetting and Distressing | 3 |
| 4. A Little Upsetting | 4 |
| 5. No Feeling Either Way | 5 |

| | |
|--------------------------|---|
| 6. A Little Encouraging | 6 |
| 7. Quite Encouraging | 7 |
| 8. Very Encouraging | 8 |
| 9. Extremely Encouraging | 9 |

11.1.4 Health status measurement model

The Health Status construct comprises established published scales. The scaling procedures are summarized in the following sections, along with the relevant literature citations.

Mental and emotional health

The Mental and Emotional Health component was developed by [Dupuy \(1972, 1974\)](#) with modifications by [Veit and Ware \(1983\)](#). Both Psychological Distress and Psychological Well Being are measured. The Psychological Distress component contains Anxiety, Depressed Mood and Loss of Behavioral and Emotional Control scales. All items are presented as 6-point Likert scales with various anchors, depending upon the stem. The Psychological Well Being component contains General Positive Affect, Emotional Ties and Life Satisfaction scales. All items are presented as 6-point Likert scales with various anchors, depending upon the stem. Each multi-item scale score is calculated as the mean value of the scale items, contingent upon a minimum number of valid responses. For each respondent, at least 50% of the scale items must be valid. Otherwise, that scale score is set to missing values.

Example of Item from the Mental and Emotional Health Scales:

How happy, satisfied, or pleased have you been with your personal life during the past month? (fill in 1 circle)

- Extremely happy, couldn't have been more satisfied or pleased
- Generally dissatisfied, unhappy
- Very happy
- Very dissatisfied, unhappy
- Generally satisfied, pleased
- Extremely dissatisfied, unhappy

Symptom impact component

The Symptom Impact component includes the Appearance-Specific Symptom Interference scale, which measures the respondent's evaluation of the degree of functional interference that results from his or her body conformation. It is a Likert scale, developed by Testa (1991, 1993), consisting of seven items concerning interference with 1) work, 2) social events, 3) recreational activities, 4) exercise and physical activities, 5) work effectiveness, 6) enjoying life and 7) feeling one's best. Each item is scored from 1 (All) to 6 (None). The scale is the mean score across the seven items. The Symptoms and Side Effects Distress scale (Testa, 1983) evaluates general, and GH, HIV and lipodystrophy-specific symptoms and side effects and completes the Symptom Impact component. It consists of 29 questions and yields overall frequency and distress severity scale scores.

Example of Item from the Appearance-Specific Symptom Interference Scale:

| | | | | | | |
|---|-----|------|------------|------|----------|------|
| <p><i>During the past month, how much of the time has your overall appearance interfered with your ability to:</i></p> <p style="text-align: center;">How much of the time during the past month? (please fill in 1 circle in each row)</p> | | | | | | |
| 1. Work at a job, do work around the home, or do daily chores | All | Most | A Good Bit | Some | A Little | None |
| | ○ | ○ | ○ | ○ | ○ | ○ |

Example of Items from the Symptoms and Side-Effects Distress Scale:

| <p>DURING THE PAST MONTH, HAVE YOU EXPERIENCED THIS SYMPTOM OR FEELING?</p> <p>Please mark: Y = Yes N = No If YES, then answer other columns</p> | <p>HOW OFTEN</p> <p>1 = Once or twice 2 = Once or twice a week 3 = Often each week 4 = Almost daily</p> | <p>HOW DISTRESSING HAS IT BEEN?</p> <p>0 = Not at all 1 = Somewhat 2 = Moderately 3 = Very much 4 = Extremely</p> |
|---|---|---|
| 1. Dryness of mouth (Y) (N) | (1) (2) (3) (4) | (0) (1) (2) (3) (4) |
| 2. General weakness (Y) (N) | (1) (2) (3) (4) (1) (2) (3) (4) | (0) (1) (2) (3) (4) |
| 3. Confusion (Y) (N) | | (0) (1) (2) (3) (4) |

General health perception

The General Health Perception component comprises 3 subscales and is adapted from previous questionnaires ([Dupuy 1984](#), [Rose 1978](#), [Jenkins 1983](#)): Vitality, General

Health Status, and Sleep Disturbance. All items are presented as 6-point Likert scales with various anchors, depending upon the stem.

Example of Item from the General Health Perceptions Scale

How much energy, pep or vitality did you have or feel during the past month? (fill in 1 circle)

- ☐ Very full of energy; lots of pep
- ☐ Generally low in energy or pep
- ☐ Fairly energetic most of the time
- ☐ Very low in energy or pep most of the time
- ☐ My energy level varied quite a bit
- ☐ No energy or pep at all; I felt drained, sapped

Global quality of life analogue scale

The Global Analogue Scale is a summary scale, consisting of 5 questions covering overall or in general, physically, emotionally, personal life and job or work. Each is a 10-point linear analogue items scored from 0 (The very worst I ever felt) to 10 (The very best I ever felt).

Other quality of life composite scales

- **Composite Psychosocial**—This scale is comprised of the mean of all subscales of Mental and Emotional Health scale and all subscales of General Health Perceptions scale.
- **Composite QOL**—This scale is comprised of the mean of all 6 Mental and Emotional Health subscales plus 3 subscales from General Health Perceptions.
- **Overall QOL item-wise**—This scale is comprised of the mean of all items from the Mental and Emotional Health scale plus the General Health Perceptions scale.

All HRQOL scales were transformed to a scale of 100 to 600, where 100 indicates a low QOL and 600 the highest possible QOL.

11.1.5 Psychometric Evidence

Reliability

Data from 327 subjects diagnosed with lipodystrophy and enrolled in a randomized clinical trial were used to assess internal consistency. Internal consistency reliability was calculated for multi-item scales. The scales were developed from a classical test theory perspective; the items are assumed to be sampled from a common underlying domain. Reproducibility (test-retest reliability) was tested for single-item scales by Pearson's correlation coefficient using subjects with valid screening and baseline values collected within 14 days; a sample of 181 subjects met the criterion.

Internal consistency was calculated for 7 multi-item Health Status scales, and the Health-Related QOL Global Analogue Scale. Internal consistency was computed using the SPSS for Windows®, Version 10.05, Reliability routine and is reported as Cronbach *alpha* for raw and standardized items. The results for the internal consistency analyses are shown in **Table 43**. The mean retest interval was 10.4 (\pm 3.6) days. Pearson correlation coefficients were calculated using SPSS for Windows®, Version 10.05, Correlation routine. The results of the reproducibility analysis for the Body Image Impact items are shown in **Table 44**.

Table 43. Internal Consistency Analysis

| Scale | Coefficient Alpha Raw Items | Coefficient Alpha Standardized Items | Test – Retest Reliability |
|-------------------------------|--------------------------------|---|------------------------------|
| Appearance Interference | 0.923 | 0.922 | 0.717 |
| Psychological Distress | | | |
| Anxiety | 0.874 | 0.879 | 0.856 |
| Depressed Mood | 0.925 | 0.926 | 0.822 |
| Beh. & Emot. Control | 0.737 | 0.743 | 1.000 |

| Scale | Coefficient Alpha Raw Items | Coefficient Alpha Standardized Items | Test – Retest Reliability |
|---|--------------------------------|---|------------------------------|
| Psychological Well Being | | | |
| General Positive Affect | 0.895 | 0.899 | 0.875 |
| Emotional Ties | | Single Item | 0.832 |
| Life Satisfaction | | Single Item | 0.704 |
| General Health Perception | | | |
| Vitality | 0.894 | 0.903 | 0.898 |
| General Perceived Health | 0.625 | 0.647 | 0.803 |
| Sleep Disturbance | 0.825 | 0.823 | 0.839 |
| Health-Related QOL Global Analogue Scale | | | |
| Overall Health Perception | 0.878 | 0.902 | 0.754 |

Table 44. Reproducibility Analysis

| Single Item Scales | Test-Retest Reliability |
|---|-------------------------|
| Body Size Evaluation | |
| Face Size Evaluation | 0.781 |
| Hump Size Evaluation | 0.782 |
| Leg Size Evaluation | 0.629 |
| Belly Size Evaluation | 0.659 |
| Breast Size Evaluation | 0.699 |
| Buttocks Size Evaluation | 0.688 |
| Arm Size Evaluation | 0.632 |
| Body Size Composite Evaluation | 0.779 |
| Body Appearance Distress | |
| Face Appearance Distress | 0.783 |
| Hump Appearance Distress | 0.744 |
| Leg Appearance Distress | 0.746 |
| Belly Appearance Distress | 0.612 |
| Breast Appearance Distress | 0.642 |
| Buttocks Appearance Distress | 0.730 |
| Arm Appearance Distress | 0.743 |
| Body Appearance Composite Distress | 0.751 |
| Belly Profile Assessment | |
| Patient Belly Profile - Current | 0.898 |
| Physician Belly Profile - Current | 0.756 |
| Weight Assessment and Overall Appearance | |
| Weight Evaluation | 0.801 |
| Weight Concern | 0.717 |
| Overall Appearance | 0.693 |

As shown in **Table 43**, all of the Health Status scales exceeded the standard of 0.70 for coefficient alpha, except general perceived health. With respect to reproducibility, all of the Health Status scales, both composite body image, belly profile, and weight assessment scales exceeded the test-retest standard of 0.70 (**Tables 43 and 44**). The average test-retest coefficient for the individual body size scales is 0.697, while the average coefficient for the individual body appearance distress scales is 0.714.

