Common Drug Review
Clinical Review Report

August 2016

Drug	Tesamorelin (Egrifta)
Indication	Treatment of excess visceral adipose tissue (VAT), as assessed by waist circumference ≥ 95 cm for males and ≥ 94 cm for females, and confirmed by a VAT level > 130 cm^2 by computerized tomography scan, in treatment-experienced adult human immunodeficiency virus-infected patients with lipodystrophy.
Listing request	As per indication.
Dosage form(s)	1 mg and 2 mg tesamorelin (as tesamorelin acetate) per vial
NOC date	27-03-2015
Manufacturer	Theratechnologies Inc.

Redactions: Confidential information in this document has been redacted at the request of the manufacturer in accordance with the *CADTH Common Drug Review Confidentiality Guidelines.*

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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ABBREVIATIONS

3TC	lamivudine
ABC	abacavir
AE	adverse event
ALT	alanine transaminase
ANCOVA	analysis of covariance
ART	antiretroviral therapy
AST	aspartate transaminase
BMI	body mass index
CI	confidence interval
COBI	cobicistat
CSR	clinical study report
CT	computerized tomography
DB	double-blind
DHHS	Department of Health and Human Services
DTG	dolutegravir
EVG	elvitegravir
EQ-5D	EuroQol 5-Dimensions Questionnaire
EQ-VAS	EuroQol visual analogue scale
FBG	fasting blood glucose
FDA	Food and Drug Administration
FTC	emtricitabine
GH	growth hormone
GRF	growth hormone–releasing factor
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
IGF-1	insulin-like growth factor-1
IGT	impaired glucose tolerance
INSTI	integrase strand transfer inhibitor
IVRS	interactive voice response system
ITT	intention-to-treat population
LOCF	last observation carried forward
LS	least squares
MID	minimally important difference
NRTI	nucleoside reverse transcriptase inhibitor
NNRTI	non-nucleoside reverse transcriptase inhibitor
NR	not reported
PI	protease inhibitor
PP	per-protocol
PRO	patient-reported outcome

PSA	prostate-specific antigen
QoL	quality of life
RAL	raltegravir
RCT	randomized controlled trial
rhGH	recombinant human growth hormone
RR	relative risk
SAE	serious adverse event
SD	standard deviation
SE	standard error
STR	single-tablet regimen
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
VAS	visual analogue scale
VAT	visceral adipose tissue
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

Introduction

Human immunodeficiency virus (HIV)–associated lipodystrophy is a medical condition characterized by body composition changes, including lipohypertrophy. Patients with lipohypertrophy typically have excess visceral adipose tissue (VAT) in the abdomen, but may also accumulate fat in other areas of the body. The underlying mechanisms of lipohypertrophy are poorly understood, thus complicating efforts to determine its etiology. Researchers hypothesize its pathogenesis to be related to the virus itself or to specific antiretroviral therapy (ART) regimens. Evidence suggests that the use of protease inhibitors, in particular, is commonly associated with the development of lipohypertrophy. Excess VAT negatively affects patients' body image and quality of life (QoL). Tesamorelin is a synthetic analogue of growth hormone–releasing factor that triggers diverse metabolic effects, including lipolysis.

Indication under review
Treatment of excess VAT, as assessed by waist circumference ≥ 95 cm for males and ≥ 94 cm for females, and confirmed by a VAT level > 130 cm^2 by computerized tomography (CT) scan, in treatment-experienced adult HIV-infected patients with lipodystrophy.
Listing criteria requested by sponsor
As per indication.

The objective of this systematic review was to evaluate the beneficial and harmful effects of tesamorelin for the treatment of excess VAT, as assessed by waist circumference ≥ 95 cm for males and ≥ 94 cm for females, and confirmed by a VAT level > 130 cm^2 by computed tomography (CT) scan, in treatment-experienced adult HIV-infected patients with lipodystrophy.

Results and Interpretation

Included Studies

The evidence for this review was drawn from three randomized controlled trials (RCTs) — LIPO-010 (N = 412), CTR-1011 (N = 404), and Stanley et al. 2014 (N = 54) — each of which compared tesamorelin 2 mg/day (subcutaneous injection) to placebo. Eligible participants in Stanley et al. 2014 also underwent a second randomization process to undergo a hyperinsulinemic euglycemic clamp. LIPO-010 and CTR-1011 comprised a 26-week double-blind (DB) main phase, followed by a 26-week extension phase (the extension phase of CTR-1011 was denoted CTR-1012). In the extension phase, participants who received tesamorelin in the main phase were re-randomized to continue receiving tesamorelin 2 mg/day (T-T group) or switched to placebo (T-P group), whereas all individuals who received placebo in the main phase were assigned to receive tesamorelin (P-T group). The study by Stanley et al. 2014 consisted of a six-month DB treatment phase. The primary efficacy outcome for LIPO-010 and CTR-1011 was the per cent change in VAT at week 26.

In LIPO-010 and CTR-1011, VAT was assessed by a CT scan from a single 5 mm slice obtained at the level of the L4-L5 intervertebral disc space. In LIPO-010 and CTR-1011, relevant secondary efficacy outcomes included patient-reported outcomes (PROs) related to body image, specifically perceived belly size, belly appearance distress, and belly profile. Other relevant efficacy outcomes measured in both trials included waist circumference and QoL. Investigators of CTR-1011 also administered the EuroQol 5-

Dimensions (EQ-5D) instrument, a generic measure of health-related quality of life (HRQoL). In Stanley et al. 2014, the co-primary efficacy outcomes were changes in VAT (measured using a single-slice CT at L4) and liver fat (not relevant for this review).

All three trials enrolled participants who were aged 18 to 65 years, HIV-positive, on a stable ART regimen, and had objective evidence of abdominal fat accumulation as follows: waist circumference ≥ 95 cm and waist-to-hip ratio ≥ 0.94 for males, and waist circumference ≥ 94 cm and waist-to-hip ratio ≥ 0.88 for females. In LIPO-010 and CTR-1011, more than half of participants in each treatment group reported taking an ART regimen that included a protease inhibitor (PI), whereas more than a third of participants did so in Stanley et al. 2014. In each trial, at least a third of participants reported taking an ART regimen that included a non-nucleoside reverse transcriptase inhibitor (NNRTI), whereas across all trials, more than 90% of participants reported taking a nucleoside reverse transcriptase inhibitor (NRTI).

Some methodological issues were identified in the trials. First, discussions with the clinical expert consulted by CADTH Common Drug Review (CDR) for the purpose of this review revealed concerns regarding the external validity of the results of the included studies. Specifically, the study populations were different from those normally seen in routine clinical practice in Canada at present with respect to the nature of the current ART. The expert indicated that, in today's clinical practice, HIV patients are much more likely to receive ART regimens that consist of backbones other than PIs, including integrase strand transfer inhibitors (INSTIs) and NNRTIs. To this end, of the six regimens recommended by the US Department of Health and Human Services to manage ART-naive patients, five are INSTI-based, and one is ritonavir-boosted PI-based. In LIPO-010, the number of participants receiving ART regimens that consist of integrase inhibitors was not reported, whereas less than 5% of participants in CTR-1011 were receiving INSTI-based therapies. In Stanley et al. 2014, the number of participants on integrase inhibitors was unclear, as the authors reported that seven (25.0%) and six (27.3%) individuals in the tesamorelin and placebo group, respectively, were receiving entry inhibitors and integrase inhibitors. Moreover, as a result of the large number of HIV treatments available today, single or multiple substitutions of the various components of an ART regimen can be made to achieve optimal virologic suppression with fewer adverse events, including a substantially reduced risk of the accumulation of visceral fat. Further, the psychometric properties of the instruments used to evaluate body image and QoL in LIPO-010 and CTR-1011 were not clear, which leaves uncertain the degree to which the results are valid and clinically meaningful.

Efficacy

Across all three included studies, tesamorelin was associated with a statistically significantly greater reduction in VAT versus placebo: the least squares (LS) mean differences (95% confidence interval [CI]) for tesamorelin versus placebo were –19.6% (–23.7% to –15.3%) in LIPO-010 at week 26, and –11.7% (–16.2% to –7.1%) in CTR-1011 week 26, and −16.6% (−30.6% to −2.6%) in Stanley et al. 2014 at six months (Table 1). In LIPO-010 and CTR-1011, tesamorelin was associated with a statistically significantly greater reduction in waist circumference at 26 weeks versus placebo, with absolute differences (95% CI) of –1.8 cm (–2.8 cm to –0.9 cm) and –1.3 cm (–2.4 cm to –0.2 cm), respectively. In the same two trials, at week 26, there were no statistically significant differences between treatment groups with respect to change in belly size evaluation, while the effects of tesamorelin versus placebo on change in belly appearance distress and patient-reported belly profile ratings were inconsistent. There were no statistically significant differences between tesamorelin and placebo with respect to changes to the overall (item-wise) QoL score at week 26.

In the extension phase, continued treatment with tesamorelin (T-T group) was associated with a statistically significantly greater reduction in VAT versus discontinuing treatment with tesamorelin (T-P group) from weeks 26 to 52: LS mean differences (95% CI) were –20.4% (–29.8 to –11.0) and –25.8% (–40.7% to –10.9%) in LIPO-010 and CTR-1012, respectively. For both trials, however, participants in the T-P group experienced increases in VAT by as much as 24.9% over the same time period. Furthermore, from weeks 26 to 52, participants in the T-T group experienced statistically significantly greater improvements in belly appearance distress and patient-reported belly profile versus those in the T-P group, although there were no statistically significant differences between treatment groups with respect to changes in belly size evaluation.

Across the trials, no analyses were conducted to evaluate the impact of waist circumference on the primary efficacy outcome. In LIPO-010, the investigators did not find a statistically significant treatment-by-baseline interaction with respect to the per cent change in VAT at week 26 ($P = 0.251$). The impact of baseline VAT was not evaluated on the primary efficacy outcome in CTR-1011 and the study by Stanley et al. 2014. In LIPO-010, with respect to the primary efficacy outcome, in one analysis of covariance (ANCOVA) model, neither the NNRTI nor the NNRTI-by-treatment interaction were statistically significant ($P = 0.711$ and $P = 0.392$, respectively); in a separate ANCOVA model, neither the ART regimen nor the treatment-by-ART regimen interaction were statistically significant ($P = 0.855$ and $P = 0.962$, respectively). In CTR-1011, neither the ART regimen nor the treatment-by-ART regimen interaction were statistically significant ($P = 0.213$ and $P = 0.810$ respectively) as they pertained to the primary efficacy outcome.

Harms

Across all three studies, at least 70% of study participants in each trial experienced a treatment-emergent adverse event (AE) at week 26 (Table 1). A greater proportion of participants in Stanley et al. 2014 experienced an AE (tesamorelin: 89.3%; placebo: 95.5%) than those in the main phase of LIPO-010, followed by those in CTR-1011. Approximately 5% more participants receiving tesamorelin (LIPO-010: 82.8%; CTR-1011: 74.1%) experienced an AE than those on placebo (LIPO-010: 75.9%; CTR-1011: 69.8%). There were no deaths in LIPO-010 and Stanley et al., whereas two participants died in CTR-1011, one in each treatment group. Across all three studies, at week 26, a greater percentage of participants receiving tesamorelin reported an injection-site–related AE, myalgia, or fluid retention or edema than those in the placebo group. In LIPO-010, one participant (0.4%) receiving tesamorelin (versus none receiving placebo) developed diabetes mellitus (recorded as a treatment-emergent AE) at week 26. In LIPO-010, a greater percentage of participants receiving tesamorelin versus placebo (2.9% versus 1.5%) developed a malignancy, whereas a smaller percentage of participants receiving tesamorelin in CTR-1011 versus those receiving placebo (0.4% versus 3.2%) developed a malignancy.

In the LIPO-010 extension phase, AEs were observed in 57.8%, 74.7%, and 73.9% of participants in the T-T, P-T, and T-P groups, respectively; the corresponding percentages in CTR-1012 were 73.9%, 57.6%, and 76.7%. Two participants died in the extension phase of LIPO-010: one individual in the T-T group and the other in the P-T group.

Conclusions

Results from three DB RCTs (LIPO-010, CTR-1011, and Stanley et al. 2014) demonstrated that six months of treatment with tesamorelin was associated with a statistically significantly greater reduction in VAT and waist circumference compared with placebo in HIV-infected patients with abdominal lipohypertrophy. The relative reduction in VAT (–12% to –20% across studies) and the absolute reduction in waist circumference (–1.3 to –1.8 cm) associated with tesamorelin treatment versus placebo exceeded the thresholds of 8% and 1 cm, respectively, that Health Canada considered to be minimal acceptable decreases that reflect clinical benefit. However, the clinical relevance of the reduction in VAT and waist circumference attributable to tesamorelin is unclear, because tesamorelin treatment was not associated with consistent improvements in body image, which is an important outcome to patients, nor did it improve QoL. Furthermore, the magnitude of reduction in VAT and waist circumference observed in the included studies is unlikely to be seen as clinically relevant by clinicians, while the fact that VAT (as measured by CT scan) is not routinely used to gauge treatment response in clinical practice limits the application of the results to support clinical decision-making. A major limitation of the clinical evidence was the limited external validity of the results, because the nature of the ART regimens used in the included studies does not reflect treatment regimens used currently in clinical practice in Canada. Specifically, more than half of patients in LIPO-010 and CTR-1011 and approximately 40% of patients in Stanley et al. 2014 were treated with PI-based ARTs that are associated with VAT accumulation, whereas current HIV treatment guidelines recommend ART regimens that mostly comprise INSTIs, which are less likely to cause abdominal lipohypertrophy. Treatment with tesamorelin was not associated with any consistent or substantial harm through 52 weeks, although longer-term studies of tesamorelin are needed to adequately assess its long-term safety. There were limited data to evaluate the effects of tesamorelin on important safety outcomes, including the risk of cardiovascular harm, as well as the occurrence of diabetes, cancer, and mortality.

TABLE 1: SUMMARY OF RESULTS (MAIN PHASE)

Outcome	LIPO-010		CTR-1011		Stanley et al. 2014	
	Tesamorelin (N = 272)	Placebo (N = 136)	Tesamorelin (N = 268)	Placebo (N = 126)	Tesamorelin (N = 28)	Placebo (N = 22)
VAT (cm^2)						
Baseline, mean (SD)	178.3 (76.9)	171.0 (76.9)	186.5 (86.6)	194.9 (95.5)	208 (98)	237 (127)
26 weeks, % change from baseline[a] (SE)	–17.8% (1.6)	2.2% (2.2)	–13.8% (1.5)	2.4% (2.2)	–9.9% (−19.7, −0.2)	6.6% (−4.1, 17.3)
26 weeks, LS mean difference[b] (95% CI), *P* value	**–19.6% (–23.7 to –15.3), *P* < 0.001**		**–11.7% (–16.2 to –7.1), *P* < 0.001**		**–16.6% (–30.6 to –2.6), *P* = NR**	
26 weeks, absolute change from baseline, LS mean[c] (SE)	–27.4 (2.2)	4.4 (3.2)	–21.0 (2.4)	–0.4 (3.5)	–34 (–53, –15)	8 (–14, 30)
26 weeks, LS mean difference[b] (95% CI), *P* value	**–31.9 (–39.5 to –24.3), *P* < 0.001**		**–20.6 (–28.8 to –12.3), *P* < 0.001**		**–42 (–71 to –14), *P* = 0.005**	
Waist circumference (cm)						
Baseline, mean (SD)	104 (9.54)	105 (9.49)	105 (9.03)	104 (9.08)	Not evaluated	
26 weeks, absolute change from baseline, mean (SD)	–2.61 (4.91)	–0.80 (4.05)	–2.15 (5.41)	–0.82 (4.73)		
26 weeks, absolute difference (95% CI), *P* value	**–1.8 (–2.8 to –0.9), *P* < 0.001**		**–1.3 (–2.4 to –0.2), *P* = 0.02**			
Belly size evaluation						
Baseline, mean (SD)	59.8 (47.7)	55.8 (52.0)	56.1 (54.2)	56.9 (57.2)	Not evaluated	
26 weeks, absolute change from baseline,[d] mean (SD)	14.6 (30.2)	13.1 (31.4)	14.8 (27.8)	11.7 (25.2)		
26 weeks, mean difference (95% CI), *P* value	NR, *P* = 0.750,[e] *P* = 0.977[f]		NR, *P* = 0.211,[f] *P* = 0.155[e]			
Belly appearance distress						
Baseline, mean (SD)	22.1 (22.23)	24.0 (25.68)	22.3 (24.19)	20.2 (22.07)	Not evaluated	
26 weeks, absolute change from baseline,[g] mean (SD)	11.6 (26.93)	6.2 (25.82)	8.4 (28.99)	5.2 (26.61)		
26 weeks, mean difference (95% CI), *P* value	NR, *P* = 0.076,[e] ***P* = 0.028**[f]		NR, ***P* = 0.022,**[f] *P* = 0.083[e]			

Outcome	LIPO-010		CTR-1011		Stanley et al. 2014	
	Tesamorelin (N = 272)	Placebo (N = 136)	Tesamorelin (N = 268)	Placebo (N = 126)	Tesamorelin (N = 28)	Placebo (N = 22)
Belly profile (patient-reported)						
Baseline, mean (SD)	3.3 (1.3)	3.2 (1.5)	3.2 (1.36)	3.3 (1.19)		
26 weeks, absolute change from baseline,[b] mean (SD)	–0.7 (1.25)	–0.3 (1.25)	–0.5 (1.29)	–0.3 (1.03)		
26 weeks, mean difference (95% CI), *P* value	**NR, *P* = 0.031,[h] *P* = 0.042[f]**		NR, *P* = 0.075,[f] *P* = 0.104[h]			
Overall QoL (item-wise)						
Baseline, mean (SD)	433.1 (73.08)	429.4 (79.48)	437.0 (77.72)	436.2 (83.96)	Not evaluated	
26 weeks, actual change from baseline, mean (SD)	1.731 (59.121)	0.038 (49.151)	–2.6 (53.67)	–11.3 (51.57)		
26 weeks, mean difference (95% CI), *P* value	NR, *P* = 0.638		NR, *P* = 0.118			
EQ-5D index						
Baseline, mean (SD)	Not evaluated		0.817 (0.18)	0.823 (0.15)	Not evaluated	
26 weeks, mean (SE)			0.819 (0.10)	0.819 (0.02)		
26 weeks, mean difference (95% CI), *P* value			NR, *P* = 1.000			
EQ-5D VAS/health state						
Baseline, mean (SD)			68.50 (23.03)	65.26 (20.75)	Not evaluated	
26 weeks, mean (SE)			68.34 (1.43)	65.60 (2.08)		
26 weeks, mean difference (95% CI), *P* value			NR, *P* = 0.279			
AEs						
Participants with > 0 AEs, n (%)	226 (82.8)	104 (75.9)	200 (74.1)	88 (69.8)	25 (89.3)	21 (95.5)
SAEs						
Participants with > 0 SAEs, n (%)	11 (4.0)	3 (2.2)	9 (3.3)	8 (6.3)	3 (10.7)	3 (13.6)

