CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-505

OFFICE DIRECTOR MEMO

Summary Basis for Regulatory Action

Date	November 10, 2010
From	Curtis J. Rosebraugh, MD, MPH Director, Office of Drug Evaluation II
Subject	Summary Review
NDA/BLA # Supp #	NDA 22505
Applicant Name	Theratechnologies Inc.
Proprietary / Established (USAN) Names	Egrifta Tesamorelin acetate
Dosage Forms / Strength	Lyophilized powder 1.1 mg 2mg subcutaneously once daily
Proposed Indication(s)	Reduction of excess abdominal fat in HIV patients with lipodystrophy
Action:	*Approval*

Introduction and Discussion

This review will be a brief summary of the basis for the regulatory action regarding tesamorelin and the reader should refer to the reviews in the action package for more detailed discussion. Tesamorelin, a new molecular entity, is a synthetic 44-amino acid peptide analog of growth hormone-releasing factor (GHRF) that causes the release of pituitary growth hormone (GH). GH itself has a number of direct, as well as indirect effects working through IGF-1 production. The proposed use of tesamorelin is to treat lipodystrophy changes that occur in some HIV-infected patients as a result of drug therapy. HIV-associated lipodystrophy is a rare adverse effect of drugs used in highly active anti-retroviral therapy (HAART), particularly protease inhibitors, characterized by abnormal body shape as a result of redistribution of body fat. The lipodystrophy is manifested as loss of peripheral subcutaneous adipose tissue (face, limbs, buttocks) and increases in adipose tissue around abdominal visceral (visceral adipose tissue-VAT) and dorsocervical area (buffalo hump). The consequence of these changes are that they can impact patients ability to perform their usually activities of daily living and the physical appearance of these changes are quite noticeable and may be psychologically distressing and stigmatizing to patients.

Also accompanying the lipodystrophic changes can be metabolic abnormalities manifested as low HDL-Cholesterol, increased triglycerides, and insulin resistance. There is some debate if these metabolic changes, as well as visceral fat accumulation, may contribute to increased cardiovascular risks in HIV-infected population. Tesamorelin was developed to decrease VAT with the goal of potentially decreasing cardiac risks and to improve quality of life in those affected by lipodystrophy. With this in mind, there are two potential paths for approval, 1) demonstrating that a decrease in VAT (or correction of metabolic abnormalities) correlated to improvement in cardiovascular outcomes, or 2) demonstrating that treatment resulted in significant improvement in patient quality of life (patient-reported outcomes-PRO).

At present there are not any approved therapies for HIV-lipodystrophy. There have been other agents considered, but they had side-effects associated with direct GH excess and indirect excess IGF-1 release that, in relation to efficacy results, were felt to not allow for an appropriate risk:benefit ratio to allow marketing. As such, the review of tesamorelin focused on expected GH-induced adverse events in relation to clinical efficacy.

While there are scientific reasons to predict that decreasing VAT or correcting metabolic abnormalities may be predictive (biomarker) of decreasing cardiovascular risk, this assumption is speculative and if we were to use modification of cardiovascular risks as sole basis of approval, we would need a demonstration of actual benefit that most likely would be in the form of a well-designed outcome trial. This would be very difficult in this population as the prevalence of lipodystrophy is low and the absolute risk for cardiovascular events (and therefore the number of 'events') is likely to be low making the size necessary to power such a trial potentially impossible. Therefore, the evaluation of the PRO for this application has great importance in demonstrating that patients will derive some benefit as the potential for cardiovascular improvement is an unknown and will likely remain that way. This line of reasoning influenced the advice that had been given to the sponsor during the development program, as the agency set a threshold of decrease in VAT of 8% (thought to perhaps be 'clinically important' based on epidemiologic study) as a demonstration that tesamorelin was effective in treating lipodystrophy, but recommended that if cardiovascular risk reduction could not be established, that demonstration of clinically meaningful improvement in body self image would probably be necessary for approval (weighed against risks).

The side-effect profile of tesamorelin included those expected with GH excess including glucose impairment and increases in IGF-1 levels (which carry unknown, but theoretical risks). Egrifta clearly met our suggestion for VAT reduction in both pivotal trials. While there is some discussion regarding the total validity of the PRO instrument, there is agreement that the BAD component can be relied upon as demonstrating clinically meaningful improvement in body self image specifically for HIV drug-induced lipodystrophy. As such, the review team has determined that the risk:benefit profile is appropriate for marketing as long as the label clearly states that there are risks and it is unknown if the benefits will extend beyond those demonstrated by the PRO (i.e. if there are any cardiovascular benefits with VAT reduction). I agree with this assessment and believe this drug should be approved with careful labeling outline the expected benefit in the face of known and unknown risks.