Validity

Five classes of validation evidence were developed for the BIIM. An expert panel derived the *content validity* for the conceptual model, which was confirmed by qualitative analyses from patient focus groups, semi-structured interviews, and postings on lipodystrophy-specific medical community websites. *Construct validity* stems from a structural equation model that characterizes both the conceptual and measurement models. Cross-sectional analysis based on known groups produced evidence for *discriminant validity*. *Responsiveness* is examined from analysis of known-group change scores. Finally, *convergent validity* is assessed for the subjects' profile evaluations.

Content validity

An expert panel comprising clinical investigators experienced in lipodystrophy, psychometricians, and biostatisticians developed the BIIM construct, component categories, and thematic areas for each scale. The panel provided feedback regarding the item-stems for each scale. Disagreements were resolved in consensus meetings. The panel reviewed the final version of the module prior to implementation. The constructs and component categories were confirmed in patient focus groups, semi-structured interviews with patients, and from qualitative analysis of lipodystrophy-specific postings on medical websites.

Construct validity: Cross-sectional structural model

Four composite scores from the measurement model operationally define health status (QOL). Mental and Emotional Health is represented by Psychological Distress (Psych

Distress: Anxiety, Depressed Mood, Behavioral Control) and Psychological Well Being (Psych WB: General Positive Affect, Emotional Ties, Life Satisfaction). General Perceived Health (Perc'd Health) is a composite score of the Vitality, Health Status, and Sleep Disturbance scales. The Symptom Impact component (Symp Dis) is a composite of the general and appearance-specific symptom impact scales.

The integrative Body Size scale (Body Size) and Body Image Distress (Body Distress) operationalize BIIM. The third element is a numeric rating evaluation of the respondent's current weight.

All of the weights are statistically significant ($p < 0.01$). Both integrative Body Size and Body Image Distress are important predictors of Body Image Impact, while weight assessment is less so. The negative sign for weight assessment indicates increased impact as "weight" is perceived to be low. Visceral adipose tissue deposits in the abdomen but with noticeably thinner face, buttocks, and limbs characterize lipodystrophy. The negative sign for Body Distress reflects the scoring direction. Higher distress is associated with higher impact.

All of the composite scales significantly predict Health Status, and all in the hypothesized direction. As hypothesized in the conceptual model, Mental and Emotional Health are key components of the Health Status construct for patients with lipodystrophy.

The standardized regression weights between the two structural components reveal the bi-directional nature of the influence. Every unit increase in overall Health Status results in nearly a 5-point improvement in Body Image Impact. Similarly, a unit decline in Body Image Impact results in a 3-point decrease in Health Status.

The data fit the conceptual model well. The overall CMIN test of fit is acceptable with a p-value of 0.04 and a X^2/df ratio of less than 2.0. Both the Normed Fit Index (NFI) and the Comparative Fit Index (CFI) have values of 0.99, indicating excellent fit. Finally, the

Root Mean Square of Approximation (RMSEA) is close to 0.05 and the PCLOSE probability estimate indicates that it is not likely larger than 0.05, indicating a close fit between the structural components and the measurement components.

Discriminant validity: Cross-sectional analysis

Evidence of discriminant validity for the BIIM is based on known-groups analysis. The conceptual model hypothesizes that Body Image Distress is a key predictor of the Health Status construct components. However, Body Size will be more predictive of General Health Perception and Symptom Impact than Mental and Emotional Health. Groups of subjects were formed on the basis of their reported body image distress and body size scores. Known groups for Body Distress and Body Size were formed from median splits of the screening scale values for the 2 scales. Group identification was the independent variable in a series of independent sample t-tests of the Health Status component scale scores.

As predicted, significant group differences ($p < 0.01$) were found for all of the scales except Emotional Ties in the Psychological Well Being component ($p = 0.11$). In each case, the High Distress group reported significantly lower responses on the Health Status scales. Consistent with the conceptual model, groups formed on the basis of Body Size scores did not differ for either Psychological Distress or Psychological Well Being scales. However, significant differences were found for the General Health Perception scales General Perceived Health ($p = 0.002$) and Vitality ($p = 0.001$). Significant differences were also yielded for both Symptom Distress scales ($p < 0.001$) but not for the Summary Scales.

Discriminant validity: Longitudinal analysis

Evidence for responsiveness was developed by known groups analysis of change scores. Responsiveness is established if between-group differences in within-group change are found for groups known to have changed on some external criterion. The conceptual model hypothesizes that change in Body Image Distress should be predictive of changes in Psychological Distress, General Health Perception, and Symptom Distress while

changes in Body Size would have more selective effects. Further, the conceptual model hypothesizes that changes in actual body conformation would produce changes in Body Image Impact and, subsequently, in Health Status.

Known groups for Body Distress and Body Size—Belly were formed from median splits of the baseline to final visit change scores for the 2 scales. Last-observation-carried-forward analysis was employed; completers participated for 12 weeks. Group identification was the independent variable in a multivariate analysis of covariance (ANCOVA) model with baseline composite quality of life and either body image distress or body size entered as covariates.

A significant multivariate effect was revealed for Body Image Distress Groups ($p < 0.001$). The positive change group had larger positive changes while the negative change group either reported no change in the health status scales or a worsening. As predicted by the model, significant effects were found for the Psychological Distress Scales ($p < 0.03$) but only for the Life Satisfaction scale in Psychological Well Being ($p = 0.034$). For the General Perceived Health component, General Health Perceptions was significant ($p < 0.034$) while Vitality showed a strong trend ($p = 0.073$). Sensibly, Appearance-Specific Distress was highly significant ($p < 0.001$) while General Symptom Distress trended towards significance ($p = 0.055$).

A significant multivariate effect was revealed for Body Size Belly Groups ($p < 0.001$). The smaller belly group had larger positive changes while the larger belly group either reported no change in the health status scales or a worsening. As predicted by the model, fewer significant effects were found. For the Psychological Distress Scales, only Depression was significant ($p = 0.009$). The General Positive Affect scale ($p = 0.013$) was significant while both Emotional Ties ($p = 0.076$) and Life Satisfaction ($p = 0.097$) showed trends towards significance in Psychological Well Being. For the General Perceived Health component, both General Health Perceptions ($p = 0.001$) and Vitality ($p = 0.001$) were sig-

nificant. Appearance-Specific Distress was highly significant ($p<0.001$) while General Symptom Distress approached, but did not meet significance ($p=0.080$).

Convergent validity

Convergent validity was assessed by two methods. The first determined whether the subjects' body conformation evaluation against a common standard predicted the internalized standards manifested by Body Image Distress. The second examined the correspondence between the physician and subject profile evaluations.

A linear regression model was constructed with change in Body Image Distress and change in the distance from "current" to "goal" profiles for both belly and hump as independent variables. The overall model was significant ($p<0.001$). Both independent variables were significant predictors. Change in distance for Belly ($b=0.38$, $p<0.001$) indicated that each unit change in distance from goal predicted a 40% increase in Body Image Distress. The effect was less dramatic but still significant for the less frequent Hump ($b=0.16$, $p=0.009$).

Physician profile analysis was examined by Pearson correlation. The most rigorous test involved correspondence between perceived changes in the distances between both the goal and the smallest beneficial change. Significant correlation coefficients were found for the Belly profile analyses but not for the Hump profiles.

11.2 Appendix II: Statistical Methods and Considerations

11.2.1 General considerations

All statistical tests were 2-sided using $\alpha=0.05$, and interactions were tested at $\alpha=0.10$. The results presented in this document are from analyses of the ITT population in studies LIPO-010 (main phase), CTR-1011, and LIPO-008 and included all patients who were injected with ≥ 1 dose of study treatment. The ITT population in LIPO-010 (extension phase) and CTR-1012 included all patients who received ≥ 1 dose of study treatment during the extension phase. A PP population was defined for each study before data unblinding, and analyses using PP patient data were done as supportive analyses. Analyses for studies LIPO-010 (main phase) and CTR-1011 were the same. Likewise, analyses for the extension phase studies LIPO-010 and CTR-1012 were the same.

All statistical analyses were done with Statistical Analysis Software (SAS[®]) version 8.0 and 9.1 with the exception of the statistical analyses on the PRO scales. The latter analyses were done using SPSS Version 12.0.