Outcome	LIPO-010		CTR-1011		Stanley et al. 2014	
	Tesamorelin (N = 272)	Placebo (N = 136)	Tesamorelin (N = 268)	Placebo (N = 126)	Tesamorelin (N = 28)	Placebo (N = 22)
WDAEs						
Participants with AEs leading to study discontinuation,[i] n (%)	26 (9.5)	4 (2.9)	26 (9.5)	12 (9.3)	3 (10.7)	1 (3.8)
Deaths						
Number of deaths, n (%)	0		1 (0.4)	1 (0.8)	0	
Notable harms						
Any injection-site condition[j]	82 (30.0)	33 (24.1)	137 (50.7)	27 (21.4)	17 (60.7)	13 (59.1)
Myalgia	21 (7.7)	3 (2.2)	10 (3.7)	2 (1.6)	3 (10.7)	0
Arthralgia	37 (13.6)	15 (10.9)	33 (12.2)	14 (11.1)	4 (14.3)	4 (18.2)
Any fluid retention/edema[j]	27 (9.9)	8 (5.8)	14 (5.2)	1 (0.8)	2 (7.1)	1 (4.5)
Diabetes mellitus	1 (0.4)	0	NR			
Any malignancy[j]	8 (2.9)	2 (1.5)	1 (0.4)	4 (3.2)	NR	

AE = adverse event; ANCOVA = analysis of covariance; EQ-5D = EuroQol 5-Dimensions Questionnaire; CI = confidence interval; LS = least squares; NR = not reported; SAE = serious adverse event; SD = standard deviation; SE = standard error; VAS = visual analogue scale; VAT = visceral adipose tissue; WDAE = withdrawal due to adverse event.
Note: Statistically significant results are bolded.
[a] Variance is 95% CI (not SE) for Stanley et al. 2014.
[b] Results reported as mean difference instead of LS mean difference for Stanley et al. 2014.
[c] Results reported as mean (95% CI) instead of LS mean (SE) for Stanley et al. 2014.
[d] Positive change from baseline indicates improvement.
[e] Parametric ANCOVA (primary analysis model in LIPO-010; supportive in CTR-1011).
[f] Ranked (non-parametric) ANCOVA (supportive analysis model in LIPO-0101; supportive in LIPO-010).
[g] Negative change from baseline indicates improvement; i.e., less dysmorphia.
[h] Mann-Whitney test.
[i] In LIPO-010 and CTR-1011, this table presents the number of participants with an AE as the primary reason for study discontinuation.
[j] Across all 3 trials, the number of participants experiencing these notable harms in both treatment groups may be overestimated due to multiple counting of individual events.
Source: FDA statistical review,[1] Stanley et al. 2014,[2] LIPO-010 Clinical Study Report (CSR),[3] Falutz et al. 2007,[4] CTR-1011 CSR,[5] Falutz et al. 2010.[6]

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Human immunodeficiency virus (HIV)–associated lipodystrophy is characterized by body composition changes, including the accumulation (lipohypertrophy) or loss (lipoatrophy) of fat, and metabolic abnormalities such as dyslipidemia and insulin resistance.[7,8] Affected patients may present with lipohypertrophy, lipoatrophy, or a combination of both.

Patients with lipohypertrophy typically have excess visceral adipose tissue (VAT) within the abdomen, but may also have enlarged supraclavicular and dorso-cervical fat pads, anterior neck fat accumulation, or breast enlargement. The underlying mechanisms of lipohypertrophy are understood poorly, which complicates efforts to determine etiology. Researchers hypothesize that pathogenesis is related to the HIV virus itself or to specific antiretroviral therapy (ART) regimens. Evidence suggests that the use of protease inhibitors (PIs), in particular, is commonly associated with the development of lipohypertrophy.[9,10] The US Department of Health and Human Services (DHHS) notes that the accumulation of visceral, truncal, dorso-cervical, and breast fat is specifically observed with use of regimens containing older PIs, such as indinavir.[11]

HIV-associated lipohypertrophy is challenging to define and diagnose, resulting in wide estimates of prevalence. Studies conducted outside Canada and published more than 10 years ago suggest that between 6% and 62% of HIV-infected patients with lipodystrophy are affected by abdominal or central fat accumulation.[12] Recent Canadian data are limited: a 2011 survey found that, among 778 HIV-positive patients in Ontario, 31% of individuals experienced lipohypertrophy in the back, abdomen, and/or breasts, while 17% had isolated central lipohypertrophy, which the researchers defined as experiencing at least one major or two minor fat accumulation changes in the back, abdomen, and/or breasts.[13] Patients with HIV-associated lipodystrophy indicate that excess VAT has a substantial negative impact on their body image and quality of life (QoL) (0).

1.2 Standards of Therapy

Potential interventions for reducing excess VAT include diet and exercise, metformin (especially among patients with diabetes mellitus), tesamorelin, and surgical interventions, including dorso-cervical fat pad liposuction and reduction mammoplasty.[14] Another option that was considered for the treatment of HIV-associated lipodystrophy was somatropin, a recombinant human growth hormone (rhGH), although the brand name product, Serostim, was not approved for this use by the US Food and Drug Administration (FDA) due to "marked increases in glucose intolerance and development of diabetes in some patients."[15] Somatropin is not approved nor used for lipodystrophy treatment in Canada.

In Canada, besides tesamorelin, there are no drugs specifically indicated for the treatment of excess VAT in treatment-experienced adult HIV-infected patients with lipodystrophy.

1.3 Drug

Tesamorelin is a synthetic analogue of growth hormone–releasing factor (GRF).[16] It mimics the pharmacology of GRF in vitro by stimulating the synthesis and secretion of human growth hormone (hGH), which binds to receptors on a variety of target cells, including adipocytes, thus resulting in diverse metabolic effects, such as lipolysis.

The recommended dose of tesamorelin in Canada is 2 mg injected subcutaneously once a day, and the recommended injection site is the abdomen.[16] Tesamorelin is not indicated for weight loss management; i.e., it has a weight-neutral effect.[16] Further, treatment with tesamorelin should be limited to patients who failed to reduce excess VAT using diet and exercise.[16]

Indication under review
Treatment of excess VAT, as assessed by waist circumference ≥ 95 cm for males and ≥ 94 cm for females, and confirmed by a VAT level > 130 cm^2 by computerized tomography (CT) scan, in treatment-experienced adult HIV-infected patients with lipodystrophy.
Listing criteria requested by sponsor
As per indication.

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of tesamorelin for the treatment of excess VAT, as assessed by waist circumference ≥ 95 cm for males and ≥ 94 cm for females, and confirmed by a VAT level > 130 cm^2 by CT scan, in treatment-experienced adult HIV-infected patients with lipodystrophy.

2.2 Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase 3 studies were selected for inclusion based on the selection criteria presented in Table 2.

TABLE 2: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Treatment-experienced adult HIV-infected patients with lipodystrophy Subgroups: – Waist circumference – Baseline VAT level – Background HIV treatment regimen
Intervention	Tesamorelin 2 mg (subcutaneous injection)
Comparators	SoC Placebo
Outcomes	**Key efficacy outcomes:** – VAT (as measured by CT scan)[a] – Waist circumference – Body image[a] – QoL/HRQoL[a] **Harms outcomes:** – Mortality[a] – SAEs – AEs – WDAEs – Notable harms (injection-site reactions,[a] myalgia, arthralgia, fluid retention/edema, diabetes, malignancies)
Study Design	Published and unpublished phase 3 RCTs

AE = adverse event; CT = computed tomography; HIV = human immunodeficiency virus; HRQoL = health-related quality of life; QoL = quality of life; RCT = randomized controlled trial; SAE = serious adverse event; SoC = standard of care; VAT = visceral adipose tissue; WDAE = withdrawal due to adverse event.
[a] Identified as an important outcome in the patient input submission to CADTH Common Drug Review.

The literature search was performed by an information specialist using a peer-reviewed search strategy (0).

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates via Ovid; Embase (1974–) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was Egrifta (tesamorelin).

No methodological filters were applied to limit retrieval. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language.

The initial search was completed on March 31, 2016. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee (CDEC) on July 20, 2016. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters checklist (https://www.cadth.ca/resources/finding-evidence/grey-matters-practical-search-tool-evidence-based-medicine):

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search.

Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 3; excluded studies (with reasons) are presented in 0.

3. RESULTS

3.1 Findings From the Literature

A total of three studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 3 and described in section 3.2. A list of excluded studies is presented in 0.

FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

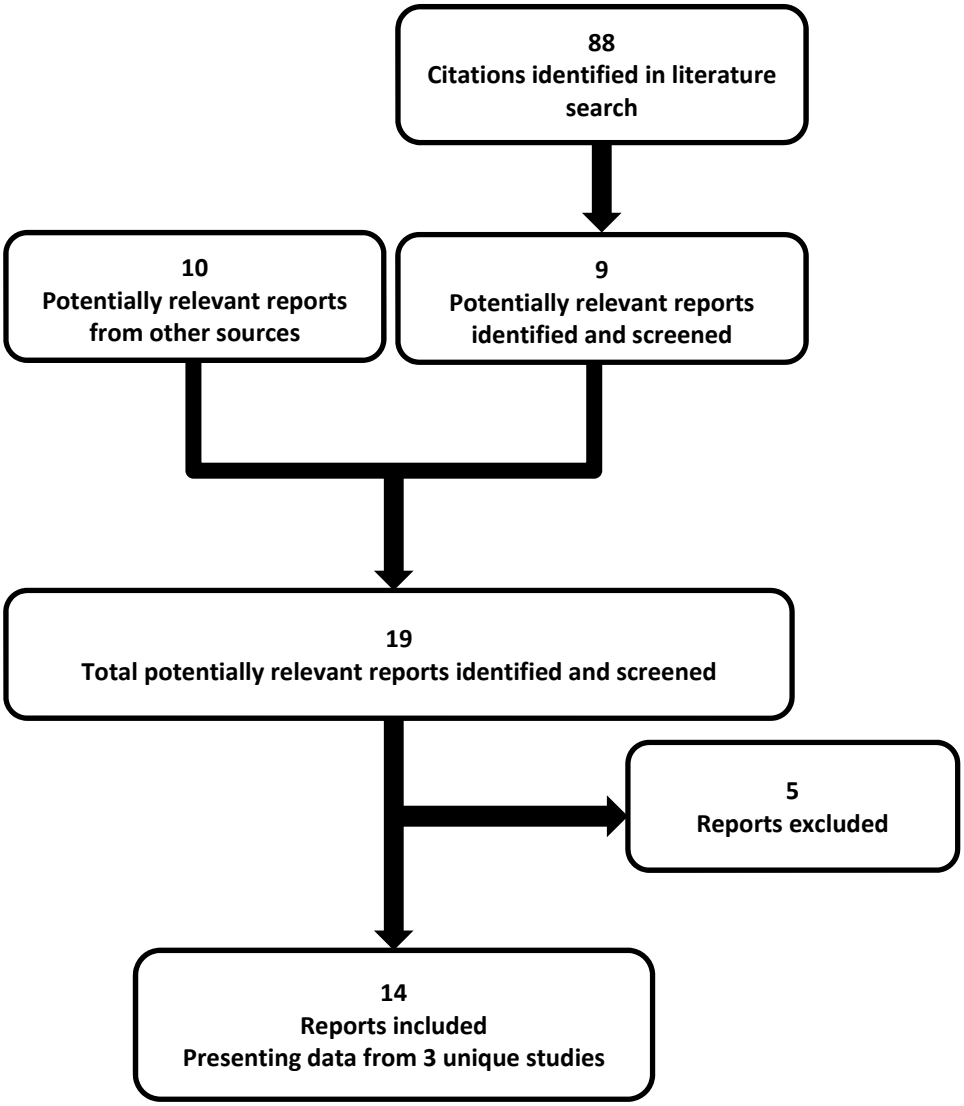


TABLE 3: DETAILS OF INCLUDED STUDIES (MAIN PHASE)

		LIPO-010	CTR-1011	Stanley et al. 2014
DESIGNS & POPULATIONS	**Study design**	Multi-centre, DB, placebo-controlled phase 3 RCT stratified by testosterone use and IGT/diabetes condition (FBG > 108 mg/dL [6 mmol/L] at screening)	Multi-centre, DB, placebo-controlled phase 3 RCT stratified by diabetes status Note: An error in the IVRS specifications precluded stratification according to site and IGT/diabetes condition (FBG > 108 mg/dL [6 mmol/L] at screening) as initially planned.	Single-centre, DB, placebo-controlled RCT stratified by sex and, for men, by physiologic testosterone use
	Participating locations	Canada, US	Belgium, Canada, France, Spain, United Kingdom, US	US
	Randomized (N)	412	404	54
	Main inclusion criteria	Male or female with HIV infection aged 18-65 years; CD4 cell count > 100 cells/mm^3 and VL < 10,000 copies/mL; on stable ART regimen for ≥ 8 weeks prior to randomization; evidence of excess VAT – waist circumference and waist-to-hip ratio of ≥ 95 cm and ≥ 0.94 for males, and ≥ 94 cm and ≥ 0.88 for females, respectively; negative pregnancy test or not lactating; normal mammography within 6 months		Male or female with HIV infection aged 18-65 years; on stable ART regimen for ≥ 3 months; evidence of excess VAT – waist circumference and waist-to-hip ratio of ≥ 95 cm and ≥ 0.94 for males, and ≥ 94 cm and ≥ 0.88 for females, respectively
	Main exclusion criteria	BMI ≤ 20 kg/m^2; opportunistic infection or HIV-related disease within 3 months prior to randomization; history of malignancy or active neoplasm; use of oral hypoglycemic or insulin sensitizing agent within 6 months prior to randomization; ALT or AST ≥ 3x ULN; serum creatinine > 1.5 mg/dL (133 µmol/L); Hb > 20 g/L below LLN; FBG ≥ 150 mg/dL (8.33 mmol/L); fasting triglycerides > 0.99 g/dL (11.3 mmol/L); untreated hypertension; change in anti-hyperlipemic regimen within 3 months prior to randomization; use of any anoretics/anorexigenic or anti-obesity agents within 3 months prior to randomization; use of any experimental or marketed GH or GRF products, GH secretagogues, IGF-1, or IGFBP-3 within 6 months prior to randomization		History of pituitary disease or cranial irradiation; use of GH or GRF during past 6 months; use of supraphysiological corticosteroids, gonadal steroids, except physiologic testosterone replacement; use of antidiabetic agents; pregnant females; history of colon cancer, prostate cancer, or pituitary malignancy; FBG > 126 mg/dL, AST > 2.5x ULN; Hb < 12 g/dL; creatinine > 1.4 mg/dL; CD4 cell count < 200 mL; males – PSA > 5 ng/mL at screening
		Type 1 diabetes; type 2 diabetic patients previously treated with insulin except during pregnancy	Prior use of tesamorelin	

		LIPO-010	CTR-1011	Stanley et al. 2014
		and not required after delivery		
DRUGS	**Intervention(s)**	Tesamorelin (2 mg/day)		Tesamorelin (2 mg/day) ± hyperinsulinemic euglycemic clamp
	Comparator(s)	Placebo		Placebo ± hyperinsulinemic euglycemic clamp
DURATION	**Treatment period**	26 weeks (followed by 26-week extension phase; the extension phase of CTR-1011 was denoted CTR-1012)		6 months
OUTCOMES	**Primary end point**	Per cent change in VAT from baseline at 26 weeks		Co-primary end points: change in VAT and change in hepatic fat at 6 months
	Other end points	Waist circumference, body image (belly size evaluation, belly appearance distress, and belly profile evaluation), HRQoL, AEs, SAEs, WDAEs, notable harms		Harms
		(No unique end points evaluated in this study)	EQ-5D	
NOTES	**Publications**	Falutz et al. 2007,[4] Falutz et al. 2008[17]	Falutz et al. 2010[6]	Stanley et al. 2014[2]

AE = adverse event; ALT = alanine transaminase; ART = antiretroviral therapy; AST = aspartate transaminase; BMI = body mass index; DB = double-blind; EQ-5D = EuroQol 5-Dimensions Questionnaire; FBG = fasting blood glucose; GH = growth hormone; GRF = growth hormone–releasing factor; Hb = hemoglobin; HRQoL = health-related quality of life; IGF-1 = insulin-like growth factor-1; IGFBP-3 = insulin-like growth factor binding protein-3; IGT = impaired glucose tolerance; IVRS = interactive voice response system; LLN = lower limit of normal; PSA = prostate-specific antigen; RCT = randomized controlled trial; SAE = serious adverse event; ULN = upper limit of normal; VAT = visceral adipose tissue; VL = viral load; WDAE = withdrawals due to adverse events.

