Common Drug Review
Pharmacoeconomic 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.
Reimbursement 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.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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ABBREVIATIONS

CDR	CADTH Common Drug Review
CT	computed tomography
HIV	human immunodeficiency virus
ICUR	incremental cost-utility ratio
MI	myocardial infarction
QALY	quality-adjusted life-year
QoL	quality of life
RR	relative risk
SoC	standard of care
VAT	visceral adipose tissue

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	Tesamorelin (Egrifta)
Study Question	"To evaluate the clinical-economic relevance of Egrifta compared with the standard care" in treating HIV-associated lipohypertrophy
Type of Economic Evaluation	Cost-utility analysis
Target Population	Patients with HIV-associated lipohypertrophy
Treatment	2 mg (two 1 mg vials) of tesamorelin injected subcutaneously once a day
Outcome	QALYs
Comparator	Standard of care (lifestyle modifications, nutrition and physical activity)
Perspective	Canadian Ministry of Health
Time Horizon	Lifetime (30 years)
Results for Base Case	$66,735 per QALY
Key Limitations	• Lack of appropriate evidence linking the surrogate outcome (reduction in VAT) to long-term clinical events related to lipohypertrophy and to non-adherence to HIV medication. This is a major limitation considering that all the predicted clinical benefits associated with tesamorelin are based on the premise that there is a direct association between VAT and events related to lipohypertrophy and medical adherence. VAT has not been validated as a surrogate for any of the clinical events modelled. • Uncertain assumption of continued treatment and full efficacy over a lifetime time horizon. • Adverse events from the drug treatment were not included in the analysis, which favours tesamorelin.
CADTH Common Drug Review Best Estimate	Assuming no difference in future clinical events mediated through lipohypertrophy or non-adherence to HIV treatment between tesamorelin and standard of care resulted in tesamorelin being more expensive ($611,657 over 30 years; $37,534 over 1 year) and equally effective compared with standard of care.

QALY = quality-adjusted life-year; VAT = visceral adipose tissue.

EXECUTIVE SUMMARY

Background

Tesamorelin (Egrifta) is indicated for the 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 computed tomography (CT) scan, in treatment-experienced adult HIV-infected patients with lipodystrophy.[1] The dosage is 2 mg (two 1 mg vials) injected subcutaneously once a day. Treatment with tesamorelin should be limited to patients who failed to reduce excess VAT using diet and exercise.[1] The submitted price is $3,085 per box of 60 vials (30-day supply).[2] The annual cost of treatment is $37,534 per patient.

The manufacturer submitted a cost-utility analysis comparing tesamorelin with standard of care (lifestyle modifications, nutrition, and physical activity) in patients with HIV-associated lipohypertrophy over a lifetime time horizon (30 years) from the perspective of a Canadian health care payer. Baseline probabilities and the increased risk of lipohypertrophy-related clinical events, costs, and quality of life data were obtained from observational literature (see APPENDIX 5: SUMMARY OF PARAMETERS USED IN THE SUBMISSION for details). Non-adherence to HIV treatment due to lipohypertrophy was obtained from observational studies. Complete responders, as defined as per the clinical trials (≥ 8% reduction in VAT), were assumed to have no increased risk of lipohypertrophy-related clinical events (revert to the same risks as for the general population) and exhibit full adherence to HIV-treatments.

Summary of Identified Limitations and Key Results

The main limitation of the manufacturer's analysis was the use of a surrogate outcome (VAT) to demonstrate the potential clinical benefit of tesamorelin. The manufacturer's model assumes that the association of HIV-related lipohypertrophy and numerous clinical events such as diabetes, hypertension, and stroke, is causal, with only observational data to support this assumption. The manufacturer also assumed that increased risks of clinical events are mediated solely through VAT, and that complete responders to treatment have no increased risk of the adverse clinical events over a lifetime (same risk as the general population). However, VAT has not been validated as a surrogate for any of the clinical events modelled. Additionally, it was assumed that non-adherence to HIV treatment in patients with HIV-related lipohypertrophy was solely mediated by lipohypertrophy, and that response to tesamorelin would assure complete HIV-treatment adherence and annul the risk of the clinical events from non-adherence to HIV treatment. This has not been demonstrated.