11.2.2 Baseline characteristics

Baseline values were from the last evaluation before the first injection of study treatment in the main phase studies, and pre re-randomization values were from the last evaluation before re-randomization into the extension phase.

Qualitative parameters were summarized by treatment group, using population size (sample size and number of patients with available data), frequencies, and percentages. Between-group differences were evaluated using Fisher's exact test.

Quantitative variables were summarized using descriptive statistics, including population size (sample size and number of patients with available data), mean and SD, median, and

the minimum and maximum values. Quantitative variables were assessed for treatment group differences by an ANOVA model including treatment group.

For the extension phase, demographic and baseline characteristics were summarized using descriptive statistics by treatment group. Differences among the 3 treatment groups were tested with the methods described for the main phase in 2 ways. A first test was performed between the 2 randomized groups that were randomized from tesamorelin to tesamorelin (T-T) or to placebo (T-P). A second test was performed using a contrast for the randomized groups combined versus the non-randomized group (P-T group).

For study LIPO-008, baseline values were compared across groups by ANOVA, with a single factor of treatment. For the combined analyses, demographic and baseline characteristics were summarized using descriptive statistics by treatment group. Quantitative variables were assessed for treatment group differences using an ANOVA model including treatment group and study. In a supportive analysis, the model included the interaction term between treatment group and study.

11.2.3 Main phase studies (LIPO-010 main and CTR-1011)

The primary efficacy endpoint was the percent change in VAT from baseline to Week 26 in the ITT population using the LOCF. The treatment effect was tested using an ANCOVA on the natural logarithm (Ln) ratio of VAT at Week 26 to VAT at baseline. The natural logarithm of baseline VAT was included in the model as a covariate. Thus, the model for the primary efficacy analysis was:

$$\text{Ln (VAT at Week 26/VAT at baseline)} = \text{Ln (VAT at baseline)} + \text{treatment}$$

After exponentiation, the dependent variable was interpreted as the ratio of VAT at Week 26 to baseline, which is similar to the percent change from baseline, except for a differ-

ence of 1. The treatment effect of tesamorelin was estimated by the placebo versus tesamorelin difference in LSMs from the ANCOVA.

For the lipid measures, an ANCOVA was performed for the change from baseline with a factor included in the model to account for the presence or absence of lipid-lowering treatments. Lipid-lowering treatment was considered present if the patient had taken lipid-lowering medication ≥ 1 time during the main phase. The ANCOVA model was:

$$\text{Change from baseline} = \text{baseline} + \text{treatment group} + \text{lipid-lowering treatment}$$

As a supportive model, the treatment-by-lipid-lowering-treatment interaction was included:

$$\begin{aligned} \text{Change from baseline} = & \text{baseline} + \text{treatment group} + \text{lipid-lowering treatment} + \text{lipid-} \\ & \text{lowering treatment by treatment group} \end{aligned}$$

For IGF-1 and body composition and anthropometric measurements, an ANCOVA was performed for the change from baseline using the model:

$$\text{Change from baseline} = \text{baseline} + \text{treatment group}$$

A non-parametric ranked ANCOVA model was fitted for “belly appearance distress” change score.

Post-dose versus pre-dose comparisons were made with a repeated-measure analysis with factors for Week 0, Week 13, and Week 26.

11.2.4 Extension phase studies (LIPO-010 extension and CTR-1012)

The treatment groups in the extension phase were T-T, in which patients who received tesamorelin in the main phase were re-randomized to receive tesamorelin in the extension phase; T-P, in which patients who received tesamorelin in the main phase were re-randomized to receive placebo in the extension phase; and P-T, in which all patients who received placebo in the main phase were switched to tesamorelin during the extension phase. Because patients in the P-T group were not re-randomized in the extension phase but automatically switched to tesamorelin treatment, this group was considered separately from the 2 randomized groups (T-T and T-P).

Within-treatment comparisons and between-treatment comparisons were performed for VAT, lipid parameters, IGF-1, body composition, and anthropometric measurements. Repeated-measures ANOVA, within-treatment comparisons were performed for the following comparisons: Week 52 versus Week 0, Week 39 versus Week 0, Week 52 versus Week 26, and Week 39 versus Week 26. The 2 main comparisons were Week 52 versus Week 26 in the T-T group and Week 52 versus Week 26 in the T-P group.

Between-treatment comparisons were performed for the 2 randomized groups, T-P and T-T. The purpose of this analysis was to evaluate if there was a difference between stopping treatment after 26 weeks versus continuing treatment for an additional 6 months. For VAT, the model was:

$$\ln(\text{VAT at Week 52}/\text{VAT at baseline}) = \ln(\text{VAT at baseline}) + \ln(\text{VAT at Week 26}/\text{VAT at baseline}) + \text{treatment (T-P and T-T groups only)}$$

For all other efficacy variables, an ANCOVA was performed at Week 39 and Week 52 for each variable, including the treatment effect and the covariates, baseline, and Week 26 minus baseline. The model used to evaluate each lipid parameter also included the lipid-lowering treatment effect. Lipid-lowering treatment was considered present if either

(1) the patients had taken lipid-lowering treatment ≥ 1 time during the main phase, or (2) the patient did not take lipid-lowering treatment in the main phase but took it ≥ 1 time during the extension phase.

11.2.5 LIPO-008 study

The main analysis for between-group differences in change from baseline for efficacy variables was an ANCOVA, with the terms baseline and treatment. Between-group differences in change from baseline for efficacy variables were also analyzed with the full model, which included the baseline*treatment interaction term. If data did not meet the ANOVA assumptions, data were rank-transformed and then analyzed by ANOVA or ANCOVA as described above. Categorical data were analyzed using Pearson's chi-square statistics, Cochran-Mantel-Haenszel statistics, or the Kruskal-Wallis test, as appropriate.

11.2.6 Combined studies

11.2.6.1 Combined main phase

The efficacy endpoints analyzed for the individual studies were also analyzed for the combined studies. Study LIPO-008 was not included in the combined analyses.

The number and percentage of patients who were included in the ITT population and the number and percentage who completed the study or were discontinued from the study were summarized. The primary reason for discontinuation was summarized using a generalized linear model, which included main effects for treatment group and study. As a supportive analysis, a model including the interaction term between treatment group and study was performed. For individual studies, treatment group differences were analyzed with a model including just treatment.

For qualitative variables, a generalized linear model using the appropriate link function was used to assess treatment group differences. This model included treatment group and study. In a supportive analysis, the model included the interaction term between treatment group and study.

The primary efficacy endpoint was the percent change in the VAT from baseline to Week 26 in the tesamorelin group versus the placebo group, using the ITT population and LOCF analysis. The baseline value was the last measurement before the first dose of study treatment. The treatment effect in the primary efficacy endpoint was tested using an ANCOVA performed on the Ln of the ratio of VAT at Week 26 to baseline VAT. The covariates included in the ANCOVA model were the Ln of the baseline VAT and study. The statistical model was:

$$\text{Ln (VAT at Week 26/VAT at baseline)} = \text{Ln (VAT at baseline)} + \text{study} + \text{treatment group}$$

The treatment effect of tesamorelin was estimated by the placebo versus tesamorelin difference in the LSMs from the ANCOVA described above.

The presence of treatment-group-by-study interaction was assessed using the following ANCOVA model:

$$\text{Ln (VAT at Week 26/VAT at baseline)} = \text{Ln (VAT at baseline)} + \text{study} + \text{treatment group} + \text{treatment-group-by-study}$$

The percent change in VAT from baseline was summarized by treatment group, using graphs of the cumulative distribution function.

Selected baseline covariates were evaluated individually and included: age in years at baseline; age based on the quartiles from the main phase of the 2 combined studies re-

corded at baseline; gender; race; IGT/diabetes condition recorded at baseline; testosterone use recorded at baseline; change in ART recorded during the main phase; and ART regimen recorded at baseline. This evaluation was performed using the following ANCOVA model:

$$\text{Ln (VAT at Week 26/VAT at baseline)} = \text{Ln (VAT at baseline)} + \text{treatment group} + \text{study} + \text{covariate}.$$

As a supportive analysis, the ANCOVA model included the covariate-by-treatment-group interaction. Pair-wise treatment LSM differences were presented by covariate.

For the covariate of anti-tesamorelin IgG antibodies and IgG titers, the following statistical model was used only in patients treated with tesamorelin:

$$\text{Ln (VAT at Week 26/VAT at baseline)} = \text{Ln (VAT at baseline)} + \text{study} + \text{IgG covariate}$$

The treatment effect for change from baseline in lipids was tested using an ANCOVA model that included terms for baseline lipid level, treatment group, study, and lipid-lowering treatment. As a supportive ANCOVA model, the treatment-by-lipid-lowering-treatment interaction was included. Pair-wise treatment LSM differences were presented by lipid-lowering therapy. To further assess the effect of study and treatment group, the treatment-group-by-study interaction term was added to the model.