Note: The following additional reports were included: FDA medical review,[18] FDA statistical review,[1] FDA summary review,[15] Health Canada reviewers' reports,[19-21] Health Canada reconsideration of the Notice of Non-compliance – withdrawal letter.[22]

Source: Study LIPO-010 Clinical Study Report (CSR),[3] Study CTR-1011 CSR,[35] Stanley et al. 2014[2]

3.2 Included Studies (Main Phase)

3.2.1 Description of Studies

LIPO-010[3] (N = 412) and CTR-1011[5] (N = 404) were similarly designed multi-centre, DB, placebo-controlled, phase 3 RCTs (Table 3). Both trials enrolled participants from US and Canada, although CTR-1011 additionally enrolled participants from Europe. In both studies, tesamorelin (2 mg/day) was compared (in a 2:1 ratio) against placebo. Each trial consisted of a 26-week main phase, followed by a 26-week extension phase (the extension phase of CTR-1011 was denoted CTR-1012) (0). Across both trials, randomization was conducted using an interactive voice response system (IVRS), and stratified by testosterone use and impaired glucose tolerance (IGT)/diabetes condition in LIPO-010, and by diabetes status in CTR-1011. In each trial, the primary efficacy outcome was the reduction in VAT at week 26.

The study by Stanley et al. 2014 (N = 54) was a single-centre, DB, placebo-controlled RCT (Table 3).[2] The study exclusively enrolled participants from the US. Eligible participants underwent two independent randomization processes: a DB 1:1 randomization to tesamorelin (2 mg/day) versus placebo; and a 1:1 randomization to undergo hyperinsulinemic euglycemic clamp in addition to other study procedures (no details provided). The authors did not provide details about the randomization process, although they indicated that it was stratified by sex and, for men, by physiologic testosterone use. The trial was initially designed to evaluate the reduction in VAT at six months as the primary end point; however, prior to trial initiation, the study investigators added hepatic fat as a co-primary end point.

3.2.2 Populations

a) Inclusion and exclusion criteria

The inclusion criteria across all three trials were similar. In particular, all trials enrolled participants who were aged 18 to 65 years, HIV-positive, on a stable ART regimen, and had objective evidence of abdominal fat accumulation as follows: waist circumference ≥ 95 cm and waist-to-hip ratio ≥ 0.94 for males, and waist circumference ≥ 94 cm and waist-to-hip ratio ≥ 0.88 for females (Table 3).[2,3,5] In LIPO-010 and CTR-1011, participants were also required to have a CD4 cell count > 100 cells/mm^3 and viral load < 10,000 copies/mL,[3,5] neither of which were listed in Stanley et al. 2014, although the latter trial excluded participants with CD4 cell count < 200/mL.[2]

All three trials excluded participants who used growth hormone (GH) or GRF within six months prior to randomization, and participants who were receiving antidiabetic agents, specifically oral hypoglycemic or insulin sensitizing agents in LIPO-010 and CTR-1011.[2,3,5] Unlike the other trials, LIPO-010 also excluded participants with type 1 diabetes, as well as those with type 2 diabetes who were treated with insulin except during pregnancy and not required after delivery.[3] The clinical expert consulted by CDR for the purpose of this review indicated that tesamorelin may result in glucose intolerance, hence the reason that individuals with diabetes were excluded from LIPO-010. All three trials also excluded participants who met or exceeded certain levels of fasting blood glucose, aspartate transaminase, hemoglobin, and serum creatinine, although the specific thresholds varied slightly across the studies. Last, unlike the trial by Stanley et al. 2014, LIPO-010 and CTR-1011 excluded participants with untreated hypertension, a history of malignancy or active neoplasm, and recent opportunistic infections, as well as those with a body mass index (BMI) ≤ 20 kg/m^2.[3,5] Tesamorelin increases serum insulin-like growth factor-1 (IGF-1) levels, which, according to the clinical expert, may be associated with the development or worsening of some cancers, hence explaining the exclusion of individuals with active malignancies.

b) Baseline characteristics

Across all three studies, study participants were predominantly male and white/Caucasian (Table 4). The mean age of participants in LIPO-010 and CTR-1011 was approximately 47 years. Baseline demographic and anthropometric measurements of participants in LIPO-010 and CTR-1011 were generally well-balanced; one exception is that participants in Stanley et al. 2014 appeared to have the greatest mean levels of VAT at baseline, followed by those in CTR-1011, then those in LIPO-010. The clinical expert consulted by CDR for the purpose of this review hypothesized that the differences may be due to enrollment of participants from centres with more PI use or the studies may date to a time when there was a longer mean time of PI use, leading to more lipohypertrophy. The expert noted that the baseline VAT levels might "mean little" with respect to effects on treatment response.

In LIPO-010, participants assigned to the tesamorelin group appeared to have been receiving ART for approximately six months longer (on average) than those assigned to placebo, although the effects on study results would be inconsequential per the clinical expert. Across the three trials, there appeared to be some imbalances in the type of current ART regimens that participants were receiving. In LIPO-010, for instance, a smaller percentage of participants receiving tesamorelin reported taking an ART regimen that included a PI than those receiving placebo (55% versus 64%). Moreover, unlike in LIPO-010 and CTR-1011, fewer than half of participants in Stanley et al. 2014 were on a PI. Across all trials, more than 90% of participants reported taking a nucleoside reverse transcriptase inhibitor (NRTI); the expert noted that this trend is consistent with the standard of ART everywhere. In CTR-1011, the mean duration of PI in both treatment arms was approximately three years, although the degree to which this affects severity of the lipohypertrophy or treatment response is unclear. Last, in LIPO-010 and CTR-1011, all participants suffered from abdominal lipohypertrophy, while more than half also suffered from general lipoatrophy; the expert did not think that the presence or absence of lipoatrophy would affect treatment response. Overall, the expert noted that any observed inequities among and between trials were minor and unlikely to substantially affect treatment response.

TABLE 4: SUMMARY OF BASELINE CHARACTERISTICS (MAIN PHASE)

Characteristic	LIPO-010		CTR-1011		Stanley et al. 2014	
	Tesamorelin (N = 273)	Placebo (N = 137)	Tesamorelin (N = 270)	Placebo (N = 126)	Tesamorelin (N = 28)	Placebo (N = 22)
Mean (SD) age (y)	47.3 (7.3)	48.3 (7.49)	47.7 (7.48)	47.7 (7.70)	NR (median = 49)	NR (median = 53)
Number of males (%)	237 (86.8)	115 (83.9)	228 (84.4)	105 (83.3)	24 (85.7)	18 (81.8)
Mean (SD) weight (kg)	89.6 (14.1)	90.0 (13.7)	89.0 (13.6)	87.1 (15.6)	NR	
Mean (SD) BMI (kg/m^2)	29.2 (4.17)	29.2 (4.24)	28.8 (4.26)	28.7 (4.22)	NR	
Mean (SD) VAT (cm^2)	178.3 (76.9)	171.0 (76.9)	186.5 (86.6)	194.9 (95.5)	208 (98)	237 (127)
Mean (SD) waist circumference (cm)	104 (9.54)	105 (9.49)	105 (9.03)	104 (9.08)	NR	
Mean (SD) duration of ART (months)	56.5 (37.14)	48.2 (31.36)	52.9 (36.5)	52.8 (36.2)	NR	
Current ART regimen, n (%)						
PI	150 (55.1)	88 (64.2)	159 (58.9)	70 (55.6)	11 (39.3)	10 (45.5)
NRTI	266 (97.8)	134 (97.8)	244 (90.4)	111 (88.1)	28 (100)	21 (95.5)
NNRTI	146 (53.7)	57 (41.6)	107 (39.6)	45 (35.7)	14 (50.0)	15 (68.2)
Entry inhibitor	10 (3.7)	6 (4.4)	51 (18.9)	23 (18.3)	7 (25.0)	6 (27.3)
Integrase inhibitor	NR		8 (3.0)	2 (1.6)		
Mean (SD) PI duration (days)	NR		1206 (815)	1,314 (994)	NR	
Mean (SD) time since initial diagnosis of lipodystrophy syndrome (months)	50.3 (39.6)	50.6 (40.0)	65.3 (43.3)	69.7 (42.6)	NR	
Lipodystrophy syndrome, n (%)						
Facial lipoatrophy	141 (51.6)	70 (51.1)	123 (45.6)	56 (44.4)	NR	
Lower limbs lipoatrophy	165 (60.4)	81 (59.1)	148 (54.8)	72 (57.1)		
Upper limbs lipoatrophy	140 (51.3)	58 (42.3)	117 (43.3)	57 (45.2)		
General lipoatrophy[a]	198 (72.5)	99 (72.3)	181 (67.0)	83 (65.9)		
Buffalo hump	116 (42.5)	63 (46.0)	93 (34.4)	44 (34.9)		
Abdominal lipohypertrophy	273 (100)	137 (100)	270 (100)	126 (100)		
Breast enlargement	111 (40.7)	60 (43.8)	105 (38.9)	39 (31.0)		
Lipid metabolism disorders	157 (57.5)	78 (56.9)	NR	NR		
Glucose metabolism disorders	23 (8.4)	9 (6.6)	NR	NR		
Other	7 (2.6)	2 (1.5)	16 (5.9)	15 (11.9)		

ART = antiretroviral therapy; BMI = body mass index; NNRTI = non-nucleoside reverse transcriptase inhibitor; NR = not reported; NRTI = nucleoside reverse transcriptase inhibitory; PI = protease inhibitor; SD = standard deviation; VAT = visceral adipose tissue.

Note: Intention-to-treat population, unless otherwise stated.

[a] Defined as presenting at least one sign among facial, lower limbs or upper limbs lipoatrophy.

Source: Study LIPO-010 Clinical Study Report (CSR),[3] FDA medical review,[18] Study CTR-1011 CSR,[5] Stanley et al. 2014.[2]

3.2.3 Interventions

Across all three trials, tesamorelin 2 mg was compared against placebo. In LIPO-010 and CTR-1011, tesamorelin was administered in 2 mL volumes, and by subcutaneous injection in the abdomen.[3,5] The injections were self-administered, although there were no details provided about the degree to which participants were trained, or whether individuals who could not self-administer were screened out. Blinding was maintaining by using placebo that was identical in appearance to tesamorelin. Stanley et al. 2014 did not provide details about the treatment and blinding procedures, except that the study was DB.[2] In that study, additionally, the authors indicated that participants receiving tesamorelin or placebo were independently randomized to undergo a hyperinsulinemic euglycemic clamp. Specifically, these participants received (following a 12-hour fast) regular insulin (400 mU × m^2 × min^{-1}) for two minutes, after which (for 118 minutes) they received a continuous infusion of 80 mU × m^2 × min^{-1} regular insulin.[2] The authors indicated that an infusion of 20% dextrose was adjusted to maintain plasma glucose concentration at 11 mmol/L (90 mg/dL). The consulting clinical expert noted that this procedure is a "research intervention and unavailable and unused in clinical medicine."

3.2.4 Outcomes

a) Efficacy

In LIPO-010[3] and CTR-1011,[5] the primary efficacy outcome was the per cent change in VAT from baseline to week 26. VAT was assessed by a CT scan from a single 5 mm slice obtained at the level of the L4-L5 intervertebral disc space.

Across both trials, relevant secondary efficacy outcomes included patient-reported outcomes (PROs) related to body image, which was assessed using the PHASE V Outcomes Information System (OIS) by Phase V Technologies Inc. (0). The instrument consists of three scales that evaluate perceived body size, body appearance distress, and body profile with respect to seven areas of the body. This review focused on the results of the three body image parameters as they related to the belly only, and body profile as reported by participants only.

1. Belly size evaluation

Participants evaluated their current appearance (size of their belly) compared with their "healthy" look. Scores ranged from –100 (smaller size) to 100 (larger size), where 0 represented a "healthy look." Positive change scores suggest improvements, while negative change scores suggest worsening when compared with baseline.

2. Belly appearance distress

Participants evaluating their degree of distress associated with their current appearance. Scores ranged from 0 (extremely upsetting) to 100 (extremely encouraging), where 50 represented a neutral feeling. Positive change scores indicate patient improvement toward "encouragement" compared with baseline.

3. Belly profile evaluation

Participants answered three questions based on six body profile silhouettes, with scores ranging from 0 to 5, where 0 represented "normal" and 5 represented the most dysmorphic silhouettes.

The manufacturer reports having derived minimal important differences (MIDs) for the above scales from the Phase V OIS reference database, and states that they were "based on the lower and upper bounds of the 95% confidence interval (CI) of the change from baseline scores in patient current belly profile assessment, belly size evaluation, and belly appearance distress, between active and placebo-control subjects participating in lipodystrophy studies."[3] However, it does not provide details about the

specific studies to which it referred. It reports the critical values for the MID to be –7.118 (belly size), 4.458 (belly appearance), and –0.628 (profile). The manufacturer also states that "the MID interval derived from Phase V's external database could not be confirmed in the clinical database," although what this meant was unclear.

There were also several other efficacy outcomes measured in both trials, of which two outcomes relevant to this review included waist circumference and QoL. The QoL instrument comprised five scales, including the perceived health scale, the appearance-specific symptom interference scale, the symptoms and side effects distress scale, the Mental and Emotional Health scale, and the General Health Perceptions scale (0). Scores on these scales were used to create three summary scales; the one that this review focused on was the overall (item-wise) score — the mean of all items in the Mental and Emotional Health scale and all items of the General Health Perceptions scale. Limited information regarding the interpretation of scores and no information about the psychometric properties of the instrument were reported by the manufacturer. Investigators of CTR-1011 also administered the EQ-5D instrument, a generic measure of health-related quality of life (HRQoL) (0).

In Stanley et al. 2014, the co-primary efficacy outcomes were changes in VAT (measuring using a single-slice CT at L4) and liver fat.[2] As liver fat was not an outcome of interest for this review, its results will not be presented in this report. No other relevant efficacy outcomes were collected in this trial.

b) Harms

All three trials collected safety data, including the occurrence of adverse events (AEs), serious adverse events (SAEs), withdrawals due to adverse events (WDAEs), and notable harms.

3.2.5 Statistical Analysis

In LIPO-010 and CTR-1011, the sample size was based on a difference of 8% in the change in VAT at week 26 between tesamorelin and placebo, a standard deviation (SD) of 18.5%, power of 90%, significance level of 5%, and a distribution ratio of 2:1.[3,5] Dropout rates of 33% and 25% were assumed in LIPO-010 and CTR-1011, respectively; no rationale for the different expected dropout rates was provided. The threshold of 8% was considered to be the minimum difference needed to detect a clinically relevant difference between tesamorelin and placebo. The manufacturer notes that this difference was recommended (for LIPO-010) and confirmed (for CTR-1011) at a post–phase 2 meeting with the FDA.[3] The choice of this cut-off is discussed further in section 0. Given the abovementioned assumptions, the required total sample sizes were 381 (254 tesamorelin, 127 placebo) and 340 in LIPO-010 and CTR-1011, respectively.[3,5]

Across both trials, the primary efficacy outcome was the per cent change in VAT from baseline to week 26 in the intention-to-treat (ITT) population; missing data were imputed using the last observation carried forward (LOCF) method, whereby baseline values were carried forward into the treatment period. A secondary analysis was conducted in the per-protocol (PP) population and featured an observed case method, in which all non-missing observations were used.

In LIPO-010, the treatment effect was tested using an analysis of covariance (ANCOVA) model that featured treatment (study group) as a fixed effect and baseline VAT as a covariate.[3] In CTR-1011, a similar ANCOVA model was used, except that it also included centre as a covariate.[5] Across both trials, several pre-specified supportive analyses for the primary efficacy outcome were conducted. In LIPO-010, relevant analyses included a baseline interaction analysis, which used the same ANCOVA model as above but with a baseline-by-treatment interaction term, as well as a covariate analysis that evaluated

the impact of the type of ART regimen followed by participants during the study. Specifically, the per cent change in VAT at week 26 was examined by several categories of ART regimen — NRTI/non-nucleoside reverse transcriptase inhibitor (NNRTI), NRTI/PI, NRTI/NNRTI-PI, NRTIs alone, and other — and the statistical significance of the ART regimen and treatment-by-ART regimen interaction were tested. The authors also appeared to conduct a post-hoc analysis examining the effects of NNRTI and the NNRTI-by-treatment interaction in a separate model after noting a statistically significant difference in the percentage of participants between the two treatment groups whose ART regimen included an NNRTI. In CTR-1011, an analysis examining the effect of any changes in ART was planned, although because most (87%) participants did not have any changes in their ART throughout the study, this analysis was not performed. Instead, an exploratory analysis evaluating the impact of the type of ART regimen followed during the study was conducted in a similar manner as in LIPO-010.

As with the primary efficacy outcome, analyses for secondary and other efficacy outcomes were primarily conducted on the ITT population using LOCF analysis, and secondarily on the PP population using observed case analysis.[3,5] To evaluate waist circumference in LIPO-010 and CTR-1011, an ANCOVA model adjusted for baseline waist circumference and treatment was used. Across both trials, the pre-specified statistical analysis plan for HRQoL and body image parameters indicated a parametric ANCOVA to analyze belly size evaluation and belly appearance distress, and a Mann-Whitney test for belly profile evaluation. Discussions between the manufacturer and the FDA, however, resulted in changes in the plan, with which the FDA agreed.[18] In particular, both groups decided that for any ongoing phase 3 studies, (1) non-parametric (ranked) ANCOVAs for all three body image parameters could be the primary analyses; and (2) parametric ANCOVAs (belly appearance distress and belly size evaluation) and the Mann-Whitney test (belly profile evaluation) must be supportive analyses. Conversely, for the completed phase 3 study: (1) parametric ANCOVAs (belly appearance distress and belly size evaluation) and the Mann-Whitney test (body profile evaluation) must be the primary analyses for the first six months; and (2) non-parametric (ranked) ANCOVAs for all three body image parameters should be supportive analyses for the first six months.[18] At the time of these discussions, the main phase of LIPO-010 had been completed, while CTR-1011 was ongoing. Given the bidirectional responses for body size evaluation, the non-parametric ANCOVA was performed on the change score calculated as the negative value of (absolute [end point] – absolute [baseline]), which yielded positive scores for participants moving toward improvement, negative scores for those moving toward worsening, and 0 for those who stayed the same distance from normal. The manufacturer highlighted that the change scores presented per the parametric ANCOVA models should be considered with caution as they did not take into consideration the direction of the change. Across LIPO-010 and CTR-1011, the manufacturer also conducted two "supportive" analyses for the body image parameters: an MID analysis and a responder analysis, the latter of which was "an anchor-based method based on each subject's judgment of the smallest amount of improvement in belly profile that he/she would find to be beneficial (the 'minimally important benefit') in the profile analysis."[3] Values of the thresholds used to define responders are presented in Table 5.