Other limitations of the manufacturer's analysis include: adverse effects associated with tesamorelin were not included in the model; mortality was not considered; the treatment was assumed to be taken by patients for a lifetime, which is not aligned with the views of the CADTH Common Drug Review (CDR) clinical expert, who anticipates the use of the drug for up to one year only; the impact of the drug on quality of life via improvement of body image was not considered, although the results from the clinical trials did not demonstrate such an impact; and finally, the manufacturer's submitted material was incomplete, the model lacked flexibility, and the presented analysis did generally not adhere to best practices in health economics.

CADTH Common Drug Review Analyses

Considering the identified limitations, the most plausible reference case for CDR was to assume no difference between comparators in clinical events associated with lipohypertrophy and non-adherence to HIV treatment, resulting in an incremental cost of $611,657 for tesamorelin and similar quality-adjusted life-years (QALYs) over the 30-year time horizon. As such, standard of care is less costly and has similar clinical effects.

Conclusions

A key area of uncertainty with the manufacturer's pharmacoeconomic submission is the reliance on a surrogate outcome (VAT) as the basis for the demonstration of clinical benefit from the use of the treatment. VAT has not been validated as a surrogate for any of the clinical events modelled, and the assumption that response to tesamorelin would assure complete HIV-treatment adherence and annul the risk of the clinical events from non-adherence to HIV treatment has not been demonstrated. Furthermore, the clinical trials assessing tesamorelin have not demonstrated an impact of the treatment on patient's quality of life (refer to clinical report), and quality of life was not an outcome included by the manufacturer in the cost-effectiveness analysis. In this context, CDR's most plausible analysis was to assume no difference between treatments in future clinical events due to lipohypertrophy or suboptimal adherence to HIV treatment; hence, no additional clinical benefit can be assumed from treatment with tesamorelin compared with standard of care. The additional cost for tesamorelin compared with standard of care, which represents only the drug cost, was calculated to be $37,534 for one year of treatment.

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

1. SUMMARY OF THE MANUFACTURER'S PHARMACOECONOMIC SUBMISSION

The manufacturer submitted a cost-utility analysis comparing tesamorelin with standard of care in a cohort of patients with HIV-associated lipohypertrophy. The time horizon was patient lifetime (30 years), and the model considered from a Canadian public payer perspective. Patients entered the model being treated either by standard of care (lifestyle modifications, nutrition, and physical activity) or tesamorelin. Patients stayed under this treatment for the model's full time horizon. Patients could experience a cascade of clinical events that are either complications/disease states associated with HIV-associated lipohypertrophy or consequences of suboptimal adherence to HIV treatment that is attributable to lipohypertrophy. Complications of lipohypertrophy included type 2 diabetes, hypertension, myocardial infarction (MI), stroke, venous thromboembolic events (deep-vein thrombosis and pulmonary embolism), mild cognitive impairment, and osteoporosis, all of which are assumed to be increased in patients with HIV-associated lipohypertrophy. Suboptimal adherence to HIV therapy resulted in an increase in the number of HIV transmissions and the costs and consequences of it: HIV resistance (initial and second), HIV opportunistic infections (tuberculosis and sepsis), and HIV coinfections including hepatitis C virus. All baseline risks of events, their relative risks of occurrence, and their associated costs and utility scores, were obtained from published literature (see APPENDIX 5: SUMMARY OF PARAMETERS USED IN THE SUBMISSION for details). The prevalence of each of the lipohypertrophy complication and non-adherence health states was assumed to increase annually by 1.85%.