For IGF-1, body composition and anthropometric measurements, and changes from baseline were provided. The treatment effects for change from baseline in IGF-1 and body composition and anthropometric measurements were tested using an ANCOVA model. The parameters included in the ANCOVA model were the baseline value, treatment group, and study. To assess the effect of study and treatment, the study-by-study treatment interaction term was added to the model. The treatment effect of tesamorelin was estimated by the placebo versus tesamorelin difference in LSM from the ANCOVA.

The influence of the following selected baseline covariates on change in trunk fat were evaluated individually: age in years at baseline; age based on the quartiles from the main phase of the 2 combined studies recorded at baseline; gender; race; IGT/diabetes condition recorded at baseline; testosterone use recorded at baseline; number of days on PI recorded during the main phase; change in ART recorded during the main phase; and ART regimen recorded at baseline. The following model was used:

$$\text{Baseline value} + \text{treatment group} + \text{study} + \text{covariate}$$

As a supportive analysis, the model included the covariate-by-treatment-group interaction.

For IGF-1, the ANCOVA model was used to evaluate IgG antibody status and titer for tesamorelin-treated patients only. The ANCOVA model included:

$$\text{Change in IGF-1} = \text{IGF-1 at baseline} + \text{study} + \text{antibodies (or titers)}$$

For change in VAT and trunk fat, descriptive statistics were provided for each of the following subgroups: age, gender, race, IGT/diabetes condition recorded at baseline, testosterone use recorded at baseline, quartiles of VAT at baseline (for change in VAT only), ART regimen at baseline, change in ART recorded during the main phase, IgG antibody status recorded during the main phase, and IgG antibody titers recorded during the main phase.

Subgroup analyses for change from baseline in IGF-1 were performed by the presence of IgG antibodies and by IgG antibody titers. These analyses included descriptive statistics for each subgroup by study and treatment group and for both studies combined by treatment group.

A subgroup analysis presenting descriptive statistics on the change from baseline in lipids by lipid-lowering treatment (yes, no) and treatment group for both studies combined and for each study individually was also done.

11.2.6.2 Combined extension phase

The number and percentage of patients who completed the study or were discontinued from the study were summarized. The primary reason for discontinuation was summarized using a generalized linear model. The generalized linear model for the combined data included main effects for treatment group and study. As a supportive analysis, a model including the interaction term between treatment group and study was performed.

Demographic and baseline characteristics were summarized using descriptive statistics by treatment group at both baseline and at Week 26 of the main phase. Quantitative variables were assessed for treatment group differences using an ANOVA model including treatment group and study. As a supportive analysis, the model included the interaction term between treatment group and study. For qualitative variables, a generalized linear model using the appropriate link function was used to assess treatment group differences. The model included treatment group and study. As a supportive analysis, the model included the interaction term between treatment group and study.

The change from baseline for VAT was summarized using descriptive statistics and presented for the within-treatment changes for each post-baseline time point. A comparison of the within-treatment values was performed separately for each treatment group (T-T, T-P, and P-T), using the repeated-measures ANOVA model with factors for week (Weeks 0, 26, 39, and 52) and study. As a supportive analysis, the interaction term for study and week was included in the model.

For comparisons between treatment groups, the ANCOVA model with factors for the Ln for baseline VAT, Ln for Week 26 VAT to baseline VAT, treatment group, and study

was performed for Week 39 and for Week 52 for the T-T and T-P groups. A supportive ANCOVA model included the treatment group and study interaction.

For patients treated with tesamorelin during the extension phase, an ANCOVA was performed for Week 39 and Week 52 that included the Ln of baseline VAT as a covariate and factors for treatment (tesamorelin administered for 52 weeks or 26 weeks), IgG antibodies (negative, positive), treatment by IgG antibodies interaction, and study. This analysis was repeated using IgG antibody titers as a covariate. As an additional supportive model, the interaction of treatment and study was also included.

For lipids, within-treatment comparisons were performed within each treatment group separately (T-T, T-P, and P-T), using the repeated-measures ANOVA model with factors for week (Weeks 0, 26, 39, and 52) and study. As a supportive analysis, the interaction term for study and week was included. For comparisons between treatment groups, the ANCOVA model with factors for baseline value, Week 26 value minus baseline value, treatment (T-T or T-P), lipid-lowering treatment, and study was performed at Week 39 and Week 52 for the T-T and T-P groups. A supportive model including the interaction between treatment and study was also performed.

In addition to the within- and between-treatment comparisons for patients treated with tesamorelin during the extension phase, an ANCOVA was performed on the change from baseline in IGF-1 level at Week 39 and Week 52, using baseline IGF-1 as the covariate with factors for treatment (tesamorelin administered for 52 or 26 weeks), presence or absence of IgG antibodies, study, and the treatment by IgG antibodies interaction term. As a supportive model, the interaction term for treatment and study was also included. A similar ANCOVA was performed using IgG antibody titers as covariate.

For IGF-1 and body composition and anthropometric measurements, within-treatment comparisons were performed within each group separately (T-T, T-P, and P-T), using the repeated-measures ANOVA model with factors for week (Weeks 0, 26, 39, and 52) and

study. As a supportive analysis, the interaction term for study and week was included. For comparisons between treatment groups, the ANCOVA model with factors for baseline value, Week 26 value minus baseline value, treatment (T-T or T-P), and study was performed for Weeks 39 and 52 for the T-T and T-P groups. A supportive model including the interaction between treatment and study was also performed.

Subgroup analyses for percent change in VAT were performed by the presence of IgG antibodies and by IgG antibody titers. Descriptive statistics for both actual and percent changes in VAT at Weeks 39 and 52 by quartile of VAT at baseline were provided for all 3 treatment groups. Subgroup analyses for change in IGF-1 were performed by the presence of IgG antibodies and IgG antibody titers.

For lipids, a subgroup analysis presenting descriptive statistics on the change in lipids by lipid-lowering treatment (yes, no) and treatment group was performed.

11.3 Appendix III: Death Case Narratives

Table 45. Deaths in Overall Clinical Program

| Study | Age/ Gender/ Race | Treatment Group | Preferred Term | Duration of Tesamorelin Exposure | Relationship to Study Treatment | Risk Fac- tors |
|----------------------------------|-------------------------|---|--|--|---------------------------------------|--|
| Phase 2 Clinical Studies | | | | | | |
| TH9507/II/HF/004 | 95/F/ White | Placebo | Myocardial infarction | NA | Unrelated | HTN |
| TH9507/II/HF/004 | 89/M/ White | Tesamorelin 2 mg/day | Death ^a | 10 days | Unrelated | Atrial fibril- lation, chronic heart failure, chronic renal insuf- ficiency |
| TH9507/II/HF/004 | 86/F/ White | Tesamorelin 2 mg/day | Chest pain Myocardial infarction | 5 days | Unrelated | HTN, COPD |
| TH9507/II/HF/004 | 81/F/ White | Tesamorelin 2 mg/day | Ischemia | 27 days | Unrelated | HTN, atheroscle- rosis, obe- sity |
| TH9507/II/COPD/003 | 53/F/ White | Tesamorelin 2 mg/day | Dyspnea Increased bronchial se- cretion | 73 days | Unrelated | COPD, salmeterol, ipratropium bromide, fluticasone, salbutamol, fluticasone, theophylline |
| TH9507/II/COPD/003 | 72/M/ White | Tesamorelin 1 mg/day | Acute myocar- dial infarction | 43 days | Unrelated | COPD, acute MI in 1989, salbuterol, fluticasone, albuterol |
| Phase 3 Clinical Studies* | | | | | | |
| TH9507-CTR-1011 | 50/M/ White | Placebo | Arrhythmia | NA | Unrelated | Marfan's syndrome, aortic aneu- rysm, HTN, previous MI with sinus tachycardia |
| TH9507/III/LIPO/010 (EXT) | 54/M/ White | Tesamorelin - Tesamore- lin 2 mg/day | Arteriosclerosis coronary artery | 215 days | Unrelated | Angioplasty, CAD, sub- stance abuse (alcohol), Lipitor |
| TH9507/III/LIPO/010 (EXT) | 50/M/ Black | Placebo - Tesamorelin | Post-procedure hemorrhage | 115 days | Unrelated | HTN, an- gioedema, |

| 2 mg/day | Asphyxiation | COPD |
|----------|--------------|------|
|----------|--------------|------|

CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; F, female; HTN, hypertension; M, male; MI, myocardial infarction; NA, not applicable.

^a Progressive deterioration of general state.

*>30 days post-treatment: A patient (TH9507-CTR-1011) who had stopped tesamorelin treatment was diagnosed with lung adenocarcinoma metastatic 5 months after the last dose and died 9 months after the last dose. This event was considered by the treating physician to be related to treatment. The patient had a history of lymphadenopathy and basal cell carcinoma.