TABLE 5: RESPONDER THRESHOLDS IN LIPO-010 AND CTR-1011

Body Image parameter	Study	
	LIPO-010	CTR-1011
Belly profile	–2.2685	2.328
Belly size	–32.099	13.756
Belly appearance distress	18.994	17.807

Source: Study LIPO-010 Clinical Study Report (CSR),[3] Study CTR-1011 CSR.[5]

In CTR-1011, treatment effects on the EQ-5D utility and visual analogue scale (VAS) scores were tested using linear mixed models that featured treatment and study visits time-point as fixed effects, and participant as random effects. Further, baseline EQ-5D utility and VAS scores, age, and gender were included in the model as covariates, and retained if significant. No details about the manner in which missing data were handled were provided.

Discussions with the FDA and the manufacturer also resulted in the creation of a "gatekeeper" strategy for the secondary efficacy outcomes to control the type 1 error in LIPO-010 and CTR-1011 (Table 6).[18]

TABLE 6: GATEKEEPER STRATEGY FOR LIPO-010 AND CTR-1011

End Point	Ranking		
	LIPO-010	CTR-1011	
		Primary	Supportive
Belly appearance distress	1	1	1
Triglycerides	2	1	NR
Total cholesterol: HDL-C ratio	3	2	2
Non–HDL-C	Not ranked	Not ranked	Supportive

HDL-C = high-density lipoprotein cholesterol.
Source: FDA medical review.[18]

Rankings of the secondary efficacy outcomes in the gatekeeper strategy were modified between studies, based on requests from the FDA, thus explaining the differences in Table 6. Across both trials, the outcomes in the gatekeeper strategy were considered for analyses only if the primary efficacy outcome and the preceding secondary efficacy outcomes were found to be statistically significant. All statistical tests were two-sided, with alpha pre-specified at 0.05, and interactions were tested at alpha pre-specified at 0.10.

The study by Stanley et al. 2014 was planned to enrol 60 participants, with 48 individuals estimated to complete the study; this calculation assumed 80% power to detect a treatment effect of 16.5% change in VAT.[2] The authors did not provide a rationale for the anticipated treatment effect. However, they did indicate that study recruitment terminated prematurely as a result of drug supply issues, resulting in 43 participants completing the study. Post-hoc power calculations revealed that, with 43 participants and new data (regarding the SD of change in VAT) from a pooled analysis of LIPO-010 and CTR-1011, the study had 85% power to detect a treatment difference of 38.5 cm^2 in the change in VAT at a two-sided alpha level of 0.05. The co-primary end points of this study were change in VAT and hepatic fat at six months. Between-group treatment effect (related to the change in VAT) was evaluated using the Student t-test. Primary analyses were conducted using all available data, with missing data treated as missing. Sensitivity analyses, which featured an imputation method, were used to corroborate results

from the primary analyses; specifically, for variables that were normally distributed, which was the case for the change in VAT, missing values were replaced with imputed values that were generated using longitudinal mixed-effects modelling. All analyses were two-sided, with alpha pre-specified at 0.05.

c) Analysis populations

In LIPO-010 and CTR-1011, the safety and ITT analysis populations were defined as randomized participants who received at least one dose of the study treatment; participants in the safety set, however, were analyzed according to the treatment they received, while those in the ITT set were analyzed according to the treatment to which they were randomized. The PP population consisted of participants in the safety population with no major protocol violations, and who had at least one post baseline assessment for the primary efficacy variable. Stanley et al. 2014 indicated using a modified ITT population (as described by the authors) among participants with available baseline and six-month follow-up data.

3.3 Participant Disposition (Main Phase)

In LIPO-010, of 570 individuals who were screened for inclusion, 158 failed screening, but no reasons for failure were provided (Table 7). A total of 412 participants were randomized, although two individuals did not receive any medications. A greater percentage of participants receiving tesamorelin (22.7%) discontinued the study than those receiving placebo (16.1%). In this study, the most common reason for withdrawal was an AE, with a greater percentage of participants receiving tesamorelin discontinuing due to this reason versus placebo (9.5% versus 2.9%). In CTR-1011, 599 individuals were screened for inclusion, of whom 195 failed screening, mostly due to not meeting the inclusion criteria (Table 7). A total of 404 participants were randomized to receive tesamorelin (N = 275) or placebo (N = 129). More than 25% of participants in each treatment arm discontinued the study, with no apparent differences between treatment arms and the two most common reasons being AEs and consent withdrawal. In the study by Stanley et al. 2014, of 76 individuals who were screened, 54 were randomized to receive tesamorelin (N = 28) or placebo (N = 26) (Table 7). Further, 13 and 11 participants receiving tesamorelin and placebo, respectively, were randomized to undergo the hyperinsulinemic euglycemic clamp. As with LIPO-010, a greater percentage of participants receiving tesamorelin (17.9%) discontinued this study versus placebo (7.7%).

TABLE 7: PARTICIPANT DISPOSITION (MAIN PHASE)

	LIPO-010		CTR-1011		Stanley et al. 2014	
	Tesamorelin	Placebo	Tesamorelin	Placebo	Tesamorelin	Placebo
Screened, N	570		599		76	
Screen failures, N (%)	158 (27.7)		195 (32.6)		22 (28.9)	
Did not meet inclusion/exclusion criteria, n (%)	NR		137 (70.3)		11 (50.0)	
Adverse event, n (%)			0		0	
Withdrew consent, n (%)			25 (12.8)		0	
Other, n (%)			32 (16.4)		0	
Missing, n (%)			1 (0.5)		0	
Declined participation, n (%)			0		8 (36.4)	
Lost to follow-up, n (%)			0		3 (13.6)	
Randomized, N	275	137	275	129	28 (13 randomized to receive clamp)	26[a] (11 randomized to receive clamp)
Discontinued study (primary reasons below), N (%)	62 (22.7)	22 (16.1)	68 (25.2)	34 (27.0)	5 (17.9)	2 (7.7)
Adverse event, n (%)	26 (9.5)	4 (2.9)	26 (9.5)	12 (9.3)	3 (10.7)	1 (3.8)
Consent withdrawal, n (%)	19 (6.9)	12 (8.8)	24 (8.7)	7 (5.4)	0	0
Lack of compliance, n (%)	8 (2.9)	0	5 (1.8)	1 (0.8)	0	0
Lost to follow-up, n (%)	7 (2.5)	2 (1.5)	5 (1.8)	7 (5.4)	0	0
Administrative problem, n (%)	1 (0.4)	2 (1.5)	0	0	0	0
Unknown, n (%)	1 (0.4)	0	0	0	0	0
Abnormal lab value, n (%)	0	2 (1.5)	0	0	0	0
Other, n (%)	0	0	8 (2.9)	7 (5.4)	2 (7.1)	1 (3.8)
ITT, N (modified ITT for Stanley et al. 2014)	273	137	270	126	23	20
PP, N	208	105	194	92	NR	
Safety, N	273	137	270	126		

ITT = intention-to-treat; PP = per-protocol; NR = not reported.

Note: Percentages for discontinuations based on the number of participants randomized.

[a] Four participants were excluded after randomization to placebo: 3 declined participation prior to the baseline visit and 1 developed an exclusionary pre-condition.

Source: Study LIPO-010 Clinical Study Report,[3] Study CTR-1011 CSR[5], Stanley et al. 2014.[2]

3.4 Exposure to Study Treatments (Main Phase)

In LIPO-010 and CTR-1011, overall treatment compliance was better than 80% in the majority of study participants. No relevant details were provided for Stanley et al. 2014.

3.5. Critical Appraisal (Main Phase)

3.5.1 Internal Validity

All three trials were DB and placebo-controlled; LIPO-010 and CTR-1011 featured appropriate randomization and allocation concealment processes, while the study by Stanley et al. 2014 did not present relevant methodological details, thus precluding an assessment of the associated risk of bias, and leaving uncertain the validity of the results. In LIPO-010 and CTR-1011, the CT scans (for VAT) were centrally reviewed and analyzed in a blinded fashion, although no details were provided about the number of individuals who examined the images, as well as any training or calibration procedures they underwent; the uncertainty regarding the reproducibility of the findings might undermine the confidence in the results. The authors of Stanley et al. 2014 did not provide information about the manner in which the CT scans were reviewed, although they indicated that, for the measurement of VAT, previous research demonstrates that single-slice CT has an estimated correlation between repeat measurements of 0.99, with errors in precision estimated at 3.9%.[5] If true, these values increase the confidence in the effects of tesamorelin on VAT.

Baseline characteristics were generally similar across treatment groups in all trials, with few differences. For instance, mean VAT levels were different across the three trials; however, discussions with the clinical expert suggested that these could be due to variations in clinical management of patients arising from temporal and/or geographical differences between the studies. Furthermore, compared with participants in CTR-1011, a smaller percentage of participants in LIPO-010 had undetectable viral loads, thus indicating that they were less healthy. It is plausible that treatment effects are artificially magnified in a less healthy population, thus making the treatment appear to be better than reality. Overall, the clinical expert consulted by CDR for the purpose of this review noted that any observed inequities between trials were minor and unlikely to substantially affect treatment response.

Both LIPO-010 and CTR-1011 used an ANCOVA model to evaluate the primary efficacy outcome; i.e., the per cent change in VAT between tesamorelin and placebo. The model included treatment as a fixed effect and baseline VAT as a covariate; in CTR-1011, an additional covariate (centre) was included in the model, although no rationale was provided. The results pertaining to this outcome presented in this report were extracted from the FDA statistical review, which appeared to generate the results (for both studies) using an ANCOVA model with treatment as fixed effect and baseline VAT as covariate. It was unclear why the FDA statistical review did not include centre as a covariate in the CTR-1011 analyses, although the results were consistent with those presented by the manufacturer.

LIPO-010 and CTR-1011 did not use a true ITT population; rather than including all randomized participants, the defined ITT analysis sets across both studies included only those participants who took at least one dose of the assigned study drug; i.e., a modified ITT population. Not adhering to the true ITT principle threatens the prognostic balance that a successful randomization process creates, thus leaving uncertain the validity of the results. Nevertheless, examining the participant disposition (Table 7) suggests that relatively few participants who were randomized did not contribute to the ITT analysis set: in LIPO-010, two participants (0.73%) in the tesamorelin group, and none in the placebo group; in CTR-1011, five participants (1.82%) in the tesamorelin group, and three participants (2.3%) in the placebo group. Missing data were imputed using the LOCF method, whereby baseline values were carried forward into the treatment period. However, carrying the last observation forward may have artificially

stabilized VAT levels among participants who dropped out; conversely, observed data could also be biased if the probability of withdrawal is related to an increase in VAT levels. Although the number of participants for whom data were imputed was unclear in both trials, there did appear to be a large difference in the number of individuals contributing to the ITT versus PP analysis sets, which possibly suggests a substantive amount of imputation, and ultimately may limit the validity of the results (Table 7). Further, in CTR-1011, it was unclear how missing data were handled for the analysis of EQ-5D data, which was analyzed using a linear mixed model, and for which as much as 35% of participants did not contribute to the analysis — missing such a substantive portion of the trial sample leaves uncertain the robustness of the results, and increases the uncertainty of the magnitude of the treatment effects on EQ-5D. The study by Stanley et al. 2014 indicated using a modified ITT population among participants with available baseline and six-month follow-up data. Excluding participants from analyses may not preserve the integrity of randomization, especially if the percentage of exclusions is large, thus limiting the validity of the results. In Stanley et al. 2014, five participants (17.9%) randomized to tesamorelin, and six participants randomized to placebo (23.1%) did not contribute to the primary analysis. The authors of the study imputed data for participants with missing observations, and found the results to be consistent with the analysis of available data. Still, the authors did not account for four of the 26 participants (15.4%) who were excluded after randomization to placebo, of whom three declined participation prior to the baseline visit, and one developed an exclusionary pre-condition. Not accounting for these participants might mean that, unlike the randomized set of participants, the analyzed set is no longer prognostically balanced, which could undermine confidence in the results.

In LIPO-010 and Stanley et al. 2014, the rates of discontinuation appeared to be disproportional across the treatment groups, with more participants in the tesamorelin arm discontinuing from the study than those receiving placebo. As above, these imbalances might have disrupted the prognostic balance that successful randomization creates, thus leaving uncertain the validity of the results. Further, across both studies, the most common reason for withdrawal was AE. Due to the unique AEs associated with tesamorelin — e.g., injection-site reactions, arthralgia, and myalgia — participants may have been inadvertently unblinded, which itself could have affected their behaviour in the trials, and consequently impacted their responses to subjective outcomes, such as QoL.

LIPO-010 and CTR-1011 were powered based on a difference of 8% in the change in VAT at week 26 between tesamorelin and placebo, while the study by Stanley et al. 2014 was based on an estimated difference of 16.5%. The cut-off of 8% appears to have been derived from the 2004 Forum for Collaborative HIV Research, which, according to the manufacturer, established an "expected decline" of 8% in VAT for patients with HIV-associated lipodystrophy receiving an rhGH product in clinical trials of up to 26 weeks in duration.[18] A Scientific Advisory Panel convened by Health Canada acknowledged that an 8% decrease in VAT is a clinically important short-term effect, although Health Canada noted that the cut-off was "largely arbitrary," and "reportedly a 'hybrid' end point derived from the VAT loss seen in a previous [phase] 2 study of the rhGH product and the 5% *total weight loss* target the FDA has adopted for development of drugs for treating obesity."[21] The authors of Stanley et al. 2014 did not provide a rationale for estimating a treatment effect of 16.5%. Although all studies were adequately powered to evaluate the primary efficacy outcome, none of the trials were powered to assess secondary efficacy outcomes or for harms outcomes.

In LIPO-010 and CTR-1011, to help contextualize changes in body image, the manufacturer reports having derived an MID for each of the three parameters from previous lipodystrophy studies. However, it does not provide details about the specific studies to which it referred, thus leaving uncertain the validity of the chosen MID values, as well as the degree to which the results are clinically meaningful. It

also reports that the instrument used to measure body image was validated,[23] although the FDA had several concerns about this claim.[24] In particular, the FDA's Study Endpoint and Labeling Development (SEALD) team concluded that the instrument had "questionable content validity," and the team raised concerns about the instrument's ability to measure a clinically important treatment effect. The SEALD team specifically reported that the manufacturer did not address whether qualitative research was done to evaluate patient understanding of the final instrument. As a result, the instrument did not meet the standards for instrument development as recommended by the FDA, nor did it meet the standard for evidence saturation. The SEALD team also reported that internal consistency reliability data had limited relevance because single items were utilized as end points instead of summary scales. In addition, the team stated that the enrolment criteria in the trials did not pre-specify a minimum PRO score, which could have made it more difficult to demonstrate improvement. Further, with respect to the instrument used to measure QoL, the manufacturer provided only limited information regarding the interpretation of scores, and no information about the psychometric properties of the instrument, which leaves uncertain the validity of the results.

Across LIPO-010 and CTR-1011, several pre-specified supportive analyses were conducted, including testing for numerous covariate-by-treatment interactions, although no adjustments for multiple comparisons appear to have been made for these analyses. A further limitation is that, in CTR-1011, the manufacturer appeared to conduct a post-hoc analysis examining the NNRTI-by-treatment interaction; a post-hoc analysis decreases the credibility of the analyses and limits certainty in the results. Moreover, both trials used gatekeeping testing strategies that, per the manufacturer, were created for labelling purposes and to help control the experiment-wise type 1 error rate at a one-sided level of 0.05. This is a common and appropriate strategy to account for multiplicity. Only the changes in VAT and belly appearance distress were considered in the testing strategy, which limits the ability to interpret the analyses of outcomes outside the gatekeeping procedure. Without controlling for multiplicity, analyses of all outcomes other than change in VAT and belly appearance distress, as well as the subgroup analyses, should be considered hypothesis-generating and interpreted with caution. No adjustments for multiplicity were performed in Stanley et al. 2014, including for the co-primary end point, although the authors did not evaluate outcomes of interest other than change in VAT.

3.5.2 External Validity

Discussions with the clinical expert consulted by CDR for the purpose of this review highlighted that generalizability of the findings of the three trials is a major concern. Chiefly, the studies appear to have been conducted at a time when HIV patients were commonly receiving ART regimens that were associated with accumulation of visceral fat. The expert indicated that, in today's clinical practice, HIV patients are substantially different from those who were enrolled in the three studies, and are much more likely to receive ART regimens that consist of backbones other than PIs, including integrase strand transfer inhibitors (INSTIs) and NNRTIs. To this end, of the six regimens recommended by the US DHHS to manage ART-naive patients, five are INSTI-based, and one is ritonavir-boosted PI (PI/r)–based:[11]

INSTI-based regimens:

- Dolutegravir/abacavir/lamivudine (DTG/ABC/3TC)
- DTG plus tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC)
- Elvitegravir (EVG)/cobicistat (COBI)/tenofovir alafenamide (TAF)/FTC
- EVG/COBI/TDF/FTC
- Raltegravir (RAL) plus TDF/FTC.

PI/r-based regimen:

- Darunavir/ritonavir plus TDF/FTC.

In Canada, three of the abovementioned preferred regimens are available as single-tablet regimens (STRs): Genvoya (EVG/COBI/FTC/TAF), Stribild (EVG/COBI/FTC/TDF), and Triumeq (DTG/ABC/3TC). The three remaining preferred regimens are available as multi-tablet regimens consisting of a two-drug backbone; e.g., FTC/TDF (Truvada) plus a third drug. STRs are preferred to multi-tablet regimens given their convenience advantage, which results in greater adherence and optimal treatment response. There are two additional STRs available, both of which are NNRTI-based, although they are listed as "alternative" regimens by the DHHS: Atripla (efavirenz/TDF/FTC), and Complera (rilpivirine /TDF/FTC). In LIPO-010, the number of participants receiving ART regimens that comprised integrase inhibitors was not reported, whereas fewer than 5% of participants in CTR-1011 were receiving INSTI-based therapies. In Stanley et al. 2014, the number of participants on integrase inhibitors was unclear, as the authors reported that seven individuals in the tesamorelin group (25.0%) and six in the placebo group (27.3%) were receiving entry inhibitors and integrase inhibitors.