Efficacy

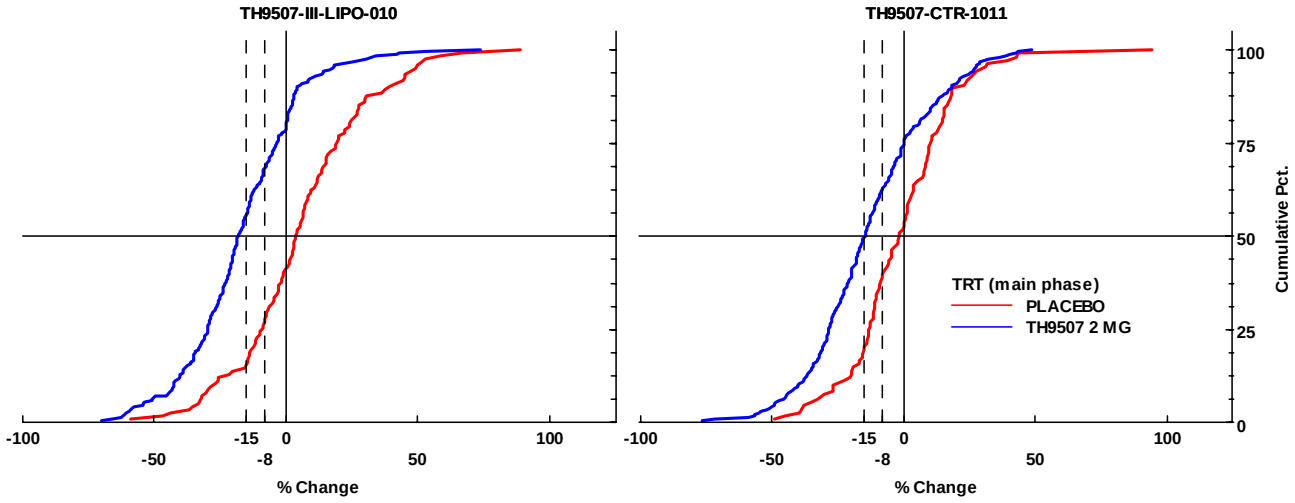
The two main trials used to demonstrate efficacy were 6-month, placebo-controlled with a primary endpoint of percent change from baseline to Week 26 in VAT defined as the change in cross-sectional area in cm^2 measured by CT scan at the L4-L5 vertebral level. There were numerous secondary endpoints including cholesterol/HDL-cholesterol ratio, triglyceride levels, IGF-1 levels, and patient reported outcomes (PROs) related to Body Image that evaluated Belly Profile, Belly Size Evaluation and Belly Appearance Distress (BAD). The primary outcome and distribution of percent change is demonstrated in the table and figure below from Dr. Pian's review (pages 6, 20).

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

Study		TH9507 (2 mg)		Placebo		Treatment difference from placebo
		n	Mean	n	Mean	LSM, (SE), [95% CI], p-value
10	Baseline (SD)	272	178.3 (76.9)	136	171.0 (76.9)	
	% change (SE)		-17.8% (1.6)		+2.2% (2.2)	**-19.6% (2.7) [-23.7, -15.3] p<0.001**
	Change (SE)	272	-27.4 (2.2)	136	+4.4 (3.2)	**-31.9 (3.9) [-39.5, -24.3] p<0.001**
11	Baseline (SD)	268	186.5 (86.6)	126	194.9 (95.5)	
	% change (SE)		-13.8% (1.5)		-2.4% (2.2)	**-11.7% (2.7) [-16.2, -7.1] p<0.001**
	Change (SE)	268	-21.0 (2.4)	126	-0.4 (3.5)	**-20.6 (4.2) [-28.8, -12.3] p<0.001**