Cases of Death in Tesamorelin Clinical Studies

DE-1: Lung adenocarcinoma, metastatic (CTR-1011)

A 49-year-old white/Caucasian man diagnosed with lipodystrophy syndrome in 2007. The patient's relevant medical history included HIV infection (1989), herpes zoster, genital HSV, depression, gastroesophageal reflux disease, insomnia, hypercholesterolemia, hyperlipidemia, sinusitis, basal cell carcinoma of the left ear and left cheek (1998), and lymphadenopathy (2003). Relevant concomitant medications included acetaminophen/hydrocodone, zolpidem tartrate, pravastatin sodium, topical testosterone, paroxetine hydrochloride, valacyclovir hydrochloride, in addition to his ART regimen, which consisted of ritonavir 100 mg qd, atazanavir 150 mg qd, didanosine 250 mg qd, and disoproxil fumarate 300 mg qd. The patient took tesamorelin 2 mg/day from 4/18/07 until 7/22/07, and prematurely discontinued the study on 8/8/07 due to an adverse reaction at the injection site. On 12/11/07, approximately 5 months after discontinuing study medication, he was diagnosed with adenocarcinoma of the lung with metastasis to the brain and spine. He died on 4/19/08. The investigator rated the event "severe" in intensity, and concluded that there was a possible relationship between the metastatic lung carcinoma and treatment with tesamorelin.

DE-2: Arrhythmia (CTR-1011)

A 50-year-old white/Caucasian man diagnosed with lipodystrophy syndrome in 2002. The patient's relevant medical history included HIV infection (1993), Marfan's syndrome, aortic aneurysm, hypertension, osteoporosis, seizures, depression, insomnia, sleep disorder, hyperlipidemia, and a previous myocardial infarction with sinus tachycardia (2006). Relevant concomitant medications included omega-3 fatty acids, verapamil, feno-

fibrate, hydrochlorothiazide, atenolol, alendronate sodium, famotidine, lansoprazole, methylphenidate, mirtazapine, lorazepam, fluticasone, and simvastatin, in addition to his ART regimen, which consisted of stavudine 20 mg bid, tenofovir 1 qd, and ritonavir 2 tabs bid. The patient began taking placebo on 6/27/07. On 12/16/07 he was found dead at home in his bed. According to the autopsy report, the patient had an enlarged heart and had died of natural causes. The study investigator considered the cardiac arrhythmia to be unrelated to study medication.

DE-3: Post-procedure hemorrhage / Asphyxiation (LIPO-010)

A 50-year-old black/African American man diagnosed with lipodystrophy syndrome in 2005. His relevant medical history included HIV infection (1993), hypertension, chronic earaches, insomnia, depression, anxiety, and gastroesophageal reflux. Relevant concomitant medications included lisinopril, losartan, hydrochlorothiazide, ranitidine, trazadone, and mirtazapine, in addition to his ART regimen, which consisted of lamivudine 150 mg bid, abacavir 300 mg bid, didanosine 400 mg qd, and fosamprenavir 400 mg bid. The patient received placebo during the main phase of the study and then started on tesamorelin 2 mg/day on 3/23/06 during the extension phase. During the study, he reported non-serious AEs of shortness of breath, COPD, angioedema, cor pulmonale, weight gain, and enlarged tonsils. After undergoing a tonsillectomy and polyp removal, the patient experienced post-procedural hemorrhage leading to asphyxiation, and died on 1/26/07. The investigator considered the patient's death to be unrelated to treatment with tesamorelin.

DE-4: Arteriosclerosis coronary artery (LIPO-010)

A 54-year-old white/Caucasian man diagnosed with lipodystrophy syndrome in 2003. His relevant medical history included HIV infection (1998), hepatitis B, angioplasty, coronary artery disease, gastroesophageal reflux, erectile dysfunction, and substance (alcohol) abuse. Relevant concomitant medications included atorvastatin calcium, aspirin, ibuprofen, tadalafil, desloratidine, and clopidogrel, along with his ART which consisted of tenofovir 300 mg bid, efavirenz 600 mg QHS, and abacavir/zidovudine/lamivudine 1 tab bid.

The patient started taking tesamorelin 2 mg/day on 3/15/06. During the study he reported an AE of increased cholesterol, for which his dose of atorvastatin calcium was increased from 20 mg to 40 mg. On 11/17/06 the patient died after experiencing an SAE of coronary atherosclerosis. The exact date of his last dose of tesamorelin was unknown, but estimated to be during the month of November 2006. The study investigator considered the patient's death to be unrelated to treatment with tesamorelin.

DE-5: Myocardial infarction (HF-004)

A 95-year-old white/Caucasian woman, died from a myocardial infarction while receiving placebo in the Phase 2 hip fracture study TH9507-II-HF-004. Her risk factors included hypertension. The study investigator considered causality to be unrelated because the patient was not exposed to tesamorelin.

DE-6: Death (HF-004)

An 89-year-old white/Caucasian man, died from what was termed "progressive deterioration of current state" while participating in the Phase 2 hip fracture study TH9507-II-HF-004. During the study, the patient had received tesamorelin 2 mg/day for a total duration of 10 days. His risk factors included atrial fibrillation, chronic heart failure, and chronic renal insufficiency. The study investigator considered the patient's death to be unrelated to treatment with tesamorelin.

DE-7: Chest pain / Myocardial infarction (HF-004)

An 86-year-old white/Caucasian woman, died after experiencing chest pain and a myocardial infarction while participating in the Phase 2 hip fracture study TH9507-II-HF-004. During the study she had received tesamorelin 2 mg/day for 5 days. Her risk factors included hypertension and COPD. The study investigator considered the patient's death to be unrelated to treatment with tesamorelin.

DE-8: Ischemia (HF-004)

An 81-year-old white/Caucasian woman, died after experiencing ischemia while participating in the Phase 2 hip fracture study TH9507-II-HF-004. During the study she had received tesamorelin 2 mg/day for 27 days. Her risk factors included hypertension, atherosclerosis, and obesity. The study investigator considered the patient's death to be unrelated to treatment with tesamorelin.

DE-9: Dyspnea / Increased bronchial secretion (COPD-003)

A 53-year-old white/Caucasian woman diagnosed with COPD in 1998. Her medical history also included headache and osteoarthritis. Relevant concomitant medications included salmeterol, ipratropium bromide, fluticasone, salbutamol, theophylline, alendronate sodium, conjugated estrogens, temazepam, and aspirin/caffeine/butalbital. The patient started taking tesamorelin 2 mg/day on 5/10/01. On 7/8/2001, she had a COPD exacerbation for which she received prednisone 50 mg PO and azithromycin 500 mg PO. There was no improvement in her condition, so azithromycin was replaced with moxifloxacin 400 mg. On 7/14/2001, the patient was hospitalized. During her hospitalization, she was treated with ipratropium 0.5 mg/fenoterol 1.25 mg, heparin sodium 10U, acetaminophen 625 mg, docusate sodium 200 mg, codeine phosphate 30-60 mg, fluticasone 250 µg, apo-cyclobenzaprine 10 mg, and senna 8.6 mg. On 7/21/01 the patient had a severe bronchospasm, for which she received salbutamol 200 µg and ipratropium 0.5 mg/fenoterol 1.25 mg by inhalation. She was transferred to the intensive care unit (ICU), where she was given rocuronium 30 mg IV, and was placed on a ventilator. She took her last dose of tesamorelin on 7/21/01. The bronchospasm was assessed by the investigator as being unrelated to treatment with tesamorelin. Concomitant medications during the ICU stay included fentanyl 10 µg, salbutamol 800 µg, pentastarch (dose unknown), morphine 2-5 mL/hr, midazolam 1 mg, ranitidine 150 mg, ipratropium/salbutamol 8 puffs every 2 hours, theophylline 150 mg, methylprednisolone 40 mg, and insulin 2-12 units to prevent hypoglycemia due to methylprednisone. The patient began to show some improvement, and on 8/3/2001 was transferred to a regular care unit

and placed on a nasal bilevel positive airway pressure (BiPAP). She was additionally treated with codeine 30 mg, lorazepam 1 mg, ciprofloxacin, and senna.

Despite intensive medical intervention, the patient remained symptomatic, with shortness of breath. On 8/7/2001 she entered the terminal phase and decided to limit her treatment to palliative care. Codeine and lorazepam treatments were stopped and subcutaneous morphine and midazolam were added. Scopolamine bromohydrate was used to decrease secretion and her prednisone dose was decreased. She died on 8/12/2001 due to acute respiratory insufficiency. The study investigator considered the COPD exacerbation to be unrelated to treatment with tesamorelin.