Moreover, as a result of the large number of treatments available today, single or multiple substitutions of the components of an ART regimen offer optimal virologic suppression with fewer AEs, such as the accumulation of visceral fat. The clinical expert consulted by CDR for the purpose of this review indicated that fewer than 5% of patients in his HIV practice are affected by serious fat deposition.

Further, although the manufacturer tested the statistical significance of treatment-by-ART regimen interactions in LIPO-010 and CTR-1011, the results may be limited by the fact that individual drugs within a class were grouped and analyzed together.

Examination of the inclusion and exclusion criteria of the included studies reveals additional factors that may limit the generalizability of the findings. First, the authors of Stanley et al. 2014 provided limited demographic information about the participants enrolled in their study, thus precluding an adequate assessment of the generalizability of the study findings to a Canadian population. With respect to LIPO-010 and CTR-1011, the exclusion of certain subgroups of participants — those with type 1 diabetes and type 2 diabetes in LIPO-010, and those treated with oral antidiabetic drugs or insulin LIPO-010 and CTR-1011 — leaves uncertain the effects of tesamorelin in patients with HIV-associated lipohypertrophy who present with certain comorbidities. Diabetes is particularly important given concerns raised by the FDA that more patients treated with tesamorelin developed glucose intolerance, and had a higher risk of developing diabetes across the clinical development program.[15]

Finally, the durations of all three trials were insufficient (even after considering the 26-week extension phases in LIPO-010 and CTR-1011) to adequately capture some important safety outcomes, including the occurrence of diabetes and cancer, thus leaving uncertain the long-term safety profile of tesamorelin.

3.6 Efficacy (Main Phase)

Only those efficacy outcomes identified in the review protocol are reported below (see Table 2). Results from the extension phases are reported in APPENDIX 6: SUMMARY OF EXTENSION PHASES OF LIPO-010 AND CTR-1011.

3.6.1 Visceral Adipose Tissue

Across all three trials, tesamorelin was associated with a statistically significantly greater reduction in VAT versus placebo (Table 8). Specifically, with respect to the per cent change in VAT at week 26, the LS mean differences (95% CI) of tesamorelin versus placebo were –19.6% (–23.7% to –15.3%) in LIPO-010, and –11.7% (–16.2% to –7.1%) in CTR-1011. In Stanley et al. 2014, the mean difference (95% CI) of the per cent change in VAT at six months was −16.6% (−30.6% to −2.6%).

TABLE 8: KEY EFFICACY OUTCOME — VISCERAL ADIPOSE TISSUE (MAIN PHASE)

Outcome	LIPO-010		CTR-1011		Stanley et al. 2014	
	Tesamorelin	Placebo	Tesamorelin	Placebo	Tesamorelin	Placebo
VAT (cm^2)						
Baseline, N	272	136	268	126	28	22
Baseline, mean (SD)	178.3 (76.9)	171.0 (76.9)	186.5 (86.6)	194.9 (95.5)	208 (98)	237 (127)
26 weeks, N	272	136	268	126	23	20
26 weeks, % change from baseline[a] (SE)	–17.8% (1.6)	2.2% (2.2)	–13.8% (1.5)	2.4% (2.2)	–9.9% (–19.7, –0.2)	6.6% (–4.1, 17.3)
26 weeks, LS mean difference[b] (95% CI), *P* value	**–19.6% (–23.7 to –15.3), *P* < 0.001**		**–11.7% (–16.2 to –7.1), *P* < 0.001**		**–16.6% (–30.6 to –2.6), *P* = NR**	
26 weeks, actual change from baseline, LS mean[c] (SE)	–27.4 (2.2)	4.4 (3.2)	–21.0 (2.4)	–0.4 (3.5)	–34 (–53, –15)	8 (–14, 30)
26 weeks, LS mean difference[b] (95% CI), *P* value	**–31.9 (–39.5 to –24.3), *P* < 0.001**		**–20.6 (–28.8 to –12.3), *P* < 0.001**		**–42 (–71 to –14), *P* = 0.005**	

CI = confidence interval; LS = least squares; NR = not reported; SD = standard deviation; SE = standard error; VAT = visceral adipose tissue.
Note: Statistically significant results are bolded.
[a] Variance is 95% CI (not SE) for Stanley et al. 2014.
[b] Results reported as mean difference instead of LS mean difference for Stanley et al. 2014.
[c] Results reported as mean (95% CI) instead of LS mean (SE) for Stanley et al. 2014.
Source: FDA statistical review,[1] Stanley et al. 2014.[2]

a) VAT by subgroups

Only the results of subgroups identified in the review protocol are reported below (see Table 2).

Waist circumference

Across the trials, no analyses were conducted to evaluate the impact of waist circumference on the primary efficacy outcome.

Baseline VAT

In LIPO-010, the investigators did not find a statistically significant treatment-by-baseline interaction with respect to the primary efficacy outcome (*P* = 0.251).[3] The impact of baseline VAT was not evaluated on the primary efficacy outcome in CTR-1011 and the study by Stanley et al. 2014.

Type of ART regimen

In LIPO-010, with respect to the primary efficacy outcome — i.e., the per cent change in VAT at week 26 — in one ANCOVA model, neither the NNRTI nor the NNRTI-by-treatment interaction were statistically significant (*P* = 0.711 and *P* = 0.392, respectively). In a separate ANCOVA model, neither the ART regimen nor the treatment-by-ART regimen interaction were statistically significant (*P* = 0.855 and *P* = 0.962, respectively).[3] In CTR-1011, neither the ART regimen nor the treatment-by-ART regimen interaction were statistically significant (*P* = 0.213 and *P* = 0.810, respectively) as they pertained to the primary efficacy outcome.[5]

3.6.2 Waist Circumference

In LIPO-010 and CTR-1011, tesamorelin was associated with a statistically significantly greater reduction in waist circumference at 26 weeks versus placebo (Table 9). Specifically, the absolute differences (95% CI) of tesamorelin versus placebo were –1.8 cm (–2.8 cm to –0.9 cm) in LIPO-010, and –1.3 cm (–2.4 cm to –0.2 cm) in CTR-1011. Waist circumference was not evaluated in Stanley et al. 2014.

TABLE 9: KEY EFFICACY OUTCOME — WAIST CIRCUMFERENCE (MAIN PHASE)

Outcome	LIPO-010 (main phase)		CTR-1011		Stanley et al. 2014	
	Tesamorelin	Placebo	Tesamorelin	Placebo	Tesamorelin	Placebo
Waist circumference (cm)						
Baseline, N	273	137	270	126	Not evaluated	
Baseline, mean (SD)	104 (9.54)	105 (9.49)	105 (9.03)	104 (9.08)		
26 weeks, N	273	137	270	126		
26 weeks, actual change from baseline, mean (SD)	–2.61 (4.91)	–0.80 (4.05)	–2.15 (5.41)	–0.82 (4.73)		
26 weeks, absolute difference (95% CI), *P* value	**–1.8 (–2.8 to –0.9), *P* < 0.001**		**–1.3 (–2.4 to –0.2), *P* = 0.02**			

CI = confidence interval; SD = standard deviation.
Note: Statistically significant results are bolded.
Source: LIPO-010 Clinical Study Report (CSR),[3] Falutz et al. 2007,[4] CTR-1011 CSR,[5] Falutz et al. 2010.[6]

3.6.3 Body Image

In LIPO-010 and CTR-1011, there were no statistically significant differences between treatment groups with respect to change in belly size evaluation at week 26 (Table 10). Across both trials, the effects of tesamorelin versus placebo on change in belly appearance distress at week 26 were inconsistent: per the parametric ANCOVA models, there were no statistically significant differences between treatment groups; conversely, per the ranked (non-parametric) ANCOVA models, tesamorelin was associated with a statistically significantly greater reduction in belly appearance distress at week 26 versus placebo. Further, with respect to belly profile ratings, tesamorelin was associated with a statistically significantly

greater reduction in belly dysmorphia versus placebo in LIPO-010 but not in CTR-1011. Body image was not evaluated in Stanley et al. 2014.

TABLE 10: KEY EFFICACY OUTCOME — BODY IMAGE (MAIN PHASE)

Outcome	LIPO-010 (Main Phase)		CTR-1011		Stanley et al. 2014	
	Tesamorelin	Placebo	Tesamorelin	Placebo	Tesamorelin	Placebo
Belly size evaluation						
Baseline, N	272	137	269	126	Not evaluated	
Baseline, mean (SD)	59.8 (47.7)	55.8 (52.0)	56.1 (54.2)	56.9 (57.2)		
Baseline, median (range)	75.0 (–100 to +100)	75.0 (–100 to +100)	75.0 (–100 to +100)	75.0 (–100 to +100)		
26 weeks, N	272	137	269	126		
26 weeks, actual change from baseline,[a] mean (SD)	14.6 (30.2)	13.1 (31.4)	14.8 (27.8)	11.7 (25.2)		
26 weeks, actual change from baseline,[a] median (range)	NR	NR	NR	NR		
26 weeks, mean difference (95% CI), *P* value	NR, *P* = 0.750,[b] *P* = 0.977[c]		NR, *P* = 0.211,[c] *P* = 0.155[b]			
Belly appearance distress						
Baseline, N	272	137	269	126	Not evaluated	
Baseline, mean (SD)	22.1 (22.23)	24.0 (25.68)	22.3 (24.19)	20.2 (22.07)		
Baseline, median (range)	12.5 (0 to 100)	12.5 (0 to 100)	12.5 (0 to 100)	12.5 (0 to 100)		
26 weeks, N	272	137	269	126		
26 weeks, actual change from baseline,[a] mean (SD)	11.6 (26.93)	6.2 (25.82)	8.4 (28.99)	5.2 (26.61)		
26 weeks, actual change from baseline,[a] median (range)	0 (-87.5 to +87.5)	0 (-87.5 to +100)	NR	NR		
26 weeks, mean difference (95% CI), *P* value	NR, *P* = 0.076,[b] ***P* = 0.028**[c]		NR, ***P* = 0.022,**[c] *P* = 0.083[b]			
Belly profile (patient-reported)						
Baseline, N	272	137	269	126	Not evaluated	
Baseline, mean (SD)	3.3 (1.3)	3.2 (1.5)	3.2 (1.36)	3.3 (1.19)		
Baseline, median (range)	3.0 (0 to 5.0)	3.0 (0 to 5.0)	NR	NR		
26 weeks, N	272	137	269	126		
26 weeks, actual change from	–0.7 (1.25)	–0.3 (1.25)	–0.5 (1.29)	–0.3 (1.03)		

Outcome	LIPO-010 (Main Phase)		CTR-1011		Stanley et al. 2014	
	Tesamorelin	Placebo	Tesamorelin	Placebo	Tesamorelin	Placebo
baseline,[d] mean (SD)						
26 weeks, actual change from baseline,[d] median (range)	0 (–5.0 to +4.0)	0 (–5.0 to +4.0)	NR	NR		
26 weeks, mean difference (95% CI), *P* value	NR, ***P* = 0.031**[e], ***P* = 0.042**[c]		NR, *P* = 0.075[c], *P* = 0.104[e]			

CI = confidence interval; NR = not reported; SD = standard deviation.
Note: Statistically significant results are bolded.
[a] Positive change from baseline indicates improvement.
[b] Parametric ANCOVA (primary analysis model in LIPO-010; supportive in CTR-1011).
[c] Ranked (non-parametric) ANCOVA (supportive analysis model in LIPO-0101; supportive in LIPO-010).
[d] Negative change from baseline indicates improvement; i.e., less dysmorphia.
[e] Mann-Whitney test.
Source: LIPO-010 Clinical Study Report (CSR),[3] CTR-1011 CSR.[5]

a) MID analysis

In LIPO-010, per the manufacturer, only the treatment differences in mean change score at week 26 for belly appearance distress exceeded the critical value for the corresponding MID. In CTR-1011, per the manufacturer, none of the between-group treatment differences exceeded the critical values for the MID for the three body image parameters.

Responder analysis

In LIPO-010, there were no statistically significant differences in the percentage of responders between the treatment groups with respect to changes in any of the three body image parameters. In CTR-1011, a statistically significantly greater percentage of participants in the tesamorelin group versus the placebo group met the responder criteria for changes in belly profile (8.2 versus 3.2%; *P* = 0.043) and belly appearance distress (25.7% versus 16.7%; *P* = 0.029), but not in belly size.

3.6.4 Quality of Life and Health-Related Quality of Life

In LIPO-010 and CTR-1011, there were no statistically significant differences between treatment groups with respect to the change in mean overall QoL scores (item-wise) at week 26 (Table 11). Further, in CTR-1011, there were no statistically significant differences between treatment groups with respect to EQ-5D index scores and VAS and health-state ratings at week 26. QoL was not evaluated in Stanley et al. 2014.

TABLE 11: KEY EFFICACY OUTCOME — QUALITY OF LIFE AND HEALTH-RELATED QUALITY OF LIFE (MAIN PHASE)

Outcome	LIPO-010 (Main Phase)		CTR-1011		Stanley et al. 2014	
	Tesamorelin	Placebo	Tesamorelin	Placebo	Tesamorelin	Placebo
Overall QoL (Item-Wise)						
Baseline, N	272	136	269	126	Not evaluated	
Baseline, mean (SD)	433.1 (73.08)	429.4 (79.48)	437.0 (77.72)	436.2 (83.96)		
26 weeks, N	NR	NR	NR	NR		
26 weeks, actual change from baseline, mean (SD)	1.731 (59.121)	0.038 (49.151)	–2.6 (53.67)	–11.3 (51.57)		
26 weeks, mean difference (95% CI), *P* value	NR, *P* = 0.638		NR, *P* = 0.118			
EQ-5D Index						
Baseline, N	Not evaluated		179	84	Not evaluated	
Baseline, mean (SD)			0.817 (0.18)	0.823 (0.15)		
26 weeks, N			NR	NR		
26 weeks, mean (SE)			0.819 (0.10)	0.819 (0.02)		
26 weeks, mean difference (95% CI), *P* value			NR, *P* = 1.000			
EQ-5D VAS/Health State						
Baseline, N	Not evaluated		187	88	Not evaluated	
Baseline, mean (SD)			68.50 (23.03)	65.26 (20.75)		
26 weeks, N			NR	NR		
26 weeks, mean (SE)			68.34 (1.43)	65.60 (2.08)		
26 weeks, mean difference (95% CI), *P* value			NR, *P* = 0.279			

CI = confidence interval; EQ-5D = EuroQol 5-Dimensions Questionnaire; HRQoL = health-related quality of life; NR = not reported; QoL = quality of life; SD = standard deviation; SE = standard error; VAS = visual analogue scale.
Source: LIPO-010 Clinical Study Report (CSR),[3] CTR-1011 CSR.[5]

3.7 Harms (Main Phase)

Only those harms identified in the review protocol are reported below (see Table 2). Results from the extension phases are reported in 0.

3.7.1 Adverse Events

Across all three studies, at least 70% of study participants in each trial experienced a treatment-emergent AE (Table 12). A greater percentage of participants in Stanley et al. 2014 experienced an AE (tesamorelin: 89.3%; placebo: 95.5%) than those in LIPO-010, followed by those in CTR-1011. Further, in LIPO-010 and CTR-1011, approximately 5% more participants receiving tesamorelin (LIPO-010: 82.8%; CTR-1011: 74.1%) experienced an AE than those on placebo (LIPO-010: 75.9%; CTR-1011: 69.8%).

3.7.2 Serious Adverse Events

Overall, a greater percentage of participants in Stanley et al. 2014 experienced an SAE (tesamorelin: 10.7%; placebo: 13.6%) than those in CTR-1011 (tesamorelin: 3.3%; placebo: 6.3%), followed by those in LIPO-010 (tesamorelin: 4.0%; placebo: 2.2%) (Table 12).

3.7.3 Withdrawals Due to Adverse Events

In LIPO-010 and Stanley et al. 2014, a greater percentage of participants receiving tesamorelin (9.5% in LIPO-010; 10.7% in Stanley et al. 2014) experienced AEs that led to early study discontinuation than those in the placebo group (2.9% in LIPO-010, 3.8% in Stanley et al. 2014) (Table 12). In CTR-1011, the percentage of participants who experienced AEs that led to early study discontinuation was similar between the tesamorelin (9.5%) and placebo (9.3%) groups.

3.7.4 Mortality

There were no deaths in LIPO-010 and Stanley et al. 2014. Two participants died in CTR-1011, one in each treatment group (Table 12).

3.7.5 Notable Harms

In LIPO-010 and CTR-1011, a greater percentage of participants receiving tesamorelin reported any injection-site condition (LIPO-010: 30.0% versus 24.1%; CTR-1011: 50.7% versus 21.4%), myalgia (LIPO-010: 7.7% versus 2.2%; CTR-1011: 3.7% versus 1.6%) than those in the placebo group (Table 12), or any fluid retention or edema (LIPO-010: 9.9% versus 5.8%; CTR-1011: 5.2% versus 0.8%). In Stanley et al. 2014, no participants receiving placebo experienced myalgia, while 10.8% of individuals in the tesamorelin group were affected. Further, in LIPO-010, one participant (0.4%) receiving tesamorelin (versus none receiving placebo) developed diabetes mellitus (recorded as a treatment-emergent AE). Moreover, in the same trial, a greater percentage of participants receiving tesamorelin versus placebo (2.9% versus 1.5%) developed a malignancy, whereas fewer participants receiving tesamorelin in CTR-1011 versus those receiving placebo (0.4% versus 3.2%) developed a malignancy.