Proportions of responders and non-responders to treatment were taken from the clinical trials,[3,4] with response defined in clinical trials as a ≥ 8% decrease in visceral adipose tissue (VAT). It was assumed that 50% of responders had a "complete" response, and the remaining 50% a "partial" one. Complete responders were assumed to revert to a risk of clinical events as per the general population; it was assumed that partial responders would have a risk on average between the complete responders and non-responders. A similar approach was taken for HIV-treatment adherence, where responders and partial responders would have complete adherence. Discontinuation of tesamorelin due to adverse events was not considered in the model. Mortality was also not modelled. The cost of tesamorelin was obtained from the manufacturer. Standard of care (lifestyle modifications, nutrition, and physical activity) was assumed to be associated with no cost.

2. MANUFACTURER'S BASE CASE

In the reference case, the manufacturer reported that tesamorelin compared with standard of care is associated with an additional 2.02 quality-adjusted life-years (QALYs) and an incremental cost of $134,803, resulting in a cost per QALY of $66,736. Tesamorelin drug cost was $611,657, and treatment with tesamorelin led to averting ~$475,000 in costs of lipohypertrophy-associated events (Table 2).

TABLE 2: SUMMARY OF RESULTS OF THE MANUFACTURER'S BASE CASE

Outcomes	
Additional QALYs for tesamorelin	2.02
Drug cost for tesamorelin	$611,657
Savings from avoided lipohypertrophy-related events for tesamorelin	$278,893
Savings from avoided non-adherence to HIV treatment events for tesamorelin	$197,963
Total cost for tesamorelin	$134,801
ICUR ($/QALY)	66,736 per QALY gained

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

3. SUMMARY OF MANUFACTURER'S SENSITIVITY ANALYSES

Uncertainty was addressed using deterministic sensitivity analyses, which varied model parameters with alternative values. The following parameters were varied: utility scores associated with clinical events (±15%); relative risk (RR) associated with clinical events attributable to lipohypertrophy (±40%); and the discounting rate (0% and 3% were used).

The following parameters increased or decreased the incremental cost per QALY gained by more than 20%:

- The RR of lipohypertrophy-related events decreased by 20% (tested up to 40%). The resulting cost per QALY was from $84,011 to $101,231
- The RR of lipohypertrophy-related events increased by 20% (tested up to 40%). The resulting cost per QALY was from $31,990 to $49,396
- Setting the discount rate to 0% resulted in standard of care being dominated by tesamorelin.

A probabilistic sensitivity analysis was not performed.

The CADTH Common Drug Review (CDR) requested a model that had removed the yearly additional and cumulative incidence applied to events, which led to an incremental cost per QALY of $97,122.

4. LIMITATIONS OF MANUFACTURER'S SUBMISSION

- **Use of surrogate outcomes:**
  Lipohypertrophy-related events: First, the manufacturer assumed that the association of HIV-related lipohypertrophy, and numerous and diverse clinical events such as diabetes, hypertension, and stroke, is causal. Only observational data are provided to support this assertion (some of which are in non-HIV populations; e.g., stroke and MI). Second, it is assumed that these risks of events are mediated solely through visceral adipose tissue (VAT), and that responders to treatment (≥ 8% reduction in VAT) will completely eliminate the risks of the adverse clinical outcomes over a lifetime. Further, if tesamorelin is effective in reducing these events, no evidence was provided that any effect would persist over time. The clinical expert consulted by CDR for this review indicated that tesamorelin is unlikely to be used for more than one year. Most importantly, VAT has not been validated as a surrogate for any of the clinical events modelled. The CDR clinical expert also indicated that the objective of treatment with tesamorelin from current expectations of clinicians would be to improve patients' self-perception and quality of life, not to modify the risks of clinical outcomes.

Non-adherence: In the manufacturer's analysis, non-adherence to HIV treatment observed in patients with HIV-related lipohypertrophy is assumed to be solely mediated by lipohypertrophy. In the model, complete responders became fully adherent to HIV treatment. It is unlikely that lipohypertrophy is the sole factor responsible for non-adherence. If body image does have a causal effect with respect to non-adherence, it is unlikely that the relatively small reduction in VAT used to define complete responders would eliminate all non-adherence. Further, the CDR clinical expert indicates that non-adherence to HIV treatment, a life-saving treatment regimen, is uncommon in this patient population.