DE-10: Acute myocardial infarction (COPD-003)

A 72-year-old Caucasian male diagnosed with COPD in 1997. His medical history also included celiac disease, controlled psoriasis, intermittent difficulty urinating, and an acute MI (1989). Serial ECGs performed during the study showed no essential change compared with his old myocardial infarction. During exercise, only a few unifocal ventricular ectopic beats were noted—this finding was unchanged from an ECG obtained in 2000. Relevant concomitant medications included salbutamol, fluticasone, albuterol/ipratropium, and aspirin. The patient started taking tesamorelin 1 mg/day on 6/15/01. On 6/29/01 he complained of shortness of breath and constipation. No treatment was given, and these events were considered unrelated to treatment with study drug. On 7/3/01, he complained of severe shortness of breath, for which he was given prednisone and formoterol. On 7/27/01 the day before his fatal MI, the patient received his last dose of study medication. The study nurse reviewed his status and noted that his shortness of breath symptoms had responded well to treatment with steroids. He had no chest pain and reported no AEs. On 7/28/01 the patient awakened from sleep just after midnight complaining of severe chest pain, and was taken to the hospital by ambulance. Upon arrival, he had severe central chest heaviness and shortness of breath. He was diagnosed with unstable angina and received 160 mg aspirin PO, 0.4 mg nitroglycerin sublingual, ipratropium 500 µg by inhalation, fentanyl 25 mg IV, and salbutamol 5 mg by inhalation. His

condition quickly deteriorated and he developed a pulseless electrical arrest (PEA). He was intubated and resuscitation was attempted. He received epinephrine 1 mg IV, atropine 1 mg IV, vasopressin 40 mg IV, calcium and sodium bicarbonate, but progressed to asystole. A cardiology team performed pericardiocentesis without success, and the patient was pronounced dead at 2:00 a.m. on 7/28/01. On the medical certificate of death, the cause of death was noted as cardiogenic shock likely due to acute myocardial infarction. The study investigator considered the patient's death to be unrelated to treatment with tesamorelin.

11.4 Appendix IV: Case Narratives – Adverse Event Leading to Withdrawal

Case Narrative #1

Patient 0420 was a 54-year-old male enrolled in Phase 3 study CTR-1011. He was randomized to receive tesamorelin 2 mg SC. The following diagnoses complete the patient's full medical history: asthma, chemical poisoning, gonorrhea, hernia repair, herpes virus infection, and neuropathy; of these, asthma and neuropathy were ongoing. His concomitant medications usage prior to and during study drug randomization included the following: albuterol sulfate, acyclovir, atorvastatin calcium, atazanavir sulfate, cyclosporine, duloxetine hydrochloride, emtricitabine + tenofovir disoproxil, ezetimibe, montelukast, naproxen, and ritonavir.

The first dose of tesamorelin was injected on September 5, 2007. As of the first dose, the patient reported mild injection-site erythema, swelling, pruritus, and urticaria. After 3 weeks of tesamorelin, the patient reported a mildly swollen tongue. After 15 weeks of treatment (December 21, 2007), the patient reported moderate tongue swelling along with continued injection-site reactions and mild sweating. Tesamorelin was discontinued on January 15, 2008.

Anti-tesamorelin antibodies were absent at baseline and at Week 6, but present at Week 13 (titer 50) and persisted at the same level 3 weeks after discontinuation of tesamorelin.

The investigator judged the AEs leading to withdrawal to be possibly related to the study medication.

Case Narrative #2

Patient 23004 was a 47-year-old Caucasian male enrolled in Phase 3 study LIPO-010. He was randomized to receive tesamorelin 2 mg QD sc. His medical history included: anal fissure, bilateral ear pain, hemorrhoids, hypercholesterolemia, hypertriglyceridemia, leg varicosity, neuropathy, peripheral neuropathy, right lower limb vein stripping, strepto-

coccal sore throat, and venous insufficiency. His concomitant medications usage prior to and during the study included: abacavir, kaletra, tenofavir, Benadryl, Tylenol and amitriptyline.

The first dose of study treatment was injected on March 23, 2006. The patient reported injection site reactions (redness, itching) starting on April 23, 2006. The symptoms appeared immediately after the injection of study drug and lasted for approximately a week. Thereafter he experienced comparable local symptoms after each daily injection. Benadryl was used occasionally to relieve the symptoms.

On July 19, 2006 (119 days on treatment), approximately 2-3 minutes after the injection of study drug, the patient experienced redness and itching at the injection site in addition to nausea, tachycardia, shortness of breath and profuse sweating. These symptoms lasted for about 1.5 minutes. The patient also reported a moderate headache from front to back that lasted most of the day. On August 2, 2006, the patient reported moderate headache that resolved in 2-3 hours with Tylenol. On August 9, 2006, approximately 3 minutes after the injection, the patient experienced face and upper body redness in addition to nausea, tachycardia, shortness of breath and profuse sweating (less intense this time). He also noted at the same time redness of all of the previous injection sites. These symptoms lasted for about 3 minutes. The patient was discontinued from the study. His last dose of study drug was on August 12, 2006.

The investigator judged the AE to be related to study drug.

11.5 Appendix V: Patient Demographics and Disease Characteristics at Baseline (Extension, ITT Population)

Table 46. Patient Demographics and Disease Characteristics at Baseline (Extension, ITT Population)

| | LIPO-010 | | | CTR-1012 | | | COMBINED | | |
|--|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| | T-T N=154 | T-P N=50 | P-T N=111 | T-T N=92 | T-P N=85 | P-T N=86 | T-T N=246 | T-P N=135 | P-T N=197 |
| Age, years^a | | | | | | | | | |
| 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) | 47.7 (7.16) | 48.1 (7.12) | 48.3 (7.73) |
| Median | 46.5 | 46.0 | 48.0 | 47.0 | 49.0 | 48.0 | 47.0 | 47.0 | 48.0 |
| Range | 28–65 | 31–60 | 31–65 | 31–62 | 32–65 | 28–65 | 28–65 | 31–65 | 28–65 |
| Gender, n (%) | | | | | | | | | |
| Male | 136 (88.3) | 43 (86.0) | 96 (86.5) | 83 (90.2) | 76 (89.4) | 75 (87.2) | 219 (89.0) | 119 (88.1) | 171 (86.8) |
| Female | 18 (11.7) | 7 (14.0) | 15 (13.5) | 9 (9.8) | 9 (10.6) | 11 (12.8) | 27 (11.0) | 16 (11.9) | 26 (13.2) |
| Ethnic origin, n (%) | | | | | | | | | |
| White/Caucasian | 120 (77.9) | 40 (80.0) | 84 (75.7) | 75 (81.5) | 73 (85.9) | 70 (81.4) | 195 (79.3) | 113 (83.7) | 154 (78.2) |
| Asian | 1 (0.6) | 1 (2.0) | 0 | 0 | 0 | 2 (2.3) | 1 (0.4) | 1 (0.7) | 2 (1.0) |
| Black/ African-American | 19 (12.3) | 4 (8.0) | 16 (14.4) | 10 (10.9) | 6 (7.1) | 5 (5.8) | 29 (11.8) | 10 (7.4) | 21 (10.7) |
| Hispanic | 12 (7.8) | 4 (8.0) | 9 (8.1) | 7 (7.6) | 5 (5.9) | 7 (8.1) | 19 (7.7) | 9 (6.7) | 16 (8.1) |
| Other | 2 (1.3) | 1 (2.0) | 2 (1.8) | 0 | 1 (1.2) | 2 (2.3) | 2 (0.8) | 2 (1.5) | 4 (2.0) |
| Time since HIV diagnosis, months | n=153 | n=50 | n=111 | n=92 | n=85 | n=86 | n=245 | n=135 | n=197 |
| Mean (SD) | 169.8 (63.53) | 161.9 (59.93) | 157.8 (65.41) | 171.0 (59.74) | 167.9 (71.33) | 166.2 (67.59) | 170.3 (62.01) | 165.7 (67.16) | 161.5 (66.34) |
| Median | 179.4 | 170.4 | 158.2 | 169.1 | 181.7 | 160.6 | 174.2 | 174.9 | 158.2 |
| Range | 21–311 | 43–278 | 8–288 | 29–283 | 10–303 | 26–308 | 21–311 | 10–303 | 8–308 |
| Viral load at baseline, n (%) Undetectable | 109 (70.8) | 29 (58.0) | 75 (67.6) | 77 (83.7) | 68 (80.0) | 76 (88.4) | 186 (75.6) | 97 (71.9) | 151 (76.6) |
| 50–400 copies/mL | 30 (19.5) | 15 (30.0) | 26 (23.4) | 8 (8.7) | 10 (11.8) | 6 (7.0) | 38 (15.4) | 25 (18.5) | 32 (16.2) |
| >400 copies/mL | 15 (9.7) | 5 (10.0) | 10 (9.0) | 7 (7.6) | 7 (8.2) | 4 (4.7) | 22 (8.9) | 12 (8.9) | 14 (7.1) |
| Missing | 0 | 1 (2.0) | 0 | 0 | 0 | 0 | 0 | 1 (0.7) | 0 |
| Viral load at Week 26, n (%)[*] Undetectable | 103 (66.9) | 32 (64.0) | 77 (69.4) | 82 (89.1) | 72 (84.7) | 75 (87.2) | 185 (75.2) | 104 (77.0) | 152 (77.2) |
| 50–400 copies/mL | 30 (19.5) | 14 (28.0) | 22 (19.8) | 4 (4.3) | 8 (9.4) | 6 (7.0) | 34 (13.8) | 22 (16.3) | 28 (14.2) |
| >400 copies/mL | 18 (11.7) | 3 (6.0) | 11 (9.9) | 5 (5.4) | 3 (3.5) | 4 (4.7) | 23 (9.3) | 6 (4.4) | 15 (7.6) |
| Missing | 3 (1.9) | 1 (2.0) | 1 (0.9) | 1 (1.1) | 2 (2.4) | 1 (1.2) | 4 (1.6) | 3 (2.2) | 2 (1.0) |
| CD4 cell count at baseline, cells/mm³ | n=154 | n=49 | n=111 | n=92 | n=85 | n=85 | n=246 | n=134 | n=196 |
| Mean (SD) | 649.7 (311.50) | 624.9 (304.29) | 572.4 (261.11) | 578.9 (300.18) | 579.8 (272.41) | 603.7 (282.83) | 623.2 (308.61) | 596.3 (284.18) | 586.0 (270.48) |
| Median | 598.0 | 597.0 | 528.0 | 527.0 | 553.0 | 540.0 | 560.5 | 566.5 | 535.0 |
| Range | 190–2021 | 93–1620 | 103–1382 | 183–1639 | 144–1599 | 104–1553 | 183–2021 | 93–1620 | 103–1553 |
| CD4 cell count at Week 26, cells/mm³ | n=151 | n=50 | n=109 | n=91 | n=83 | n=84 | n=242 | n=133 | n=193 |
| Mean (SD) | 641.9 (289.98) | 631.2 (264.50) | 577.8 (260.06) | 570.8 (282.40) | 570.1 (255.75) | 629.3 (281.12) | 615.2 (288.63) | 593.1 (259.78) | 600.2 (269.93) |