TABLE 12: HARMS (MAIN PHASE)

	LIPO-010		CTR-1011		Stanley et al. 2014	
	Tesamorelin (N = 273)	Placebo (N = 137)	Tesamorelin (N = 270)	Placebo (N = 126)	Tesamorelin (N = 28)	Placebo (N = 22)
Participants with > 0 AEs, n (%)	226 (82.8)	104 (75.9)	200 (74.1)	88 (69.8)	25 (89.3)	21 (95.5)
Participants with > 0 SAEs, n (%)	11 (4.0)	3 (2.2)	9 (3.3)	8 (6.3)	3 (10.7)	3 (13.6)
Participants with AEs leading to study discontinuation,[a] n (%)	26 (9.5)	4 (2.9)	26 (9.5)	12 (9.3)	3 (10.7)	1 (3.8)
Number of deaths, n (%)	0	0	1 (0.4)	1 (0.8)	0	0
Notable harms						
Any injection-site condition[b]	82 (30.0)	33 (24.1)	137 (50.7)	27 (21.4)	17 (60.7)	13 (59.1)
Myalgia	21 (7.7)	3 (2.2)	10 (3.7)	2 (1.6)	3 (10.7)	0
Arthralgia	37 (13.6)	15 (10.9)	33 (12.2)	14 (11.1)	4 (14.3)	4 (18.2)
Any fluid retention/edema[b]	27 (9.9)	8 (5.8)	14 (5.2)	1 (0.8)	2 (7.1)	1 (4.5)
Diabetes mellitus	1 (0.4)	0	NR	NR	NR	NR
Any malignancy[b]	8 (2.9)	2 (1.5)	1 (0.4)	4 (3.2)	NR	NR

AE = adverse event; NR = not reported; SAE = serious adverse event.
Note: Safety population.
[a] In LIPO-010 and CTR-1011, this table presents the number of participants with an AE as the primary reason for study discontinuation.
[b] Across all 3 trials, the number of participants experiencing these notable harms in both treatment groups may be overestimated due to multiple counting of individual events.
Source: Study LIPO-010 Clinical Study Report (CSR),[3] Study CTR-1011 CSR,[5] Stanley et al. 2014.[2]

4. DISCUSSION

4.1 Summary of Available Evidence

The evidence for this review was drawn from three RCTs — LIPO-010 (N = 412), CTR-1011 (N = 404), and Stanley et al. 2014 (N = 54) — each of which compared tesamorelin 2 mg/day (subcutaneous injection) with placebo. LIPO-010 and CTR-1011 consisted of a 26-week main phase, followed by a 26-week extension phase. The study by Stanley et al. 2014 was six months in duration. The primary efficacy outcome for LIPO-010 and CTR-1011 was the per cent change in VAT at week 26, while the co-primary end points in Stanley et al. 2014 were the changes in VAT and hepatic fat at six months. Other relevant efficacy outcomes from LIPO-010 and CTR-1011 included body image, specifically belly size evaluation, belly appearance distress, and belly profile evaluation, waist circumference, and QoL. Investigators of CTR-1011 also administered the EQ-5D instrument. Relevant harms outcomes were mortality, AEs, SAEs, WDAEs, and notable harms, including injection-site reactions, myalgia, arthralgia, fluid retention or edema, diabetes, and malignancies. In all, the type of evidence from the three trials was congruent with patient expectations (0).

All three trials enrolled participants who were aged 18 to 65 years, HIV-positive, on stable ART regimen, and had objective evidence of abdominal fat accumulation as follows: waist circumference ≥ 95 cm and waist-to-hip ratio ≥ 0.94 for males, and waist circumference ≥ 94 cm and waist-to-hip ratio ≥ 0.88 for females. Some limitations were noted for the trials. First, discussions with the clinical expert consulted by CDR for the purpose of this review highlighted that the populations in all three trials were substantially different than those seen in routine clinical practice in Canada today. In particular, the studies appear to have been conducted at a time when HIV patients were commonly receiving ART regimens that were associated with accumulation of visceral fat. The expert indicated that today's HIV patients are much more likely to receive ART regimens consisting of backbones other than PIs, including INSTIs and NNRTIs. To this end, of the six regimens recommended by the US DHHS to manage ART-naive patients, five are INSTI-based and one is PI/r-based. In LIPO-010, the number of participants receiving ART regimens consisting of integrase inhibitors was not reported, whereas fewer than 5% of participants in CTR-1011 were receiving INSTI-based therapies. The number of participants on integrase inhibitors was unclear, as the authors reported that seven individuals in the tesamorelin group (25.0%) and six in the placebo group (27.3%) were receiving entry inhibitors and integrase inhibitors. Further, as a result of the large number of HIV treatments available today, single or multiple substitutions of the components of an ART regimen offer optimal virologic suppression with fewer AEs, such as the accumulation of visceral fat. In addition, the psychometric properties of the instruments used to evaluate body image and QoL in LIPO-010 and CTR-1011 are not clear, which leaves uncertain the degree to which the results are valid and clinically meaningful.

4.2 Interpretation of Results

4.2.1 Efficacy

Across all studies, tesamorelin was associated with a statistically significantly greater reduction in VAT versus placebo at week 26 (LIPO-010 and CTR-1011) or six months (Stanley et al. 2014). Both the FDA and Health Canada accepted that an 8% decrease in VAT was an appropriate measure of clinical benefit, although Health Canada noted that this cut-off is "arbitrary."[21] While tesamorelin consistently exceeded this magnitude of effect versus placebo in the main phases of the included trials, the degree to which these results are clinically meaningful is unclear. The FDA, for instance, concluded that tesamorelin is "clearly effective on modifying a biomarker but what the clinical benefit is with this degree of VAT reduction is uncertain."[15] In particular, while there is evidence suggesting that increased visceral fat is

associated with greater cardiometabolic risk,[18] the FDA indicated that the "link between VAT reduction and improved cardiovascular risk has not been established" in patients with HIV-associated lipodystrophy.[15] Health Canada also raised a question about the extent to which tesamorelin provides *added* benefit to a structured diet and exercise regimen, specifically noting that a "substantial" percentage of placebo-treated participants achieved a decrease of ≥ 8% of VAT at week 26 in the two manufacturer-conducted studies — 25.0% in LIPO-010 and 34.1% in CRR-1011 — even though neither trial included a specified diet and exercise regimen.[21] Nevertheless, a post-hoc pooled analysis of LIPO-010 and CTR-1011 suggested that tesamorelin responders experienced statistically significantly improved endocrine and metabolic changes, including triglyceride levels, adiponectin levels, and preservation of glucose homeostasis, as well as statistically significantly greater decreases in waist circumference and VAT over 52 weeks compared with non-responders.[25] However, this study is associated with several important limitations, including the post-hoc nature of the analyses and a failure to adjust for multiplicity, which necessitate caution when interpreting the results. Furthermore, the relevance of the aforementioned endocrine changes to hard clinical end points, such as cardiovascular events and death, is unknown.

Further, in LIPO-010 and CTR-1011, with respect to change in VAT at week 26, neither the ART regimen nor the treatment-by-ART regimen interaction were statistically significant in the analytical model, thus suggesting that type of ART regimen did not statistically significantly affect the results. However, these results may be limited by the fact that individual drugs within a class were grouped and analyzed together. Moreover, the clinical expert indicated that VAT (as measured by CT scan) is not routinely used to gauge treatment response, thus limiting the application of the VAT results to support clinical decision-making. Setting aside the utility of VAT, results from the 26-week extension phases of LIPO-010 and CTR-1011 demonstrated that participants who discontinued treatment with tesamorelin experienced increases in VAT to levels that were similar to those measured at baseline or even higher (0, Figure 2). Thus, in order to maintain any reductions in VAT that might appear in the short term, patients would have to require chronic treatment with tesamorelin.

Per the FDA, the manufacturer acknowledged the assessment of VAT through routine CT scans, and proposed monitoring treatment response based on changes in waist circumference.[15] In LIPO-010 and CTR-1011, tesamorelin was associated with a statistically significantly greater reduction in waist circumference versus placebo at week 26. Health Canada noted that a 1 cm reduction in waist circumference "should be considered as the minimal acceptable decrease for a satisfactory response" following six months of treatment with tesamorelin.[26] Across both studies, the magnitude of the treatment effect exceeded the threshold of 1 cm, specifically an absolute difference of 1.8 cm in LIPO-010 and 1.3 cm in CTR-1011. However, discussions with the clinical expert suggested that these differences are unlikely to be clinically meaningful, especially when considering the baseline waist circumferences, as well as how relatively little they decreased in each treatment group. The expert elaborated that the effects on waist circumference will "likely change little in terms of appearances or how people feel about themselves."

The clinical expert also emphasized that changes to body image and QoL are the primary factors in guiding the management of patients with HIV-associated lipohypertrophy; feedback from patients appears to indicate that they, too, prioritize improvements to these parameters over other clinical benefits (0). Both LIPO-010 and CTR-1011 collected several PROs related to body image, including belly size evaluation, belly appearance distress, and belly profile evaluation. The FDA considered belly appearance distress a "consequential component" of the PRO evaluation, and required the manufacturer to show a positive effect on this parameter to support the primary efficacy outcome.

Across both trials, the effects of tesamorelin versus placebo on change in belly appearance distress at week 26 were inconsistent: specifically, per the parametric ANCOVA models, there were no statistically significant differences between treatment groups; conversely, per the ranked (non-parametric) ANCOVA models, tesamorelin was associated with a statistically significantly greater reduction in belly appearance distress at week 26 versus placebo. Health Canada considered the non-parametric ANCOVA model to be the "most appropriate robust method" given that the data were not normally distributed.[20] Across both trials, there were no statistically significant differences between treatment groups with respect to change in belly size evaluation at week 26. Further, tesamorelin was associated with a statistically significantly greater reduction in belly dysmorphia (belly profile evaluation) versus placebo at week 26 in LIPO-010 but not in CTR-1011. However, the degree to which the observed results are clinically meaningful is uncertain due to the relatively unknown psychometric properties of the instrument used to evaluate changes to body image (0). In particular, the FDA's SEALD team concluded that the instrument used in the two trials had "questionable" validity, and it raised concerns regarding the instrument's ability to measure a clinically important treatment effect.[24] Still, the FDA voted unanimously in favour of approving tesamorelin, primarily citing the "powerful" patient testimonies,[15] which "indicated that whether or not the statistical data holds up, patients subjectively believe treatment with the drug had a beneficial impact in their psychological well-being."[18]

4.2.2 Harms

Across all three studies, at least 70% of study participants in each trial experienced a treatment-emergent AE. A greater percentage of participants in Stanley et al. 2014 experienced an AE (tesamorelin: 89.3%; placebo: 95.5%) than those in the main phase of LIPO-010, followed by those in CTR-1011. Further, across the main phases of LIPO-010 and CTR-1011, approximately 5% more participants receiving tesamorelin (LIPO-010: 82.8%; CTR-1011: 74.1%) experienced an AE than those on placebo (LIPO-010: 75.9%; CTR-1011: 69.8%). Results from the 26-week extension phases of LIPO-010 and CTR-1011 were inconsistent with respect to the relative occurrence of AEs between participants who continued tesamorelin from the main phase versus those who switched to placebo (0).

Across all three studies, a greater percentage of participants receiving tesamorelin reported any injection-site condition, myalgia, or any fluid retention or edema than those in the placebo group. According to the clinical expert consulted by CDR for the purpose of this review, these types of AEs are consistent with the administration method and biological properties of tesamorelin. Another notable harm associated with tesamorelin use is glucose intolerance, and, while pre-existing diabetes was an exclusionary criterion, at least for LIPO-010, it is important to highlight the development of diabetes among those participants enrolled in the trial. In LIPO-010, one participant (0.4%) receiving tesamorelin (versus none receiving placebo) developed diabetes mellitus; this was recorded as a treatment-emergent AE, and the manner in which diabetes mellitus was defined was unclear. However, both the FDA and Health Canada note that the odds of developing diabetes (as defined by hemoglobin A1C ≥ 6.5%) was approximately three-fold greater (statistically significant) among participants receiving tesamorelin versus placebo.[18,26] Tesamorelin also increases serum IGF-1, which, according to the clinical expert, may be associated with the development or worsening of some cancers. In LIPO-010, a greater percentage of participants receiving tesamorelin versus placebo (2.9% versus 1.5%) developed a malignancy, whereas fewer participants receiving tesamorelin in CTR-1011 versus those receiving placebo (0.4% versus 3.2%) developed a malignancy. Last, there were no deaths in the main phase of LIPO-010 and Stanley et al. 2014. Two participants died in CTR-1011, one in each treatment group. Two participants died in the extension phase of LIPO-010: one who continued tesamorelin from the main phase and another individual who switched from placebo to tesamorelin (0).

The durations of all trials included in this review were insufficient to adequately capture some important safety outcomes, including the risk of cardiovascular diseases, as well as the occurrence of diabetes and cancer, thus leaving uncertain the long-term safety profile of tesamorelin. To that end, Health Canada notes that treatment with tesamorelin "should be discontinued in patients with IGF-1 standard deviation scores greater than 2 after 26 weeks."[26] Given the increase in IGF-1 levels, the tesamorelin product monograph also indicates that individuals who are receiving ongoing treatment with tesamorelin should be monitored for development or worsening of retinopathy.[26] To provide evidence for the long-term safety of tesamorelin, the manufacturer is conducting a 10-year prospective cohort study in which HIV-infected patients with abdominal lipohypertrophy and receiving tesamorelin will be compared with a similar group of individuals who are not receiving the treatment.[27] The primary outcome of this study is the time to development of malignancies, while secondary outcomes are the time to development or worsening of type 2 diabetes mellitus, diabetic retinopathy, hypersensitivity reactions, hepatic and renal function, AEs and major adverse cardiovascular events. However, the FDA required more conclusive evidence on the risk of developing diabetic retinopathy with tesamorelin,[15] so the manufacturer is also conducting a randomized, placebo-controlled, DB non-inferiority trial in patients with HIV-associated lipodystrophy and type 2 diabetes mellitus.[28]

Overall, Health Canada and the FDA concluded that the data from the manufacturer-submitted trials are inadequate to assess the long-term safety of tesamorelin.[15,19] Nevertheless, the FDA noted that the safety concerns "are not immediately life-threatening or severe to reasonably argue against the availability of Egrifta to the HIV population with lipodystrophy who have few to no options."[15]

4.3 Potential Place in Therapy

The information in this section is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

The prevalence of lipodystrophy in HIV-infected persons is uncertain, particularly as regard the prevalence among patients treated with more recently approved antiviral therapies.

The changes associated with lipodystrophy can be subdivided into the following categories: metabolic changes (elevated low-density lipoprotein cholesterol, reduced high-density lipoprotein cholesterol, elevated triglycerides, glucose intolerance); lipoatrophy (fat thinning, typically involving the face, arms, legs and buttocks); and lipohypertrophy (fat deposition, typically involving the abdomen, the base of the neck posteriorly, and the anterior neck). Metabolic changes, which are mostly associated with PI use, usually respond to a change in antiviral therapy or to therapies like HMG CoA reductase inhibitors ("statins"), whereas lipoatrophy, typically associated with NRTI therapy (especially stavudine, didanosine, and zidovudine), is at best slowly and incompletely reversible with treatment change or discontinuation, although these remain the best treatment option.[29-31]

Abdominal lipohypertrophy is the result of fat deposition around the viscera within the abdomen, not underneath the skin. Although associated with a number of risk factors, it appears to be associated with the use of older PIs, such as ritonavir and indinavir. Abdominal lipohypertrophy may be cosmetically displeasing[32] or associated with glucose intolerance and dyslipidemia.[33-36] It is uncommon to see lipohypertrophy develop in treated HIV-infected patients in the present era, as the antiviral therapies that have been implicated in developing lipohypertrophy are no longer in common use in clinical practice. For those patients who have lipohypertrophy, changing or discontinuing antiretroviral therapy to reduce or resolve fat deposition is not always successful, and there are therefore a small number of patients who remain with this problem.

Even though lipohypertrophy is an increasingly uncommon problem, it remains a clinically and psychologically important issue in a small percentage of HIV-infected persons[32] and there are few effective treatment options. Treatment options for abdominal lipohypertrophy, at present, are limited. Visceral fat accumulation is not amenable to surgical removal or liposuction. As noted above, lipohypertrophy does not consistently resolve or improve with a change in HIV antiviral therapy. Dietary and lifestyle modifications may be beneficial,[37] as may be treatment with metformin,[38,39] but these are inconsistent and modest in effectiveness at best. There are no therapies to offer besides tesamorelin. The primary goal of treatment with tesamorelin would be to improve quality of life through improving self-image, and therefore would be patient-guided. Although there is evidence of a reduction in triglyceride and glucose levels among responders to tesamorelin,[25] there is no evidence that treatment of abdominal lipohypertrophy with tesamorelin is associated with reduced cardiovascular risk, and therefore it is unlikely that tesamorelin would be used to treat the metabolic changes associated with HIV lipodystrophy.

Barriers to treatment with tesamorelin include its formulation as an injected therapy administered daily, the potential for local and systemic side effects, and the need for VAT assessment using a CT scan, which is not standard medical care in Canada.

5. CONCLUSIONS

Results from three DB RCTs (LIPO-010, CTR-1011, and Stanley et al. 2014) demonstrated that six months of treatment with tesamorelin was associated with a statistically significantly greater reduction in VAT and waist circumference compared with placebo in HIV-infected patients with abdominal lipohypertrophy. The relative reduction in VAT (–12% to –20% across studies) and the absolute reduction in waist circumference (–1.3 cm to –1.8 cm) associated with tesamorelin treatment versus placebo exceeded the thresholds of 8% and 1 cm, respectively, that Health Canada considered to be minimal acceptable decreases that reflect clinical benefit. However, the clinical relevance of the reduction in VAT and waist circumference attributable to tesamorelin is unclear, because tesamorelin treatment was not associated with consistent improvements in body image, which is an important outcome to patients, nor did it improve QoL. Furthermore, the magnitude of reduction in VAT and waist circumference observed in the included studies is unlikely to be seen as clinically relevant by clinicians, while the fact that VAT (as measured by CT scan) is not routinely used to gauge treatment response in clinical practice limits the application of the results to support clinical decision-making. A major limitation of the clinical evidence was the limited external validity of the results, because the nature of the ART regimens used in the included studies does not reflect treatment regimens used currently in clinical practice in Canada. Specifically, more than half of patients in LIPO-010 and CTR-1011 and approximately 40% of patients in Stanley et al. 2014 were treated with PI-based ARTs that are associated with VAT accumulation, whereas current HIV treatment guidelines recommend ART regimens that mostly comprise INSTIs, which are less likely to cause abdominal lipohypertrophy. Treatment with tesamorelin was not associated with any consistent or substantial harm through 52 weeks, although longer-term studies of tesamorelin are needed to adequately assess its long-term safety. There were limited data to evaluate the effects of tesamorelin on important safety outcomes, including the risk of cardiovascular harm, as well as the occurrence of diabetes and cancer, and mortality.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Group(s) Supplying Input

One patient group, the Canadian Treatment Action Council (CTAC), provided input for this submission. CTAC is a national non-governmental organization addressing access to treatment, care, and support for people living with HIV and hepatitis C. CTAC engages various stakeholders, including community members, service providers, and policy-makers, to identify, develop, and implement policy and program solutions.