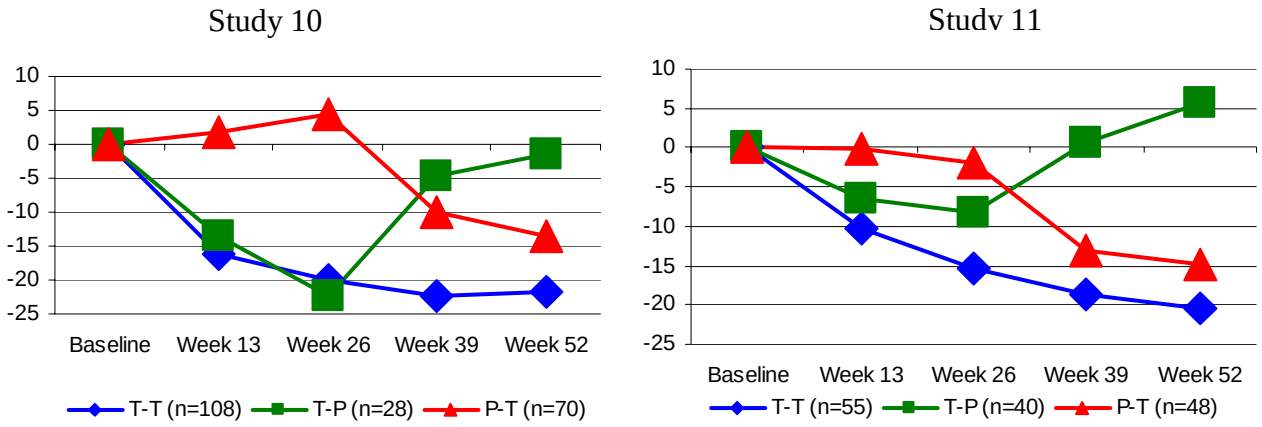
*Analysis of covariance model with treatment as fixed effect and baseline VAT as covariate

Figure 1 Cumulative distribution of VAT % change from baseline to Week 26 by main phase treatment – ITT excluding patients with baseline carried forward



The table and figure demonstrates that tesamorelin clearly decreased VAT greater than the pre-specified endpoint of 8% compared to placebo. Both of these trials had randomized withdrawal phases which also demonstrated that VAT: 1) decreased in those subjects originally started on placebo that were then switched to tesamorelin and 2) re-accumulated without continued tesamorelin exposure (lack of durability of effect). This is demonstrated from the figure below from Dr. Parks' review (Page 7).

Figure 2: Changes in VAT from Weeks 0 through 52 in Study 10 and 11



Waist circumference was also assessed in this trial, and on average was found to be 1.5 cm less in those exposed to tesamorelin compared to placebo. Most of the secondary endpoints, while not robust, trended in the direction favoring tesamorelin therapy, some more in one trial than in the other. Subjects receiving tesamorelin also experienced increases in lean body mass compared to placebo as demonstrated below in table below from Dr. Pian's review (page 28)

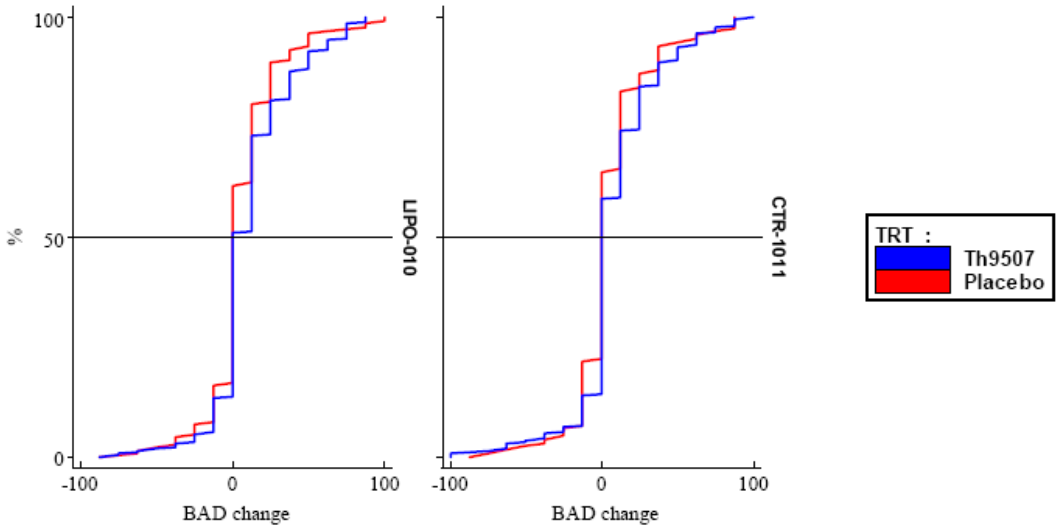
Table 2 ANCOVA* results for Lean Body Mass change (kg) from baseline to Week 26 – ITT, LOCF

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

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

The main secondary endpoint of interest is the PRO as without data to support that decrease in VAT led to an improved cardiovascular outcome, there needs to be a demonstration that subjects experienced a meaningful improvement in body self image or function. The sponsor used a PRO tool that evaluated the Body Image Impact Module (BIIM). The Study Endpoints and Label Development (SEALD) group determine that the overall BIIM had questionable content validity, but that the belly appearance distress (BAD) component of the BIIM may be a valid measure to support labeling in this specific application. The results of the PRO measures are present in the figure below from Dr. Parks' review (Page 8).