| | LIPO-010 | | | CTR-1012 | | | COMBINED | | |
|--|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| | T-T N=154 | T-P N=50 | P-T N=111 | T-T N=92 | T-P N=85 | P-T N=86 | T-T N=246 | T-P N=135 | P-T N=197 |
| Median | 592.0 | 582.5 | 540.0 | 531.0 | 563.0 | 608.5 | 555.0 | 566.0 | 549.0 |
| Range | 173–1831 | 94–1310 | 122–1217 | 130–1733 | 142–1220 | 116–1312 | 130–1831 | 94–1310 | 116–1312 |
| CD8 cell count at baseline, cells/mm³ | n=153 | n=47 | n=110 | n=91 | n=85 | n=85 | n=244 | n=132 | n=195 |
| Mean (SD) | 966.8 (458.39) | 968.7 (375.21) | 1013 (410.87) | 994.4 (525.23) | 975.1 (410.35) | 933.0 (395.68) | 977.1 (483.51) | 972.8 (396.76) | 977.9 (405.22) |
| Median | 895.0 | 973.0 | 933.0 | 845.0 | 879.0 | 845.0 | 882.5 | 945.0 | 905.0 |
| Range | 251–4247 | 238–2065 | 10–2373 | 248–3848 | 266–2263 | 247–2020 | 248–4247 | 238–2263 | 10–2373 |
| CD8 cell count at Week 26, cells/mm³ | n=150 | n=50 | n=109 | n=91 | n=83 | n=84 | n=241 | n=133 | n=193 |
| Mean (SD) | 967.7 (474.09) | 939.7 (330.69) | 987.8 (414.95) | 946.2 (425.23) | 903.8 (367.09) | 964.5 (454.25) | 959.6 (455.47) | 917.3 (353.01) | 977.6 (431.50) |
| Median | 895.5 | 901.5 | 919.0 | 885.0 | 823.0 | 844.0 | 892.0 | 872.0 | 902.0 |
| Range | 232–3166 | 339–1779 | 371–2329 | 127–2213 | 244–1959 | 197–2490 | 127–3166 | 244–1959 | 197–2490 |
| Duration of ART, months† | n=154 | n=50 | n=110 | n=92 | n=85 | n=86 | n=246 | n=135 | n=196 |
| Mean (SD) | 62.4 (36.33) | 68.6 (44.81) | 53.7 (30.72) | 65.4 (42.17) | 58.5 (35.18) | 60.5 (36.35) | 63.5 (38.56) | 62.2 (39.17) | 56.7 (33.39) |
| Median | 53.8 | 60.1 | 49.5 | 50.9 | 53.2 | 53.0 | 53.0 | 57.0 | 50.1 |
| Range | 11–180 | 3–237 | 11–159 | 14–196 | 14–202 | 14–152 | 11–196 | 3–237 | 11–159 |
| Type of ART regimen, n (%)‡ | | | | | | | | | |
| NRTI and NNRTI (with no PI) | 60 (39.0) | 27 (54.0) | 31 (27.9) | 32 (34.8) | 23 (27.1) | 28 (32.6) | 92 (37.4) | 50 (37.0) | 59 (29.9) |
| NRTI and PI (with no NNRTI) | 66 (42.9) | 17 (34.0) | 53 (47.7) | 40 (43.5) | 37 (43.5) | 43 (50.0) | 106 (43.1) | 54 (40.0) | 96 (48.7) |
| NRTI, NNRTI, and PI | 18 (11.7) | 4 (8.0) | 15 (13.5) | 5 (5.4) | 13 (15.3) | 2 (2.3) | 23 (9.3) | 17 (12.6) | 17 (8.6) |
| NRTI alone | 8 (5.2) | 0 | 9 (8.1) | 8 (8.7) | 2 (2.4) | 3 (3.5) | 16 (6.5) | 2 (1.5) | 12 (6.1) |
| Other | 2 (1.3) | 2 (4.0) | 3 (2.7) | 7 (7.6) | 10 (11.8) | 10 (11.6) | 9 (3.7) | 12 (8.9) | 13 (6.6) |
| Time since lipodystrophy syndrome diagnosis, months | n=148 | n=49 | n=109 | n=89 | n=81 | n=84 | n=237 | n=130 | n=193 |
| Mean (SD) | 52.3 (39.66) | 48.1 (36.82) | 50.2 (39.77) | 66.9 (41.50) | 62.1 (47.80) | 71.4 (42.57) | 57.8 (40.90) | 56.8 (44.36) | 59.4 (42.25) |
| Median | 46.8 | 44.4 | 47.4 | 61.1 | 46.1 | 67.6 | 51.7 | 44.9 | 55.2 |
| Range | 0–189 | 0–140 | 0–192 | –5–194 | 0–211 | 1–259 | –5–194 | 0–211 | 0–259 |
| Lipodystrophy syndrome clinical assessment, n (%) | | | | | | | | | |
| Facial lipatrophy | 83 (53.9) | 25 (50.0) | 53 (47.7) | 36 (39.1) | 42 (49.4) | 42 (48.8) | 119 (48.4) | 67 (49.6) | 95 (48.2) |
| Lower limbs lipatrophy | 103 (66.9) | 29 (58.0) | 66 (59.5) | 48 (52.2) | 46 (54.1) | 51 (59.3) | 151 (61.4) | 75 (55.6) | 117 (59.4) |
| Upper limbs lipatrophy | 86 (55.8) | 27 (54.0) | 46 (41.4) | 44 (47.8) | 33 (38.8) | 39 (45.3) | 130 (52.8) | 60 (44.4) | 85 (43.1) |
| General lipatrophy | 117 (76.0) | 36 (72.0) | 80 (72.1) | 57 (62.0) | 59 (69.4) | 61 (70.9) | 174 (70.7) | 95 (70.4) | 141 (71.6) |
| Buffalo hump | 68 (44.2) | 21 (42.0) | 50 (45.0) | 30 (32.6) | 27 (31.8) | 29 (33.7) | 98 (39.8) | 48 (35.6) | 79 (40.1) |
| Abdominal lipohypertrophy | 154 (100) | 50 (100) | 111 (100) | 92 (100) | 85 (100) | 86 (100) | 246 (100) | 135 (100) | 197 (100) |
| Lipodystrophy syndrome clinical assessment, n (%) | | | | | | | | | |

| | LIPO-010 | | | CTR-1012 | | | COMBINED | | |
|---|--------------|-------------|--------------|-------------|-------------|-------------|--------------|--------------|--------------|
| | T-T N=154 | T-P N=50 | P-T N=111 | T-T N=92 | T-P N=85 | P-T N=86 | T-T N=246 | T-P N=135 | P-T N=197 |
| Breast enlargement | 53 (34.4) | 21 (42.0) | 50 (45.0) | 34 (37.0) | 34 (40.0) | 27 (31.4) | 87 (35.4) | 55 (40.7) | 77 (39.1) |
| Subjects with ≥1 of the following signs: general lipoatrophy, buffalo hump, or breast enlargement | 140 (90.9) | 45 (90.0) | 101 (91.0) | 72 (78.3) | 71 (83.5) | 72 (83.7) | 212 (86.2) | 116 (85.9) | 173 (87.8) |

ART, antiretroviral therapy; HIV, human immunodeficiency virus; ITT, intent-to-treat; NNRTI, non-nucleoside reverse transcriptase inhibitors; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; P-T, placebo-tesamorelin; SD, standard deviation; T-P, tesamorelin-placebo; T-T, tesamorelin-tesamorelin.