Adverse events not modelled: Glycated hemoglobin A1C was shown to be elevated in the tesamorelin arm of the pivotal studies, raising the two following major safety concerns: glucose tolerance and new onset diabetes.[1] The manufacturer did not consider this in its analysis and because of the assumed impact of VAT on events, it assumed a reduction in diabetes mellitus. Furthermore, tesamorelin induces the release of endogenous growth hormone (GH), a known growth factor.[1] From this, the CDR clinical expert indicated that there is concern regarding the potential of increased risk for cancer. Also, the trials showed frequently observed adverse drug reactions related to the induction of GH secretion, such as arthralgia, extremity pain, peripheral edema, and myalgia.[1]

- **Mortality not modelled:** All patients remain alive over the 30-year time horizon of the model regardless of the events that occur; i.e., age-related and disease-related mortality are ignored. It is unclear whether this has major implications, as high-quality evidence supporting a difference in mortality is not available.
- **Treatment duration and continued efficacy over time:** The trials' duration is short and it is assumed full efficacy persists throughout a patient's lifetime. The CDR clinical expert indicated that tesamorelin may not be used long term, and the impact of this is not clear.
- **Body image–associated differences in quality of life:** Patients and the CDR clinical expert indicated that the major impact of treatment of tesamorelin is likely to be realized through improvement in body image and functional status, which would be reflected in improvements in health-related quality of life. This is not considered in the model; however, it may be appropriate, as no difference in quality-of-life measure was noted in available trials (refer to CDR clinical report).
- **Incomplete documentation, non-modifiable model, and non-adherence to best modelling practices:** The original documentation was suboptimal and non-transparent with respect to description of methods, requiring multiple requests for clarifications by CDR to the manufacturer. Additionally, the provided model was not amenable to testing; CDR was unable to test variations in parameters. Key areas of uncertainty were not explored by the manufacturer in sensitivity analysis (components of relative treatment efficacy), reporting of results was not appropriate (negative incremental cost-utility ratios [ICURs]), and poor assumptions were used.

5. COMMON DRUG REVIEW ANALYSES

CDR considered the following analyses to address the limitations identified above. As previously mentioned, the economic model provided by the manufacturer lacks flexibility to test parameters, limiting the conduction of supplementary sensitivity analyses. On the other hand, the main limitation of the analysis was on the validity of VAT as a surrogate endpoint for clinical events, and thus CDR analyses focused on varying this component. Of note, because of the model's weaknesses in terms of quality, the analyses performed by CDR were calculated based on values provided in the report and not directly from the model.

1. **Elimination of the clinical events due to adherence**. When it was assumed that treatment with tesamorelin does not affect adherence to HIV treatment, it resulted in an ICUR of $319,965 per QALY for tesamorelin versus standard of care.
2. **Variation on the assumptions related to the clinical events due to lipohypertrophy.** When it was assumed that tesamorelin does not alter the risk of clinical events associated with lipohypertrophy (diabetes, MI, etc.), the ICUR increased to $422,137 per QALY. If treatment with tesamorelin causes a 40% reduction in lipohypertrophy-related events in complete responders (instead of a 100% reduction), the ICUR is $127,484 per QALY.
3. **Plausible CDR reference case.** This reference case assumes no difference between treatment arms in clinical events associated with lipohypertrophy and in lipohypertrophy-associated non-adherence to HIV medication. Incremental cost = $611,657 and incremental QALY = 0; tesamorelin is dominated (standard of care preferred). If only 12-month tesamorelin is prescribed, incremental cost = $37,534 and incremental QALY = 0; tesamorelin is dominated.

6. ISSUES FOR CONSIDERATION

Tesamorelin is indicated for "the treatment of excess VAT, as assessed by a 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."[1] According to the CDR clinical expert, neither waist circumference measurement nor CT scan are performed during clinical visits, which may lead to questions regarding the optimal use of the treatment.