In fiscal 2015-2016, CTAC received unrestricted organizational and educational grants from Gilead Sciences, Abbott/AbbVie, Janssen, and ViiV Healthcare. No declarations of conflicts of interest were provided.

2. Condition-Related Information

CTAC gathered information through an online survey following a national patient input consultation webinar. In total, CTAC compiled data from seven surveys, of which four were from female respondents, and three were from males. Six respondents identified as HIV-positive, and, on average, reported being on treatment for 20 years. Four participants reported living with HIV-associated lipodystrophy for an average of 12 years.

HIV-associated lipodystrophy is the accumulation (lipohypertrophy) or loss (lipoatrophy) of fat in the body. It is uncertain whether the condition is related to the HIV infection itself or to the use of highly active antiretroviral therapies (HAART) used to treat HIV. Lipodystrophy can result in the increase of visceral adipose tissue (VAT), which is an accumulation of fat deep in the abdomen area and can surround internal organs, characterized as "hard" fat. VAT is difficult to reduce with diet and exercise. CTAC cited research that noted that the condition can lead to neurocognitive disorders, increased mortality, decreased HAART adherence, and cardiometabolic problems. Per CTAC, approximately 10% of patients infected with HIV suffer from excess VAT. According to the survey respondents, excessive VAT, regardless of its cause, is a serious problem. One respondent noted: "*My arms and legs have no fat and little muscle. My abdomen is huge. YOU PUT UP WITH THIS*." Other respondents also noted that excessive VAT is associated with self-esteem issues, negative body image, impacts on quality of life, and problems socializing.

Respondents highlighted some of the issues with providing care for people living with HIV in rural areas. One caregiver noted: *"The challenges involve the lack of rural medical staff. Ignorance and discrimination by LGBT agenda that refuses to include ALL people with HIV."* According to CTAC's interpretation, it is suggested that there is an additional stigma associated with those who suffer from lipodystrophy in the HIV community.

3. Current Therapy-Related Information

CTAC was unaware of any other therapy available in Canada for the treatment of HIV-associated accumulation of VAT. They do not indicate any information of relevance to current therapies.

4. Expectations About the Drug Being Reviewed

Tesamorelin is an injected therapy that is designed to treat lipodystrophy resulting in increased VAT. CTAC survey respondents with treatment experience using tesamorelin noted that it is the only treatment option available, and expect it to be reimbursed. One patient commented: "*I did not have problems with side effects, not even injection-site reactions*," and "*the side effects already reported 'make sense' and are 'manageable*.'" An important caveat noted by patients was that tesamorelin needs to be taken chronically for life; otherwise, there is a possibility of reversal of effects. Another patient highlighted the "*difficulty of administering treatment (injection to prepare in several steps) and challenges to mobility (travelling with syringes, water and freezer pack difficult for air travel and refrigeration away from home)*."

One health care provider commented on the potential of tesamorelin to "*positively impact body image, self-esteem, physical and mental health, quality of life and well-being*." However, this individual did not think that tesamorelin "*is a quick and easy fix to abdominal lipohypertrophy. It is another medication people have to take. It is administrated SQ (which is complex on its own). Its effects are not permanent. Regardless of this, I think it should be made available and covered because it constitutes one option — the only one on the market — to address this problem*." Patients emphasized high hopes for this treatment in helping improve self-esteem issues associated with negative body image; they commented that any positive clinical benefits associated with reduced VAT were a bonus. Patients also highlighted that reduction in overall mortality associated with reduced VAT was an important factor, and one patient hoped that "*having less body fat will improve [high triglycerides] and help me fight any cardiovascular illness in the future.*"

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	March 31, 2016
Alerts:	Weekly search updates until July 20, 2016
Study Types:	No search filters were applied
Limits:	No date or language limits were used

SYNTAX	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj	Requires words are adjacent to each other (in any order)
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.po	Population group [PsycInfo only]
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
1.	(egrifta* or tesamorelin* or TH9507 or TH-9507 or MQG94M5EEO).ti,ab,ot,rn,hw,nm,kf.
2.	218949-48-5.rn.
3.	1 or 2
4.	3 use pmez
5.	*tesamorelin/
6.	(egrifta* or tesamorelin* or TH9507 or TH-9507 or MQG94M5EEO).ti,ab,kw.
7.	5 or 6
8.	7 use oemezd
9.	4 or 8
10.	remove duplicates from 9

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	March 2016
Keywords:	Egrifta, tesamorelin
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for searching health-related grey literature" (https://www.cadth.ca/resources/finding-evidence/grey-matters-practical-search-tool-evidence-based-medicine) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
Falutz et al. 2005[40]	Phase 2 study
Falutz et al. 2010[41]	Pooled analysis
Mangili et al. 2015[42]	Pooled analysis
Stanley et al. 2012[25]	Pooled analysis
Stanley et al. 2011[43]	Not randomized controlled trial; sub-study

APPENDIX 4: SUMMARY OF BODY IMAGE INSTRUMENT

The effect of tesamorelin on patient-related outcomes (PROs) related to body image was assessed using the PHASE V Outcomes Information System by Phase V Technologies Inc. Patients and investigators were asked to complete questionnaires at weeks –4 (pre-screening), 0, 26, and 52 in LIPO-010 and at week –4 (pre-screening), day 1 (baseline), and weeks 13 and 26 in CTR-1011.

Body Image

The PRO body image instrument consists of three scales that evaluate: (1) perceived body size; (2) distress with body appearance; and, (3) body profile with respect to the following seven areas of the body:

i. Face
ii. Back of neck or between shoulder blades
iii. Legs
iv. Belly
v. Breasts
vi. Buttocks
vii. Arms

This review focused on the results of the three body image parameters as they related to the belly only.

1. Body size evaluation

To measure perceived belly size, patients were asked to evaluate their current appearance (size of their belly) compared with their "healthy" look using the pre-defined answers presented in Table 13. The belly size scores were calculated based on values ranging from –100 (smaller size) to 100 (larger size), where 0 represents "healthy look." Positive change scores suggest improvements, while negative change scores suggest worsening when compared with baseline.

TABLE 13: PERCEIVED BODY SIZE SCORING SCHEME

Score	Patient's Answer	
–100	A great deal less/very smaller or thinner	Far from healthy
–75	A lot less/much smaller or thinner	↑
–50	Somewhat less, smaller or thinner	
–25	A little less, smaller or thinner	
0	About right	On target
25	A little more or bigger	
50	Somewhat more or bigger	↓
75	A lot more or much bigger	
100	A great deal more or very much bigger	Far from healthy

2. Body appearance distress

Patients were asked to evaluate their degree of distress associated with their current appearance (size of their belly) using the pre-defined answers presented in Table 14. Body appearance distress scores were calculated based on scores ranging from 0 (extremely upsetting) to 100 (extremely encouraging), where 50 represents a neutral feeling. Positive change scores indicate patient improvement toward "encouragement" compared with baseline.

TABLE 14: DISTRESS WITH BODY APPEARANCE SCORING SCHEME

Score	Patient's answer
0.0	Extremely upsetting and distressing
12.5	Very upsetting and distressing
25.0	Quite upsetting and distressing
32.5	A little upsetting and distressing
50.0	No feeling either way
62.5	A little encouraging
75.0	Quite encouraging
87.5	Very encouraging
100.0	Extremely encouraging

3. Body profile evaluation

The third scale, body profile, consists of both a patient- and investigator-reported section. This review considers only the patient-reported section. Patients were asked to answer three questions based on six body profile silhouettes with increasing belly or hump area provided in the questionnaire:

a) How do you think you look today?
b) How would you most like to look?
c) What is the smallest amount of improvement that you consider beneficial to your health and well-being?

Answer scores ranged from 0 to 5 with larger scores representing an increased dysmorphic state, where 0 represents "normal" and 5 represents the most dysmorphic silhouettes. The change from baseline was assessed.

While the manufacturer claims that the body image instrument is validated,[23] the FDA had several concerns about this claim.[24] In particular, the FDA Study Endpoint and Labeling Development (SEALD) team concluded that the instrument used in the two trials had "questionable content validity," and the team raised concerns about the instrument's ability to measure a clinically important treatment effect. The SEALD team reports that the PRO did not address whether qualitative research was done to evaluate patient understanding of the final instrument; therefore, it does not meet the standards for instrument development as recommended within the FDA PRO Guidance for Industry, nor does it meet the standard for evidence saturation. The SEALD team also reported that internal consistency reliability data also had limited relevance, because single items were utilized as end points instead of summary scales. In addition, they stated that the enrolment criteria in the trials did not pre-specify a minimum PRO score, which can make it more difficult to demonstrate improvement.[24]

APPENDIX 5: SUMMARY OF QUALITY OF LIFE and HEALTH-RELATED QUALITY OF LIFE OUTCOME INSTRUMENTS

Quality-of-Life Instrument

The quality-of-life (QoL) instrument used in LIPO-010 and CTR-1011 consisted of five scales:

1. **The perceived health scale (global analogue scale).**
   This scale consisted of five questions associated with how patients feel in the previous month with respect to (1) overall and in general, (2) physically, (3) emotionally, (4) personal life, and (5) about job or work. Each question was scored on a 10-point Likert scale from 1 ("The worst I ever felt") to 10 ("The very best I ever felt.") The scale score was the mean of the scores for the five items in that scale.

2. **The appearance-specific symptom interference scale.**
   This scale consisted of seven questions concerning (1) work, (2) social events, (3) recreational activities, (4) exercise and physical activities, (5) work effectiveness, (6) enjoying life, and (7) feeling your best due to "overall appearance." Each question was scored on a six-point Likert scale from 1 ("All") to 6 ("None") in terms of the time overall appearance has interfered in the last month. The scale score was the mean of the scores for the seven items in that scale.

3. **The symptoms and side effects distress scale.**
   This scale included a total of 29 questions on general, HIV, and HIV-associated Adipose Redistribution Syndrome–specific symptoms that yield overall incidence and distress scales.

4. **The Mental and Emotional Health scale.**
   This scale consisted of 24 questions that produce subscales for anxiety, depression, and loss of behavioural and emotional control and a summary psychological distress scale, as well as subscales for life satisfaction, positive well-being, and emotional ties along with a summary psychological well-being scale.

5. **The General Health Perceptions scale.**
   This scale included 11 questions that produce subscales for sleep disturbance, vitality, and general health status, as well as a composite general perceived health scale.

The scoring scheme for each question in the symptoms and side effects distress, the Mental and Emotional Health and the general health perception scales was transformed to a scoring scheme ranging from 100 to 600, where a score of 100 indicated generally low QoL and a score of 600 indicated the highest possible QoL.

The above questions and subscales were used to create three summary scales:

1. **The Composite Psychosocial summary scale.**
   This score was the mean of all the subscales of Mental and Emotional Health and all subscales of General Health Perceptions.

2. **The Composite QoL summary scale.**
   This was the mean of all six subscales of Mental and Emotional Health, and three subscales from General Health Perceptions.

3. **The Overall (item-wise) score.**
   This score was the mean of all items in the Mental and Emotional Health scale and all items of the General Health Perceptions scale.

This review considered only the Overall (item-wise) summary scale to assess QoL. No information regarding the score range, score interpretation, or psychometric properties — i.e., validity, reliability, responsiveness — was found.

EuroQol 5-Dimensions Questionnaire

The EuroQol 5-Dimensions (EQ-5D) is a generic health-realted QoL instrument that has been applied to a wide range of health conditions and treatments.[44,45] The first of two parts of the EQ-5D is a descriptive system that classifies respondents (aged ≥ 12 years) into one of 243 distinct health states. The descriptive system consists of the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three possible levels (1, 2, or 3) representing "no problems," "some problems," and "extreme problems," respectively. Respondents are asked to choose one level that reflects their own health state for each of the five dimensions. A scoring function can be used to assign a value (EQ-5D index score) to self-reported health states from a set of population-based preference weights.[44,45] The second part is a 20 cm visual analogue scale (EQ-VAS) that has end points labelled 0 and 100, with respective anchors of "worst imaginable health state" and "best imaginable health state," respectively. Respondents are asked to rate their own health by drawing a line from an anchor box to the point on the EQ-VAS that best represents their own health on that day. Hence, the EQ-5D produces three types of data for each respondent:

1. A profile indicating the extent of problems on each of the five dimensions represented by a five-digit descriptor, such as 11121, 33211, etc.
2. A population preference-weighted health index score based on the descriptive system.
3. A self-reported assessment of health status based on the EQ-VAS.

The EQ-5D index score is generated by applying a multi-attribute utility function to the descriptive system. Different utility functions are available that reflect the preferences of specific populations (e.g., US or UK). The lowest possible overall score (corresponding to severe problems on all five attributes) varies depending on the utility function that is applied to the descriptive system (e.g., −0.59 for the UK algorithm and −0.109 for the US algorithm). Scores less than 0 represent health states that are valued by society as being worse than dead, while scores of 0 and 1.00 are assigned to the health states "dead" and "perfect health," respectively. The minimal clinically important difference for the EQ-5D ranges from 0.033 to 0.074.[46] No additional information on the EQ-5D's psychometric properties and minimal clinically important difference were found for the treatment of excess visceral adipose tissue.

APPENDIX 6: SUMMARY OF EXTENSION PHASES OF LIPO-010 AND CTR-1011

1. Objective

To summarize the extension study (CTR-1012) to the CTR-1011 trial and the extension phase of LIPO-010, which evaluated the effectiveness and safety of tesamorelin 2 mg/day (subcutaneous injection) for treatment-experienced adult HIV-infected patients with lipodystrophy.

2. Findings

Study Design

CTR-1012 and the extension phase of LIPO-010 were phase 3, multi-centre, double-blind, placebo-controlled, randomized controlled trials in which patients and investigators were blinded to treatment allocation. CTR-1012 included three treatment groups; those who received tesamorelin in CTR-1011 were re-randomized (in a blinded fashion) to continue receiving once-daily tesamorelin 2 mg (the T-T group) or to switch to identical placebo (the T-P group), whereas participants who received placebo in the main phase were assigned to receive tesamorelin (the P-T group). The re-randomization ratio was 1:1 and an interactive voice response system was used for randomization along with a three-block algorithm, whereas the re-randomization ratio was 3:1 in the LIPO-010 extension phase and was distributed as it was in the LIPO-010 main phase. The extension phase entailed six months of follow-up with patients returning for follow-up visits at weeks 6, 13, 19, and 26 of the extension phase.

Patients participating in CTR-1011 were eligible to participate in the CTR-1012 only if they met the following criteria:

- Completed the 26-week efficacy phase of CTR-1011
- Fasting plasma glucose (FPG) < 150 mg/dL (8.33 mmol/L)

Patients participating in LIPO-010 were eligible to participate in the extension phase only if they met the following criteria:

- Completed the 26-week efficacy phase of LIPO-010 main phase
- FPG < 150 mg/dL (8.33 mmol/L)
- Received antiretroviral therapy (ART) for at least eight weeks
- Excessive accumulation of abdominal fat (defined as a waist circumference of at least 95 cm and a waist-to-hip ratio of at least 0.94 for men and a waist circumference of at least 94 cm and a waist-to-hip ratio of at least 0.88 for women).

Assessment

The treatment effect of tesamorelin for the primary and secondary outcomes was estimated by comparing tesamorelin with placebo. Specifically, to measure visceral adipose tissue (VAT), comparisons were made for those patients in the T-T group versus those in the T-P group. To measure between-group differences, the least squares (LS) means were generated from the analysis of covariance model, using the intention-to-treat (ITT) population and the last observation carried forward (LOCF) method for imputation of missing data.

Efficacy was assessed by monitoring VAT by CT scans from a single 5 mm slice at the L4-L5 intervertebral disc level and body image assessed by Phase V Technologies questionnaire at week 26 (baseline) and

week 52. Safety was assessed by monitoring adverse events (AEs), serious AEs, and withdrawal due to AEs.

Results

A total of 202 participants in the treatment group and 92 participants in the placebo group completed CTR-1011. Of the 202 participants in the treatment group, 92 were re-randomized to the T-T group and 85 were re-randomized to the T-P in the extension phase. Of the 92 participants in the placebo group that completed CTR-1011, 88 were allocated to the P-T group in the extension phase. No information was provided for the 29 (25 in the tesamorelin group and four in the placebo group) outstanding participants. A total of 12 (13.0%), 22 (25.9%), and 14 (16.3%) participants discontinued the study in the T-T, T-P, and P-T groups, respectively. Participant disposition is detailed in Table 15. Baseline characteristics are detailed in Table 16 and are similar across CRT-1011 and CTR-1012. Baseline characteristics between treatment groups in CTR-1012 also appeared to be similar.

A total of 273 participants received the study drug and 137 participants received placebo in the LIPO-010 main phase. Of the 273 participants in the treatment group, 154 were re-randomized to the T-T group and 50 were re-randomized to the T-P in the LIPO-010 extension phase. Of the 137 participants who received placebo in the LIPO-010 main phase, 111 were allocated to the P-T group in the extension phase. A total of 25 (16.2%), 10 (20.0%), and 24 (21.6%) participants discontinued the study in the T-T, T-P, and P-T groups, respectively. Participant disposition is detailed in Table 15. Baseline characteristics are detailed in Table 16 and are similar across the LIPO-010 main phase and extension phase. Baseline characteristics between treatment groups in the LIPO-010 extension phase also appeared to be similar.