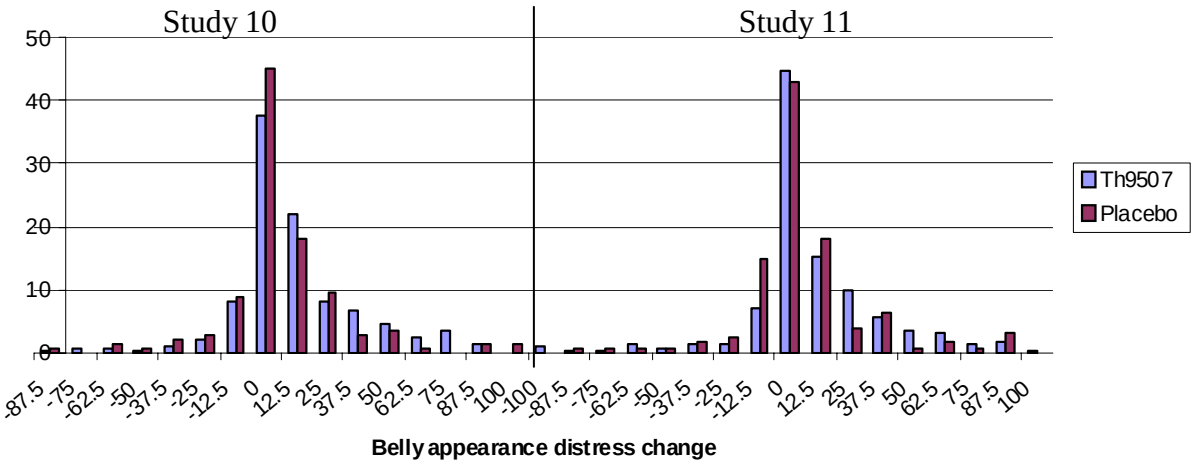
Figure 50 Cumulative distribution of Belly Appearance Distress change from baseline to Week 26 – ITT, LOCF



negative=worse and positive=better

Dr. Papadopoulos concluded that the treatment effect based on BAD was very modest and that most of the separation was seen in a subset of the total population. I think this is also demonstrated in the Figure below from Dr. Pian's review (page 58) where a small group of subjects seem to have derived the most benefit, which in a few cases may have been substantial.

Figure 2 Percentage of patients by BAD change from baseline – ITT, LOCF



negative=worse and positive=better

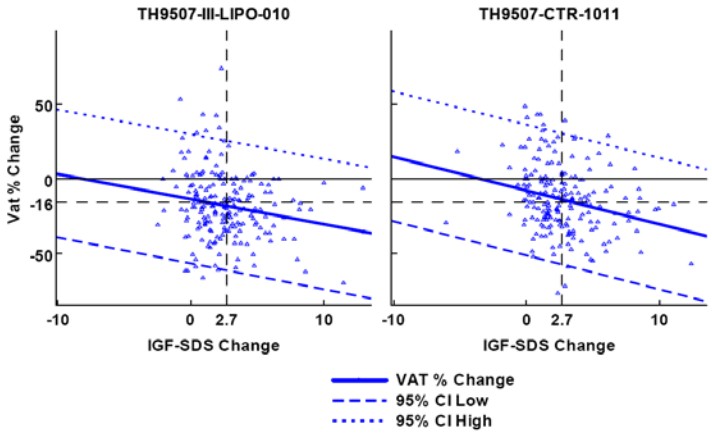
I agree with Dr. Papadopoulos' assessment and note that it is not unusual that trials where efficacy is demonstrated may be driven by a sub-population of the total group. As such, the results of the PRO evaluation indicated there are some patients that will experience improvement, but many will have little to none and (b) (4)

Safety

Because the effect of GHRH is through release of GH, it is expected that tesamorelin would have a safety profile consistent with the administration of exogenous GH. For the most part, this is what was found. One particular concern is the possibility of tesamorelin increasing IGF-1 concentrations which theoretical may increase cancer risk. IGF-1 was increased in subjects with about 30% of subjects having elevations > 3 standard deviations. While a increase in carcinogenesis is not proven, it does remain a concern and as such, it would be prudent to monitor IGF-1 levels and make appropriate adjustments in those subjects with increases. Dr. Pian performed an analysis for me to see if IGF-1 levels correlated with VAT or BAD (figure below), and they did not (nor did they correlate with BAD), so we would not expect adjusting dosing based on IGF-1 levels to have an effect on efficacy.