The clinical expert consulted by CDR indicated that tesamorelin might be prescribed to help back and joint pain and shortness of breath regardless of a patient's waist circumference. The anticipated effect of treatment with tesamorelin, according to the CDR clinical expert's opinion, is to improve a patient's self-perception and quality of life, rather than modify clinical outcomes. Patient quality of life was not demonstrated to be improved by the treatment in clinical trials, and this outcome was not included in the economic evaluation. However, self-perception benefits from treatment may not have been captured by the clinical studies and the cost-effectiveness assessment.

The product monograph indicates that treatment with tesamorelin should be limited to patients who failed to reduce excess VAT using diet and exercise.[1] This was not accounted for in the model, the main comparator in the economic assessment actually being diet and exercise.

7. PATIENT INPUT

Patients report that excessive VAT is associated with self-esteem issues, negative body image, impacts on quality of life, and problems socializing. As mentioned above, these benefits may not have been adequately captured and demonstrated by the clinical trials and effectiveness assessments.

Some patients noted experience with tesamorelin. Patients noted that they might need to take the drug chronically for life; otherwise, there is a possibility of reversal of effects after stopping treatment. Patients also report difficulty administering the drug, as the injection is prepared in several steps. There are also challenges to mobility when travelling with syringes, and difficulties with water and freezer packs for air travel and refrigeration when away from home. This was not accounted for in the cost-effectiveness assessment.

8. CONCLUSIONS

A key area of uncertainty with the manufacturer's pharmacoeconomic submission is the reliance on a surrogate outcome (VAT) as the basis for the demonstration of clinical benefit from the use of the treatment. However, VAT has not been validated as a surrogate for any of the clinical events modelled, and the assumption that response to tesamorelin would assure complete HIV-treatment adherence and annul the risk of the clinical events from non-adherence to HIV treatment has not been demonstrated. Furthermore, the clinical trials assessing tesamorelin have not demonstrated an impact of the treatment on patient's quality of life (refer to Clinical Review Report), and quality of life was not an outcome included by the manufacturer in the cost-effectiveness analysis. In this context, CDR's most plausible analysis was to assume no difference between treatments in future clinical events due to lipohypertrophy or suboptimal adherence to HIV treatment; therefore, no additional clinical benefit can be assumed from treatment with tesamorelin compared with standard of care. The additional cost for tesamorelin compared with standard of care, which represents only the drug cost, was calculated to be $37,534 for one year of treatment.

APPENDIX 1: COST COMPARISON

As confirmed by clinical experts, tesamorelin is the only pharmacological drug available for the treatment of patients with HIV-associated lipohypertrophy. Lifestyle modifications, nutrition, and physical activity represent current standard of care. Table 3 shows the cost of the use of tesamorelin in its approved indication.

TABLE 3: COST TABLE FOR TESAMORELIN FOR THE TREATMENT OF HIV-ASSOCIATED LIPOHYPERTROPHY

Drug	Strength	Dosage Form	Price ($)[a]	Recommended Dose	Average Annual Drug Cost ($)
Tesamorelin (Egrifta)	1 mg/mL	1 mg per vial	$51.4166 per vial $3,085.0000 per box of 60 vials (30-day supply)	2 mg injected subcutaneously once a day	37,534

[a] Manufacturer's submitted price.

APPENDIX 2: SUMMARY OF KEY OUTCOMES

TABLE 4: WHEN CONSIDERING ONLY COSTS, OUTCOMES AND QUALITY OF LIFE, HOW ATTRACTIVE IS TESAMORELIN RELATIVE TO THE STANDARD OF CARE?

Tesamorelin Versus Standard of Care	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)					X	
Drug treatment costs alone					X	
Clinical outcomes			X			
Quality of life			X			
Incremental CE ratio or net benefit calculation	Tesamorelin is dominated by standard of care, being more costly ($37,534 per year) and equally effective.					

CE = cost-effectiveness; NA = not applicable.
Note: Based on the CADTH Common Drug Review reference case.

