

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-505**

**SUMMARY REVIEW**

## Division Director Memo

<b>Date</b>	November 5, 2010
<b>From</b>	Mary H. Parks, M.D.
<b>Subject</b>	Division Director Summary Review
<b>NDA/BLA #</b> <b>Supplement #</b>	22505
<b>Applicant Name</b>	Theratechnologies Inc.
<b>Date of Submission</b>	May 29, 2009
<b>PDUFA Goal Date</b>	March 29, 2009
<b>Proprietary Name /</b> <b>Established (USAN) Name</b>	Egrifta (tesamorelin acetate)
<b>Dosage Forms / Strength</b>	Lyophilized powder containing 1.1 mg tesamorelin Recommending dosing 2 mg sc once daily
<b>Proposed Indication(s)</b>	Reduction of excess abdominal fat in HIV patients with lipodystrophy
<b>Action/Recommended Action for NME:</b>	Approval

### 1. Introduction and

### 2. Background

This new drug application proposes for the use of Egrifta (tesamorelin acetate), a synthetic growth hormone releasing factor (GHRF) analog, for the reduction of excess abdominal fat in HIV patients with lipodystrophy. Egrifta is a 44-amino acid peptide of human GHRF that has been modified with a hexenoyl moiety at the N-terminus to extend its half-life while retaining its biological activity as a hypothalamic peptide stimulating the release of pituitary GH.

HIV-lipodystrophy was first observed in the 1990s after the wide use of highly active anti-retroviral therapies (HAART), particularly protease inhibitors. The syndrome is characterized by loss of peripheral subcutaneous adipose tissue (SAT), especially in the face, limbs, and buttocks; increased visceral fat accumulation or visceral adipose tissue (VAT); and lipomas, particularly in the dorsocervical area (buffalo hump). Accompanying these dysmorphic features are metabolic abnormalities such as low HDL-C, increased TGs, and insulin resistance - changes thought to contribute to increase CV risk in the HIV-infected population. The physical stigma of the syndrome is psychologically distressing to patients and many have raised concerns that this would result in noncompliance to effective anti-retrovirals.

There are currently no approved therapies for HIV-lipodystrophy although several interventions have been studied which have been discussed in the reviews of Drs. Mohamadi and Roman. (b) (4)

rhGH at pharmacologic doses was found to be effective at reducing VAT with improvements on several patient reported outcomes. However, the FDA did not approve the use of Serostim® for the treatment of HIV-lipodystrophy because of the marked increases in glucose intolerance and development of diabetes in some patients. The overall conclusion was that the manifestations of excess GH, some of which are known to convey excess CV risks, negated any expected benefit of VAT reduction with Serostim®.

It is with this background knowledge on the efficacy and safety of rhGH in HIV-lipodystrophy that Egrifta was reviewed, with careful attention to the GH-stimulating effects of this drug.

As presented by the applicant in its clinical overview of this application (See Module 2.5 of NDA 22-505), abdominal obesity and increased VAT is associated with increased CV risk that is often attributed to the accompanying dyslipidemia and glucose impairment. The rationale for Egrifta development in the HIV population was based on the extension of concerns over this increased CV risk to a population that is already at increased risk of type 2 diabetes and CVD as a result of anti-retroviral therapies.<sup>1,2</sup> In addition to increased CV risks associated with HIV lipodystrophy, the applicant also argued that self-perception of fat accumulation due to anti-retroviral therapies contributed to nonadherence to these highly effective treatment regimens that have dramatically reduced the fatality rate of HIV.<sup>3</sup>

Despite the well-reasoned rationale and suggested clinical benefits of Egrifta on these endpoints by lead investigators such as Dr. Steven Grinspoon<sup>4,5</sup>, the clinical development program of Egrifta was not designed to show conclusive evidence of decreased CV risks from VAT reduction or improved compliance/adherence to HAART. At an EOP2 meeting on March 30, 2005, the applicant asked the FDA if a decrease in VAT of 8 to 10% would be an acceptable primary endpoint to support an indication to treat HIV-lipodystrophy. The FDA agreed to this endpoint; however, the following advice was relayed in those meeting minutes:

*In that the link between VAT reduction and improved cardiovascular risk has not been established in HARS patients, the Division believes that the demonstration of clinically meaningful improvement in body self image measured by a well validated instrument (correlated with a significant reduction in VAT) is an essential component of any NDA*

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<sup>1</sup> Currier, JS and Havlir DV (2004). Complications of HIV disease and antiretroviral therapy. Highlights of the 11<sup>th</sup> Conference on Retroviruses and Opportunistic Infections, February 8-11, 2004, San Francisco, California, USA. Top.HIV.Med, 12, 31-45.

<sup>2</sup> D-Arminio A et al Cardio and cerebrovascular events in HIV-infected persons. AIDS, 18, 1811-1817.

<sup>3</sup> Duran S et al. Failure to maintain long-term adherence to highly active antiretroviral therapy: the role of lipodystrophy. AIDS, 15, 2441-2444.

<sup>4</sup> Falutz J et al. Metabolic effects of a GH-releasing factor in patients with HIV. N Engl J Med 2007;357:2359-70.

<sup>5</sup> Falutz J and Grinspoon S. Effects of GH-releasing factor in HIV-infected patients. Authors reply to correspondence. N Engl J Med 2008;358:969-970.

*submission supporting an indication for the treatment of excessive VAT in HARS patients. Furthermore, it is strongly recommended that an attempt should be made to correlate the improvement in body self image with enhanced compliance with antiretroviral HAART therapy.*

In other words, the FDA did not require evidence of CV risk reduction associated with the VAT changes for this NDA. However, there was much reliance on demonstration of improved self-image and the FDA referred the applicant to Phase V Technologies for the development of the patient-reported outcomes assessment.

At the EOP2 meeting the applicant was also advised to conduct its two pivotal trials sequentially using blinded data from the first trial to determine how much change in patient-reported body self image is associated with a clinically meaningful reduction in VAT and the second trial would serve to validate the PRO instruments.

Egrifta clearly met its primary efficacy endpoint in two pivotal studies. However, the significant reductions in VAT were not accompanied by robust or consistent changes in secondary supportive efficacy measures of improved patient's self-perception of body image or lipid abnormalities. Instead, Egrifta displayed similar side-effects (albeit attenuated) to that of rhGH with a higher incidence of fluid-retaining adverse events, glucose impairment/risk of diabetes, and increases in IGF-1 levels compared to placebo. Despite the unanswered question on what the clinical benefit of VAT reduction is to the HIV population, an advisory committee panel voted unequivocally in favor of approval of Egrifta. In reviewing the explanations for their vote, several members cited the powerful testimonials given by some patients during the open public hearing and the absence of an approved therapy for this condition which weighed into their recommendation.

FDA heard the plea from the medical and patient community on making this therapy available. However, all parties here must be keenly aware that data are absent on the long-term clinical benefits of Egrifta on CV risk reduction, compliance to HAART and the long-term risks of elevated IGF-1 levels. And it is with this understanding that the label for Egrifta must be demarcated for the intended population and clearly states the unknown benefits and potential risks. It should also be clearly conveyed that the approval of Egrifta based on VAT reduction in this limited patient population with few alternatives, is not an FDA endorsement of this endpoint as a validated surrogate for drug approval in other highly prevalent conditions (e.g., metabolic syndrome, obesity, atherosclerosis).

This memo will focus primarily on the clinical efficacy and safety concerns of Egrifta, labeling to inform prescribers and consumers on the appropriate use of this product, and postmarketing requirements to further understand the long-term benefits and risks of this product. The reader is referred to other discipline reviews for details of the complete development program for Egrifta.

### **3. CMC/Device**

Please see reviews/memos from Drs. Leginus, Tran, Fong, and Al-Hakim. ONDQA has recommended approval of this NDA. Office of Compliance has also completed its inspection of the different manufacturing and testing facilities and has provided an overall Acceptable recommendation.