TABLE 15: PARTICIPANT DISPOSITION (EXTENSION PHASE)

	CTR-1012			LIPO-010		
	T-T	T-P	P-T	T-T	T-P	P-T
Completed the main phase, N	202	92		273	137	
Randomized, N	92	85	86	154	50	111
Discontinued study (primary reasons below), N	12 (13.0)	22 (25.9)	14 (16.3)	25 (16.2)	10 (20.0)	24 (21.6)
Adverse event, n (%)	1 (1.1)	4 (4.7)	5 (5.8)	5 (3.2)	3 (6.0)	12 (10.8)
Consent withdrawal, n (%)	8 (8.7)	10 (11.8)	7 (8.1)	12 (7.8)	4 (8.0)	6 (5.4)
Lack of compliance, n (%)	1 (1.1)	3 (3.5)	1 (1.2)	7 (4.5)	1 (2.0)	2 (1.8)
Lost to follow-up, n (%)	2 (2.2)	2 (2.4)	1 (1.2)	1 (0.6)	2 (4.0)	3 (2.7)
Abnormal laboratory value, n (%)	0	0	0	0	0	1 (0.9)
Unknown, n (%)	0	3 (3.5)	0	0	0	0
Completed the extension phase, N	80 (87.0)	63 (74.1)	72 (83.7)	129 (83.8)	40 (80.0)	87 (78.4)

P-T = allocated placebo in the main phase and tesamorelin in the extension phase; T-P = allocated tesamorelin in the main phase and placebo in the extension phase; T-T = allocated tesamorelin in the main phase and tesamorelin in the extension phase.
Source: Falutz et al. 2008,[17] Falutz et al. 2010.[6]

TABLE 16: SUMMARY OF BASELINE CHARACTERISTICS (EXTENSION PHASE)

Characteristic	CTR-1012			LIPO-010		
	T-T (N = 92)	T-P (N = 85)	P-T (N = 86)	T-T (N = 154)	T-P (N = 50)	P-T (N = 111)
Mean (SD) age (years)	47.7 (6.9)	48.9 (7.2)	48.4 (7.9)	48 (7)	47 (7)	48 (8)
% of males	90.2	89.4	87.2	88	86	86
Mean (SD) weight (kg)	88.0 (12.6)	89.9 (13.6)	86.6 (15.4)	89.1 (13.7)	92.1 (17.3)	90.4 (13.6)
Mean (SD) BMI (kg/m^2)	28.3 (3.9)	29.0 (3.9)	28.5 (4.3)	28.9 (4.2)	30.2 (4.7)	29.1 (4.2)
Mean (SD) VAT (cm^2)	197 (91.2)	200 (86.3)	199 (100)	181 (78)	174 (72)	NR
Mean (SD) Waist circumference (cm)	104 (8)	106 (9)	104 (9)	104 (9)	105 (12)	105 (10)
Mean (SD) Duration of ART (months)	NR	NR	NR	NR	NR	NR
Current ART regimen, %						
PI	52.2	61.2	53.5	NR	NR	NR
NRTI	92.4	87.1	90.7	NR	NR	NR
NNRTI	41.3	42.4	34.9	NR	NR	NR
Entry inhibitor	NR	NR	NR	NR	NR	NR
Integrase inhibitor	NR	NR	NR	NR	NR	NR

ART = antiretroviral therapy; BMI = body mass index; NNRTI = non-nucleoside transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitory; PI = protease inhibitor; P-T = allocated placebo in the main phase and tesamorelin in the extension phase; SD = standard deviation; T-P = allocated tesamorelin in the main phase and placebo in extension phase; T-T = allocated tesamorelin in the main phase and tesamorelin in extension phase; VAT = visceral adipose tissue.
Source: Falutz et al. 2008,[17] Falutz et al. 2010.[6]

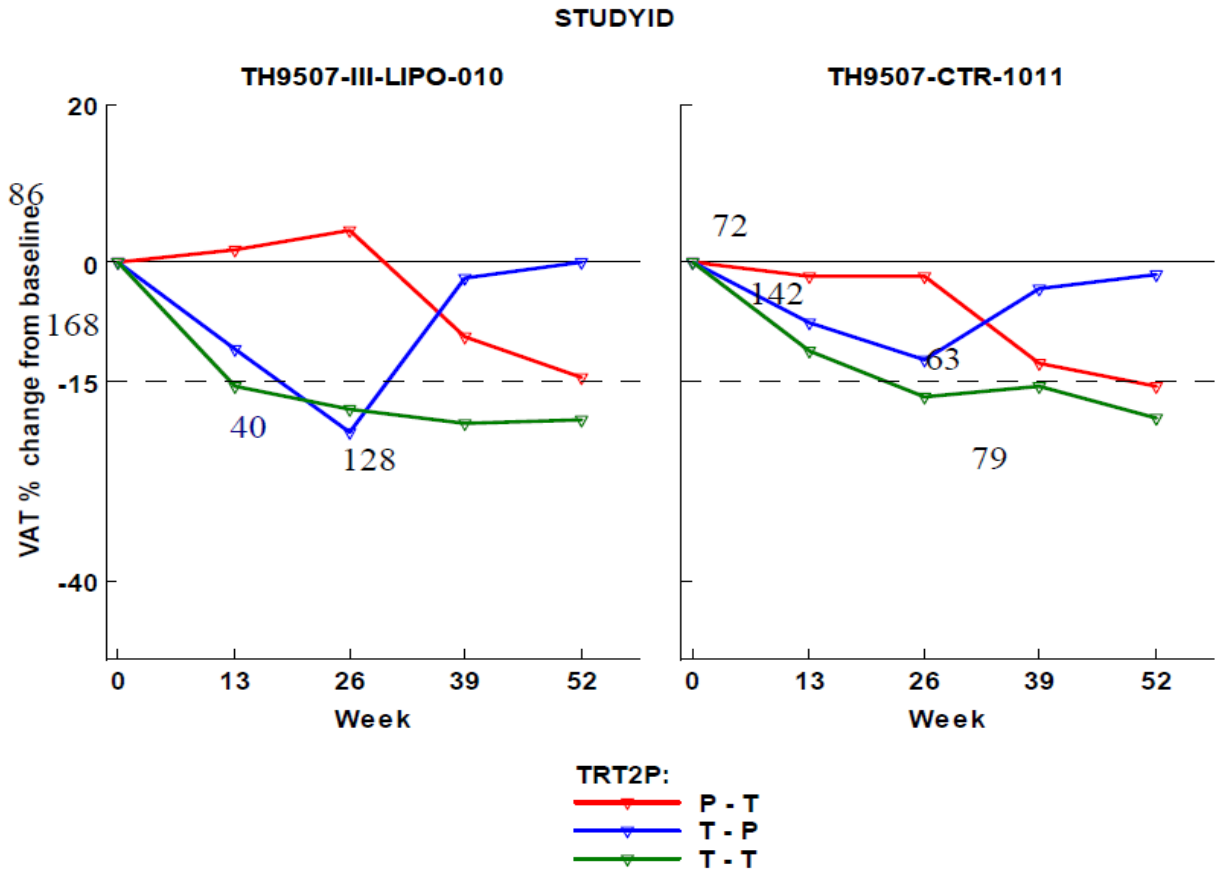
Efficacy

VAT

The results from CTR-1012 indicated a –1.4% change in VAT from week 26 to 52 in the T-T group, whereas the corresponding change in the T-P group was 24.5% (Figure 2). The LS mean difference (95% CI) of tesamorelin (T-T) versus placebo (T-P) was –25.8% (–40.7% to –10.9%) (*P* = 0.0008) (Table 17).

The corresponding results from the LIPO-010 extension phase indicated a 4.5% change in VAT from week 26 to 52 in the T-T group, whereas the corresponding change in the T-P group was 24.9% (Table 17). The LS mean difference (95% CI) of tesamorelin (T-T) versus placebo (T-P) was –20.4% (–29.8 to –11.0) (*P* = 0.0001).

FIGURE 2: MEAN VAT % CHANGE BY TREATMENT SEQUENCE (MAIN AND EXTENSION PHASES)



P-T = allocated placebo in the main phase and tesamorelin in the extension phase; T-P = allocated tesamorelin in the main phase and placebo in the extension phase; T-T = allocated tesamorelin in the main phase and tesamorelin in the extension phase; VAT = visceral adipose tissue.
Source: Reproduced from FDA statistical review.[1]

TABLE 17: KEY EFFICACY OUTCOME — VISCERAL ADIPOSE TISSUE (EXTENSION PHASE)

	CTR-1012			LIPO-010		
Outcome	T-T	T-P	P-T	T-T	T-P	P-T
VAT (cm^2)						
Baseline at 26 weeks, N	92	85	86	154	50	111
Baseline at 26 weeks, mean (SD)	197 (91.2)	200 (86.3)	199 (100)	181 (78)	174 (72)	NR
52 weeks, N	92	85	86	154	50	111
52 weeks, % change from 26 weeks (SE)	–1.4 (5.2)	24.5 (5.4)	NR	4.5 (2.4)	24.9 (4.1)	NR
52 weeks, LS mean difference (95% CI), *P* value	**–25.8% (–40.7 to –10.9), *P* = 0.0008**		NR	**–20.4% (–29.8 to –11.0), *P* < 0.0001**		NR

CI = confidence interval; LS = least squares; NR = not reported; P-T = allocated placebo in the main phase and tesamorelin in the extension phase; SD = standard deviation; SE = standard error; T-P = allocated tesamorelin in the main phase and placebo in in the extension phase; T-T = allocated tesamorelin in the main phase and tesamorelin in the extension phase; VAT = visceral adipose tissue.
Note: Statistically significant results are bolded.
Source: Falutz et al. 2008,[17] Falutz et al. 2010,[6] FDA statistical review.[1]

Body Image

In the LIPO-010 extension phase and CTR-1012, there were no statistically significant differences between treatment groups with respect to change in belly size evaluation from week 26 to week 52 (Table 18). Across both trials, tesamorelin was associated with a statistically significantly greater reduction in belly appearance distress and in belly profile ratings from week 26 to week 52 versus placebo.

TABLE 18: KEY EFFICACY OUTCOME — BODY IMAGE (EXTENSION PHASE)

	CTR-1012			LIPO-010		
Outcome	**T-T**	**T-P**	**P-T**	**T-T**	**T-P**	**P-T**
Belly size evaluation						
Baseline, N	92	85	86	153	50	111
Baseline, mean (SD)	31.0 (54.64)	30.0 (61.33)	48.0 (56.00)	37.1 (51.55)	25.5 (52.12)	34.5 (54.78)
52 weeks, N	92	85	86	153	50	111
52 weeks, actual change from baseline, mean (SE)	–2.7 (32.05)	1.5 (30.15)	–1.8 (29.32)	2.0 (30.82)	-4.0 (34.02)	3.6 (33.68)
52 weeks, mean difference (95% CI), *P* value[a]	0.101			0.408		
Belly appearance distress						
Baseline, N	92	85	86	153	50	111
Baseline, mean (SD)	31.5 (24.41)	32.2 (27.44)	25.4 (26.80)	35.9 (27.46)	36.8 (21.49)	30.5 (28.04)
52 weeks, N	92	85	86	153	50	111
52 weeks, actual change from baseline, mean	4.9 (24.35)	–5.7 (29.33)	4.3 (32.42)	–2.0 (25.06)	–8.3 (29.41)	0.5 (25.11)

	CTR-1012			LIPO-010		
Outcome	**T-T**	**T-P**	**P-T**	**T-T**	**T-P**	**P-T**
(SE)						
52 weeks, mean difference (95% CI), *P* value[b]	**0.005**			**0.020**		
Belly profile (patient-reported)						
Baseline, N	92	85	86	153	50	111
Baseline, mean (SD)	2.4 (1.58)	2.8 (1.57)	3.0 (1.47)	2.6 (1.40)	2.4 (1.54)	2.9 (1.52)
52 weeks, N	92	85	86	153	50	111
52 weeks, actual change from baseline, mean (SE)	–0.2 (1.33)	0.1 (1.42)	–0.7 (1.24)	–0.2 (1.34)	0.4 (1.19)	–0.3 (1.24)
52 weeks, mean difference (95% CI), *P* value[c]	**0.018**[c]			**0.0033**		

ANCOVA = analysis of covariance; CI = confidence interval; P-T = allocated placebo in the main phase and tesamorelin in the extension phase; SD = standard deviation; SE = standard error; T-P = allocated tesamorelin in the main phase and placebo in the extension phase; T-T = allocated tesamorelin in the main phase and tesamorelin in the extension phase; VAT = visceral adipose tissue; vs. = versus.

Note: Statistically significant results are bolded.

[a] Ranked ANCOVA for between-treatment comparison (T-T vs. T-P) including relevant covariates (e.g., gender, age) for absolute belly size change scores.

[b] Ranked ANCOVA for between-treatment comparisons (T-T vs. T-P) including relevant covariates (e.g., gender, age) for belly appearance distress change scores.

[c] Ranked ANCOVA for between-treatment comparisons (T-T vs. T-P) including relevant covariates (e.g., gender, age) for belly profile change scores.

Source: Falutz et al. 2008,[17] Falutz et al. 2010.[6]

Safety

A total of 73.9% of participants in the T-T group experienced AEs compared with 57.6% of participants in the T-P group (Table 19). Among participants in the P-T group, 76.7% experienced AEs. The most common (> 5%) AEs across the three groups were injection-site pruritus, arthralgia, pain in extremity, diarrhea, injection-site erythema, injection-site pain, upper respiratory tract infection, musculoskeletal stiffness, paresthesia, and insomnia. Overall, serious AEs occurred in 3.3% of participants in the T-T group, 1.2% of participants in the T-P group, and 3.5% of participants in the P-T group. AEs resulting in study discontinuation were observed in in 2.2% of participants in the T-T group, 4.7% of participants in the T-P group, and 4.7% of participants in the P-T group. No deaths were reported in CTR-1012.

Occurrences of AEs were inconsistent across treatment groups in the LIPO-010 extension phase and were observed in 57.8% in the T-T group, 74.8% in the P-T group, and 66.0% in the T-P group. The most common (> 5%) AEs observed across the three treatment groups were arthralgia, upper respiratory tract infection, nasopharyngitis, pain in extremity, injection-site erythema, injection-site pruritus, sinusitis, diarrhea, rash, back pain, and cough. Overall, serious AEs were more common in the T-P group, occurring in 4.0% of participants versus 2.6% of participants in the T-T group, and 2.7% of participants in the P-T group. AEs resulting in study discontinuation were observed in 2.6% of participants in the T-T group, 6.0% of participants in the T-P group and 11.7% of participants in the P-T group. Two deaths

occurred in the LIPO-010 extension phase; however, the investigators reported that the deaths were not related to the study drug. Detailed data outlining adverse events are presented in Table 19.

TABLE 19: HARMS (EXTENSION PHASE)

	CTR-1012			LIPO-010		
	T-T (N = 92)	T-P (N = 85)	P-T (N = 86)	T-T (N = 154)	T-P (N = 50)	P-T (N = 111)
AEs, %						
Any	73.9	57.6	76.7	57.8	66.0	74.8
Resulting in study discontinuation	2.2	4.7	4.7	2.6	6.0	11.7
Most common AE,[a] %						
Injection-site pruritus	4.3	0	10.5	NR	NR	NR
Arthralgia	8.7	7.1	16.3	NR	NR	NR
Pain in extremity	6.5	1.2	12.8	NR	NR	NR
SAEs, %						
Any	3.3	1.2	3.5	2.6	4.0	2.7

AE = adverse event; P-T = allocated placebo in the main phase and tesamorelin in the extension phase; SAE = serious adverse event; T-P = allocated tesamorelin in the main phase and placebo in the extension phase; T-T = allocated tesamorelin in the main phase and tesamorelin in the extension phase.
[a] Frequency > 10%
Source: Falutz et al. 2008,[17] Falutz et al. 2010.[6]

Limitations

The trials consist of a carryover design, in which participants on the study drug in CTR-1011 and the LIPO-010 extension phase were re-randomized to tesamorelin or placebo. As a result, those in the T-P group can demonstrate a carryover effect between the phases, which can make it difficult to assess the true efficacy of the study drug. Additionally, the population included in CTR-1012 and the LIPO-010 extension phase were required to complete the main phase of the previous trials, making it a highly select sample that may compromise the generalizability of the results. Further, it appears that a considerable proportion of participants included in the CTR-1012 were on protease inhibitors (PIs). This can affect the generalizability of the results, as in today's clinical practice, HIV patients are much more likely to receive ART regimens that consists of backbones other than PIs. In addition, it appears that a larger proportion of participants in the T-P group are on PIs compared with the other treatment groups in the extension phase. This imbalance can likely be considered a confounder, whereby PI use is known to be associated with increased VAT, therefore leading to a larger VAT difference between the placebo group and the treatment group. This can likely lead to an overestimation of the treatment effect. Further, there were considerably more withdrawals in the T-P group compared with the other treatment groups in CTR-1012, which can compromise randomization and may lead to uncontrolled confounding, making it hard to ascertain the true effect of the study drug. Finally, CTR-1012 and the LIPO-010 extension phase did not use a true ITT population; rather than including all randomized participants, the defined ITT analysis sets across both studies only included those participants who took at least one dose of the assigned study drug; i.e., a modified ITT population. Missing data were imputed using the LOCF method, whereby baseline values were carried forward into the treatment period. However, carrying the last observation forward may artificially stabilize VAT levels among participants who dropped out; conversely, observed data could also be biased if the probability of withdrawal is related to increase in VAT levels.

3. Summary

In general, results from CTR-1012 and the LIPO-010 extension phase suggest that all improvements observed with tesamorelin at week 26 in CTR-1011 are reversed at week 52 in participants who were discontinued treatment with tesamorelin. Overall, treatment with tesamorelin was generally well-tolerated and raised no new safety concerns (relative to the main phase), although more frequent adverse events for those allocated to tesamorelin were reported.

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