APPENDIX 3: ADDITIONAL INFORMATION

TABLE 5: SUBMISSION QUALITY

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?		X	
Comments *Reviewer to provide comments if checking "no"*			
Was the material included (content) sufficient?			X
Comments *Reviewer to provide comments if checking "poor"*	Additional information request was sent to the manufacturer. The provided economic model was non-transparent and difficult to perform additional sensitivity analysis on. Inappropriate reporting (negative ICURs) that required CDR clarification.		
Was the submission well organized and was information easy to locate?		X	
Comments *Reviewer to provide comments if checking "poor"*			

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio.

TABLE 6: AUTHOR INFORMATION

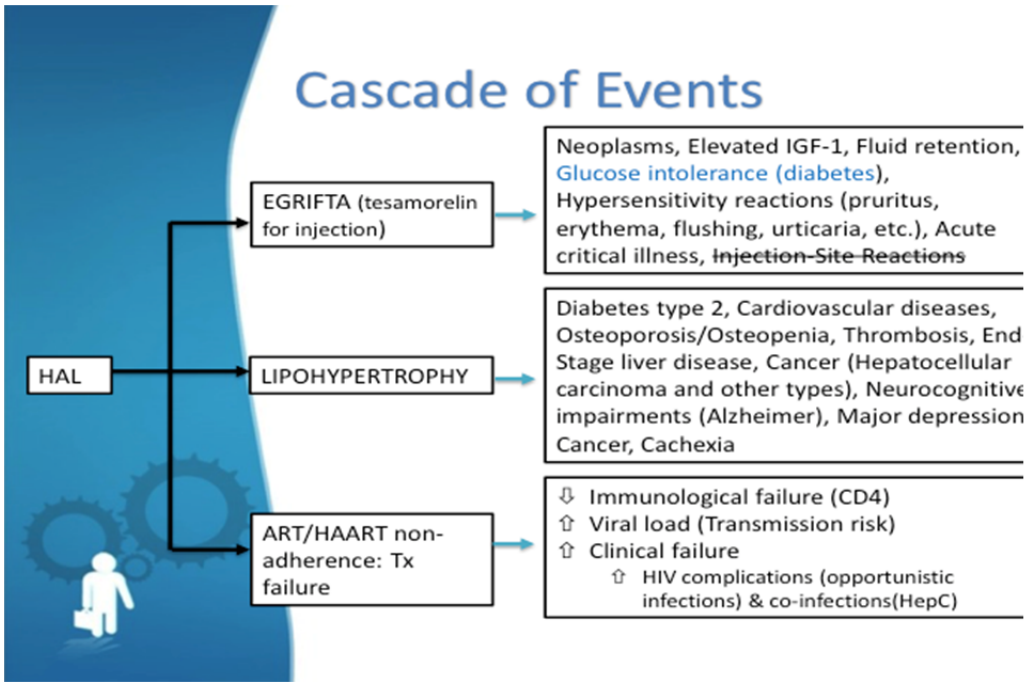
Authors	Affiliations
Not available	Data 4 Actions Inc.

	Yes	No	Uncertain
Authors signed a letter indicating agreement with entire document		X	
Authors had independent control over the methods and right to publish analysis			X

APPENDIX 4: REVIEWER WORKSHEETS

Manufacturer's Model Structure

FIGURE 1: CASCADE OF EVENTS DESCRIPTION



ART = antiretroviral therapy; HAART = highly active antiretroviral therapy; Tx = treatment; HepC = hepatitis C; IGF-1 = insulin-like growth factor 1
Source: Manufacturer's pharmacoeconomic submission.[2]

TABLE 5: DATA SOURCES

Data Input	Description of Data Source	Comment
Efficacy – lipohypertrophy-related clinical events	The relative risks of the association of lipohypertrophy and clinical events (diabetes, cardiovascular diseases, etc.) were obtained from observational literature studies, some that considered a non-HIV population (for MI and stroke).	Inappropriate. There are no trial data indicating causal relationship between reducing VAT and prevention of events.
Efficacy – lipohypertrophy-related clinical events	"Responders" would have a risk of clinical events identical to the general population.	Inappropriate. It is unlikely that "responders" would have the same risk as the general population.
Efficacy – lipohypertrophy-related clinical events	The effect of reduction or amelioration of clinical events would persist over a lifetime.	Uncertain. Persistence with treatment and its effect over time are not well known.
Efficacy – clinical events due to suboptimal adherence	VAT and body image issues lead to non-adherence. Treatment of VAT with tesamorelin will reduce non-adherence	Uncertain. There is a lack of evidence that fat accumulation causes non-adherence and that