Tesamorelin acetate is a synthetic analog of human GH releasing factor. It is comprised of the identical 44 amino acid sequence as the naturally occurring hormone but with a hexenoyl moiety attached to the tyrosine residue at the N-terminal part of the molecule. The impurities and degradants generated during synthesis and storage of the drug substance have been qualified and determined to be within acceptable limits.

The drug product is a sterile, lyophilized powder that is packaged as the free base of tesamorelin acetate 1.1 mg overfill to ensure the availability of 1.0 mg actual dose administered after reconstitution. The vial also contains one excipient, mannitol USP, but no preservative, as it is indicated for immediate single-use injection. The drug product is photo labile and while the clear glass vial will not protect from exposure to light, the opaque carton has been deemed sufficient to protect against degradation. The product will have a shelf life of 24 months stored at 2° to 8°C.

Egrifta is going to be supplied as a kit comprised of two boxes:

- Box 1 is the Medication Box and contains 60 vials, each containing 1.1 mg tesamorelin acetate. This medication box, which contains a 30-day supply of Egrifta, must be refrigerated.
- Box 2 is the Injection Kit box and contains thirty 10-mL vials of Sterile Water for Injection, USP and the appropriate needles and syringes necessary for reconstitution and injection of drug product

The patient must reconstitute two vials of tesamorelin acetate using sterile water drawn up from one 10-mL vial supplied in Box 2. The reconstituted drug product is to be injected immediately.

Dr. Steven Fong has not identified any deficiencies in his microbiology assessment of this NDA to preclude its approval. However, he is concerned that the packaging of the drug product in two vials (each containing 1.1 mg tesamorelin) requiring reconstitution and injection to achieve the recommended 2.0 mg daily dosing regimen could increase the risk for microbiological contamination. He is recommending that the applicant commit to providing Egrifta in a single dose vial containing 2.2 mg of the product. In his review he describes the timelines for conducting single vial feasibility studies as follows:

Time after NDA Approval	Time after Initiation of Stability Studies	Milestone
No later than 1 month	0 months	Feasibility studies initiated
No later than 15 months	No later than 14 months	Sponsor submits a <i>In Response to the Requirements for Phase 4 Commitments</i> correspondence that summarizes the results of studies conducted during the first year
No later than 31 months	No later than 30 months	If a suitable process for providing the daily dose of the drug product in a single vial is determined, sponsor submits a supplement proposing manufacturing with this process. If a process is not found, the sponsor submits a second <i>In Response to the Requirements for Phase 4 Commitments</i> correspondence that justifies why provision of the daily drug dose in a single vial drug is

		not feasible
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This will be a postmarketing requirement.

## 4. Nonclinical Pharmacology/Toxicology

Please see reviews and memos written by Drs. Lauren Murphree Mihalcik and Todd Bourcier. The final recommendation from Pharmacology/Toxicology is approval of NDA 22-505. The nonclinical program essentially identified toxicities that are reflective of excess GH. In rats and dogs dosed chronically (6 mos and 52 wks, respectively), some animals developed glucose intolerance or severe diabetes, elevated cholesterol levels, increased organ weight, and acromegalic features.

In their original review signed off on March 1 and 2, 2010, a Seg 2 repro-tox study was recommended as a postmarketing required study to characterize the risk of hydrocephaly in offspring of treated dams. Pregnancy Category C was also recommended at that time. After consultation with the Maternal Health Team, there was concurrence that this drug should be labeled as Pregnancy Category X because no clinical benefit could be identified for use during pregnancy to offset the potential risk of hydrocephaly or reduced VAT during pregnancy. With that designation, an embryofetal study was no longer necessary as the drug would be contraindicated for use during pregnancy and the findings from an additional nonclinical study would not alter such labeling. An addendum to the pharmtox review dated August 27, 2010, outlines the updated recommendations of Drs. Murphree Mihalcik and Bourcier to reflect concurrence on Pregnancy Category X labeling and retracting a prior recommendation for the Seg 2 repro-tox study.

## 5. Clinical Pharmacology/Biopharmaceutics

Please see review by Drs. Ritesh Jain and Sally Choe who have not identified a deficiency in their discipline to preclude approval.