Correlation between IGF-SDS change and VAT percent change at Week 26
The correlation coefficient was -0.19 for Study 10 and -0.25 for Study 11 (-0.22 pooled). R square was 0.04 and 0.06 (0.05, pooled), respectively. Consequently, the variability of the VAT % change from baseline that could be explained by the IGF-SDS change from baseline was only 4% to 6% (wide 95% CI in Figure 36).

Figure 36 Correlation between IGF-SDS change and VAT % change from baseline with 95% confidence interval



Increased GH is associated with developing glucose intolerance and diabetes, and such was the case in this application. The glucose intolerance seemed to resolve with discontinuation of tesamorelin therapy. It would therefore be prudent to monitor HgbA1C and should it rise to levels indicative of glucose intolerance, make decisions regarding continued treatment with tesamorelin based on the perceived benefit to the individual patient.

Since tesamorelin is a protein, it has the potential to be immunogenic. Approximately 50% of subjects developed anti-tesamorelin antibodies during the study period. A subset of this group also had cross-reactivity with human GH-releasing factor and evidence of neutralizing antibodies, but this did not seem to be associated with loss of efficacy. There also were immunogenic reactions compared to placebo (27 vs 1), most resolving spontaneously or with antihistamines. A consult review by the Division of Pulmonary, Allergy and Rheumatology Products (DPARP) did not identify any serious cases of hypersensitivity reaction or cases of anaphylaxis.

Subjects with diabetes treated with insulin or oral anti-diabetic agents were excluded from the clinical studies. However, since this is the only option for lipodystrophy, it seems likely that it will be used in this population. Because of this, a safety study should be done to monitor for changes in glucose control and also to evaluate for potential IGF-1 induced retinopathy as outlined in Dr. Parks' review.

Advisory Committee Meeting

An advisory committee meeting was held on May 27, 2010. The committee voted 16 to 0 for approval of tesamorelin. While many members expressed the marginal results of the PRO, they did recognize that VAT was affected, and that there did appear to be a subgroup of subjects that would experience improved body image. They were probably also influenced by some wrenching testimonials during the open public session of patients that suffer from this condition and the desire to make therapy available for this group.

Conclusions and Recommendations

Lipodystrophy can have a devastating effect to the lives of those when it occurs, and like other diseases there is a great deal of urgency to find effective treatments. However, as with all diseases in which we seek effective treatments, we cannot allow urgency to substitute for evidence of efficacy. Tesamorelin did demonstrate that it decreased VAT and this is supported by evidence of patient reported improved satisfaction as measured by BAD. The results however are marginal demonstrated by the limited change in waste size circumference, tenuous results for BAD and are likely to only occur in a limited number of patients. While the effects are not impressive, I believe they are real, although they are mostly limited to a subgroup that cannot be pre-identified. Therefore, I believe that tesamorelin should be available for this group, although the only way to know if it will work for any given patient is to try therapy and see if there are results. If there does not seem to be perceived benefit, tesamorelin should be discontinued so as not to have continued exposure of patients to unnecessary risks. It should be clear, that tesamorelin is not a miracle cure, and that most will probably have only a marginal, if any, effect for most. However, there are not any other therapies at present, and some will benefit.

It is important to determine if someone is getting adequate benefit from therapy with the goal of stopping the drug in those that aren't as there are not any drug therapies free of risk, and tesamorelin is not an exception. There are non-serious adverse events (arthralgias, headache) and the potential for serious adverse events such as the development of diabetes or immune reactions. As well, there are theoretical adverse events, not proven or disproven, such as cancer and retinopathy.

I believe tesamorelin should be approved if we can agree to adequate labeling. A PMR should be part of the approval to evaluate its effect, and potential for adverse effects, in diabetic populations. The team is considering other commitments of observational studies to accumulate epidemiologic data looking for cancer signals or cardiovascular benefit, and this seems appropriate as well.

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/s/

CURTIS J ROSEBRAUGH
11/10/2010