Data Input	Description of Data Source	Comment
	with HIV therapy.	treatment would modify adherence. The CDR clinical expert indicates that non-adherence due to lipohypertrophy is a rare event.
Efficacy – clinical events due to suboptimal adherence	All relative risks for clinical events due to suboptimal adherence were obtained from published literature (all observational studies).	Reasonable, but uncertain.
Utilities	Utilities from the clinical events were obtained from related published literature.	Reasonable, although none of these were specifically for HIV-associated lipohypertrophy.
Adverse events	Direct discontinuation due to adverse events was not considered in the model.	Uncertain. The CDR clinical expert indicated that tesamorelin might be related to an increased risk of cancer. Also, concerns were raised about impaired glucose tolerance and new onset diabetes.[1]
Mortality	Not modelled. All patients remain alive over the 30-year time horizon regardless of the events that occur.	Inappropriate. Age-related and disease-related mortality are ignored.
Costs		
Drug	Annual cost ($37,534) from manufacturer.	Appropriate.
Standard of care	Assumed to incur zero cost.	Appropriate.
Events	Direct medical costs for clinical costs were obtained from published and unpublished Canadian studies.	Appropriate.

CDR = CADTH Common Drug Review; MI = myocardial infarction; VAT = visceral adipose tissue.

TABLE 6: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	Comment
Treatment effect was assumed to remain constant over the 30-year model time horizon.	Unlikely. The extension phase indicates that patients' VAT is likely to return to baseline after stopping taking the drug.
Probabilities of developing lipohypertrophy-related clinical events are the same as those in the observational studies.	Inappropriate. Lipohypertrophy and VAT are not validated surrogates. Some of the studies were not HIV-related.
Probabilities of developing clinical events due to suboptimal adherence were modified by tesamorelin.	Uncertain. The CDR clinical expert indicated that adherence due to lipohypertrophy is rare.
Complete responders to treatment have risks of lipohypertrophy-related events identical to the general population.	Unlikely. The CDR clinical expert indicated that HIV patients have a higher risk of cardiovascular diseases and this is independent of VAT.
Complete responders have zero risk of non-adherence.	Unlikely to be different than for non-responders; the CDR clinical expert indicated that non-adherence due to lipohypertrophy is rare.

CDR = CADTH Common Drug Review; VAT = visceral adipose tissue.

Manufacturer's Results

All relevant manufacturer base case and sensitivity analysis results are presented in the main body of the report.

CADTH Common Drug Review Reanalysis

CADTH Common Drug Review Analyses

All relevant manufacturer base-case and sensitivity analysis results are presented in the main body of the report.

APPENDIX 5: SUMMARY OF PARAMETERS USED IN THE SUBMISSION

TABLE 7: COMPLICATIONS OF HIV-ASSOCIATED LIPOHYPERTROPHY

Health states	Annual risk complete responders (normal patient population; from literature)	Relative risk for patients with HIV lipohypertrophy (from literature)	Annual risk partial responders[b]	Annual risk SoC (non-responders)	Annual incidence rate applied to risk (assumption)	Annual Cost of health state (from literature)	Utility score of health state[a] (from literature)
Diabetes	16.2%	2.8	30.78%	45.4%	1.85%	$8,639 for 10 years[c]	0.69
Hypertension	32.2%	2.5	56.35%	80.5%	1.85%	$2,341	0.774
MI	6.63%	1.16	7.16%	7.7%	1.85%	$20,423	0.6575
Stroke	4.13%	2.7	7.63%	11.1%	1.85%	$27,500	0.5
VTE	0.5%	PE 4.5 DVT 4.5	1.38%	2.25%	1.85%	$2,507	0.63
MCI: Dementia	0.75%	3.0	1.5%	2.3%	1.85%	$32,865	Alzheimer: 0.226 Mild: 0.62 Moderate: 0.4
Osteoporosis	9.3%	2.19	12.07%	20.4%	1.85%	$1,642	0.6909

DVT = deep-vein thrombosis; MI = myocardial infarction; MCI = mild cognitive impairment; PE = pulmonary embolism; SoC = standard of care; VTE = Venous thromboembolic events.