Note: Tesamorelin refers to tesamorelin 2 mg/day.

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

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

* p=0.047 for T-T vs T-P in the combined results (generalized linear model [specifying multinomial distribution for dependent variable], with treatment group and study in the model, including the T-T and T-P groups).

† p=0.009 for P-T vs (T-T and T-P) in LIPO-010 (1-factor [treatment] ANOVA).

‡ p=0.030 for P-T vs (T-T and T-P) in the combined results (generalized linear model [specifying multinomial distribution for dependent variable], with treatment group and study in the model, including all treatment groups).

11.6 Appendix VI: Summary of SAEs (Phase 3 Studies)

Table 47. Summary of SAEs (Phase 3 Studies)

| | MAIN | | EXTENSION | | |
|---|------------------------|--------------------|----------------|----------------|----------------|
| | Tesamorelin (N=543) | Placebo (N=263) | T-T (N=246) | T-P (N=135) | P-T (N=197) |
| Number of unique SAEs | 25 | 12 | 7 | 3 | 7 |
| Patients with SAEs, n (%) | 20 (3.7) | 11 (4.2) | 7 (2.8) | 3 (2.2) | 6 (3.0) |
| Blood and lymphatic system disorders | 1 (0.2) | 0 | 0 | 0 | 0 |
| Anemia | 1 (0.2) | 0 | 0 | 0 | 0 |
| Cardiac disorders | 1 (0.2) | 2 (0.8) | 1 (0.4) | 0 | 0 |
| Arrhythmia | 0 | 1 (0.4) | 0 | 0 | 0 |
| Arteriosclerosis coronary artery | 0 | 0 | 1 (0.4) | 0 | 0 |
| Cardiac arrest | 0 | 1 (0.4) | 0 | 0 | 0 |
| Cardiac failure congestive | 1 (0.2) | 0 | 0 | 0 | 0 |
| Eye disorders | 0 | 0 | 1 (0.4) | 0 | 0 |
| Chorioretinopathy | 0 | 0 | 1 (0.4) | 0 | 0 |
| Gastrointestinal disorders | 2 (0.4) | 1 (0.4) | 0 | 1 (0.7) | 1 (0.5) |
| Abdominal hernia obstructive | 0 | 1 (0.4) | 0 | 0 | 0 |
| Abdominal pain | 0 | 0 | 0 | 1 (0.7) | 0 |
| Diarrhea | 1 (0.2) | 0 | 0 | 0 | 0 |
| Intestinal perforation | 0 | 0 | 0 | 0 | 1 (0.5) |
| Small intestinal obstruction | 1 (0.2) | 0 | 0 | 0 | 0 |
| General disorders and administration site conditions | 0 | 1 (0.4) | 1 (0.4) | 0 | 0 |
| Chest pain | 0 | 1 (0.4) | 1 (0.4) | 0 | 0 |
| Hepatobiliary disorders | 0 | 1 (0.4) | 0 | 0 | 0 |
| Cholecystitis acute | 0 | 1 (0.4) | 0 | 0 | 0 |
| Immune system disorders | 0 | 1 (0.4) | 0 | 0 | 0 |
| Hypersensitivity | 0 | 1 (0.4) | 0 | 0 | 0 |
| Infections and infestations | 5 (0.9) | 1 (0.4) | 2 (0.8) | 1 (0.7) | 1 (0.5) |
| Cellulitis | 0 | 0 | 1 (0.4) | 0 | 1 (0.5) |
| Sepsis | 2 (0.4) | 0 | 0 | 0 | 0 |
| Abdominal abscess | 1 (0.2) | 0 | 0 | 0 | 0 |
| Appendiceal abscess | 1 (0.2) | 0 | 0 | 0 | 0 |
| Appendicitis | 0 | 1 (0.4) | 0 | 0 | 0 |
| Bronchitis viral | 1 (0.2) | 0 | 0 | 0 | 0 |
| Ludwig angina | 0 | 0 | 0 | 1 (0.7) | 0 |
| Perianal abscess | 1 (0.2) | 0 | 0 | 0 | 0 |
| Pneumonia | 0 | 0 | 1 (0.4) | 0 | 0 |
| Upper respiratory tract infection | 1 (0.2) | 0 | 0 | 0 | 0 |

| | MAIN | | EXTENSION | | |
|--|------------------------|--------------------|----------------|----------------|----------------|
| | Tesamorelin (N=543) | Placebo (N=263) | T-T (N=246) | T-P (N=135) | P-T (N=197) |
| Injury, poisoning and procedural complications | 1 (0.2) | 1 (0.4) | 0 | 0 | 1 (0.5) |
| Humerus fracture | 1 (0.2) | 0 | 0 | 0 | 0 |
| Post-procedural hemorrhage | 0 | 0 | 0 | 0 | 1 (0.5) |
| Procedural pain | 0 | 1 (0.4) | 0 | 0 | 0 |
| Rib fracture | 1 (0.2) | 0 | 0 | 0 | 0 |
| Investigations | 1 (0.2) | 1 (0.4) | 0 | 0 | 0 |
| Electrocardiogram abnormal | 1 (0.2) | 1 (0.4) | 0 | 0 | 0 |
| Metabolism and nutrition disorders | 1 (0.2) | 0 | 0 | 0 | 0 |
| Dehydration | 1 (0.2) | 0 | 0 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | 2 (0.4) | 0 | 0 | 0 | 0 |
| Arthralgia | 1 (0.2) | 0 | 0 | 0 | 0 |
| Mobility decreased | 1 (0.2) | 0 | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 2 (0.4) | 2 (0.8) | 0 | 1 (0.7) | 1 (0.5) |
| Anal cancer | 0 | 0 | 0 | 1 (0.7) | 0 |
| Basal cell carcinoma | 1 (0.2) | 0 | 0 | 0 | 0 |
| Breast cancer in situ | 0 | 1 (0.4) | 0 | 0 | 0 |
| Hodgkin's disease | 0 | 1 (0.4) | 0 | 0 | 1 (0.5) |
| Rectal cancer | 1 (0.2) | 0 | 0 | 0 | 0 |
| Nervous system disorders | 3 (0.6) | 0 | 0 | 0 | 0 |
| Cerebellar syndrome | 1 (0.2) | 0 | 0 | 0 | 0 |
| Neuropathy peripheral | 1 (0.2) | 0 | 0 | 0 | 0 |
| Trigeminal neuralgia | 1 (0.2) | 0 | 0 | 0 | 0 |
| Pregnancy, puerperium and perinatal conditions | 0 | 0 | 1 (0.4) | 0 | 0 |
| Abortion spontaneous | 0 | 0 | 1 (3.7) | 0 | 0 |
| Psychiatric disorders | 1 (0.2) | 1 (0.4) | 1 (0.4) | 0 | 0 |
| Bipolar II disorder | 1 (0.2) | 0 | 0 | 0 | 0 |
| Dependence | 1 (0.2) | 0 | 0 | 0 | 0 |
| Major depression | 0 | 1 (0.4) | 0 | 0 | 0 |
| Mental status changes | 0 | 0 | 1 (0.4) | 0 | 0 |
| Renal and urinary disorders | 0 | 0 | 0 | 0 | 1 (0.5) |
| Nephrolithiasis | 0 | 0 | 0 | 0 | 1 (0.5) |
| Reproductive system and breast disorders | 1 (0.2) | 0 | 0 | 0 | 0 |
| Benign prostatic hyperplasia | 1 (0.2) | 0 | 0 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | 0 | 0 | 0 | 0 | 2 (1.0) |
| Asphyxia | 0 | 0 | 0 | 0 | 1 (0.5) |
| Dyspnea | 0 | 0 | 0 | 0 | 1 (0.5) |

P-T, placebo-tesamorelin; SAEs, serious adverse events ; T-P, tesamorelin-placebo; T-T, tesamorelin-tesamorelin.

Note: Tesamorelin refers to tesamorelin 2 mg/day.

11.7 Appendix VII: Key Articles

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