[a] Utility score for the complete responders with no complication is 0.825.

[b] Risk for partial responders is the average of complete responders and SoC.

[c] Cost of diabetes is assumed to be 25% of $8,639 in the first year, increased by 10% until the average cost is reached around year 10. All other costs are presented in annual cost.

Source: Content of the table from the manufacturer's pharmacoeconomic submission.[2]

Example (Diabetes):
For diabetes, the risk for the complete responders (16.2%) is obtained from the Centers for Disease Control and Prevention on general population aged 45 to 64 years (65, 66); the risk for the standard of care (SoC) (non-responders) is 16.2% × RR 2.8 = 45.4%; the risk of the partial responders is the average of the two = 30.78%. The weighted risk for tesamorelin is the average of complete and partial responders = 23.49%.

The cost is calculated based on the incremental risk between tesamorelin and SoC = 45.4% – 23.49% = 21.87%. This incremental risk is also increased by the incidence rate of 1.85% annually. Thus, the incremental risk is 22.27% in the second year and 22.69% in the third year, etc.

The undiscounted incremental cost of diabetes in the first year would be 25% × $8,639 × 21.87% = $472, and so forth for the remaining years. All the costs would then be totalled, discounted, and summed up for all the events.

For quality-adjusted life-years (QALYs), the utility score for complete responders is 0.825 (population quality of life [QoL]), utility score for SoC is 0.69, and the QALY for partial responders is the average of 0.7575. The weighted utility score for tesamorelin is 0.79125. Thus the incremental QALY gained per year is 0.10125 (assuming no mortality). All the QALYs would then be totalled for 30 years, discounted and summed up for all the events.

TABLE 8: OUTCOMES ASSOCIATED WITH NON-ADHERENCE

Events	Risk Complete Responders (Assumption)	Risk Partial Responders (Assumption)	SoC (Non-Responders) (From Literature)	Incidence Rate (Assumption)	Cost of Health State (From Literature)	Utility Score of Health State (From Literature)
HIV transmission	0%	0%	8.66%	1.85%	$14,484	0.735
HIV resistance	0%	0%	Initial: 17.19%; second: 8.6%	1.85%	Initial: $8,688; second: $12,212	0.525
HIV-tuberculosis	0%	0%	2.13%	1.85%	$47,000	0.7557
HIV-hepatitis C	0%	0%	5.73%	1.85%	$64,213 (Cost of Solvadi)	0.3543
HIV-related sepsis	0%	0%	3.43%	1.85%	$43,709	0.7267

Source: Content of the table from the manufacturer's pharmacoeconomic submission.[2]

Example (HIV-sepsis):
For HIV-related sepsis, the risk for both complete and partial responders is 0. Based on the assumption that 22.9% patients on SoC would be non-adherent, the risk for SoC is 22.9% × 15% = 3.43%.

The cost is calculated based on the incremental risk between tesamorelin and SoC = 3.43% – 0% = 3.43%. This incremental risk is also increased by the incidence rate of 1.85% annually. Thus, the incremental risk is 3.50% in the second year and 3.57% in the third year etc.

The undiscounted incremental cost of sepsis in the first year would be $43,709 × 3.43% = $1,503, and so forth for the remaining years. All the costs would then be totalled, discounted, and summed up for all the events.

For QALYs, the utility score for complete responders is 0.825 (population QoL), utility score for SoC is 0.7267, and the utility score for partial responders is the average of 0.7759. The weighted utility score for tesamorelin is 0.7759. Thus, the incremental QALY gained per year is 0.0492 (assuming no mortality). All the QALYs would then be totalled for 30 years, discounted, and summed up for all the events.

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