The clinical pharmacology program consisted of 10 studies: six single or multiple dose PK or PK/PD studies in healthy and HIV-infected individuals; two BA studies; and two drug-drug interaction studies. The results of these studies have sufficiently characterized the PK/PD of tesamorelin acetate in the indicated population, the dose-response and appropriateness of the proposed dosing regimen, and not identified concerning potential DDIs.

## 6. Clinical Microbiology

Not applicable.

## 7. Clinical/Statistical-Efficacy

Please see reviews from Drs. Mohamadi, Roman, and Lee for a complete discussion of the Phase 2 and 3 trials. There was one dose-finding trial (LIPO 008) which was a 12-week study in patients with HIV-lipodystrophy randomized to placebo, tesamorelin 1 mg or 2 mg daily. This study supported the selection of the 2 mg daily dosing regimen for Phase 3.

The two Phase 3 trials consisted of a randomized, double-blind, placebo-controlled period of 26 weeks' duration referred to as the Main Phase. Both of these trials were similar with respect to patient eligibility criteria and study design. The primary efficacy endpoint was the percent change from Baseline to Week 26 in VAT, defined by a change in the cross-sectional area in cm<sup>2</sup> measured by CT scan at L4-L5. Secondary endpoints included TC/HDL-C, TG levels, IGF-1 levels, and PROs. Additional exploratory endpoints are described in the medical and statistical reviews.

In both Phase 3 trials, tesamorelin 2 mg qd resulted in statistically significant reductions in VAT from Baseline at Week 26. The following table from Dr. Pian's statistical review summarizes the primary efficacy results in these trials.

**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 LSM, (SE), [95% CI], p-value
	n	Mean	n	Mean	
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

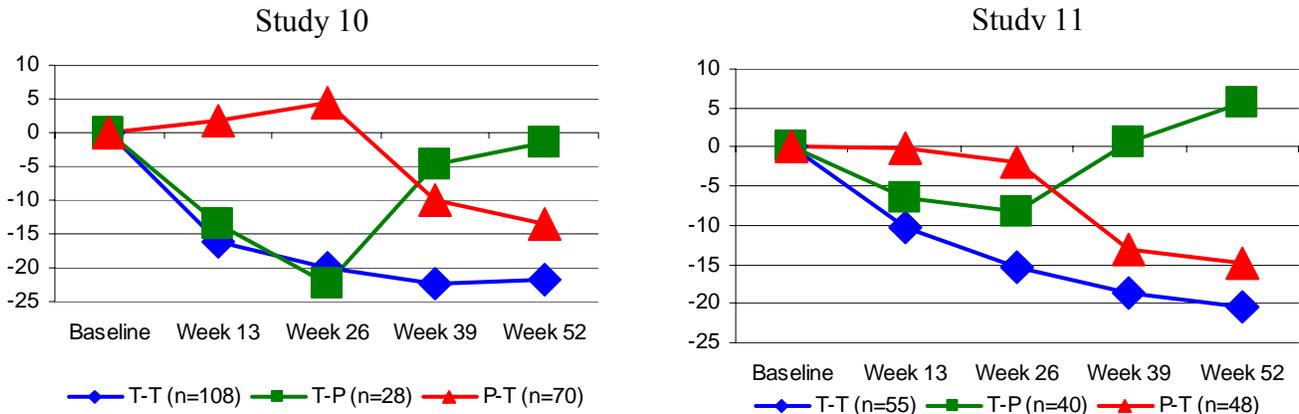
\*Analysis of covariance model with treatment as fixed effect and baseline VAT as covariate

There was no clear explanation for the more robust response in Study 10.

The Main Phase of both trials was followed by an Extension Phase in which patients previously randomized to placebo were switched to tesamorelin 2 mg qd and patients previously treated with tesamorelin 2 mg qd were re-randomized to receive either placebo or continue on tesamorelin at the same dosing regimen for another 26 weeks' duration. The Extension Phase provided additional information on the long-term efficacy and safety in patients treated with tesamorelin 2 mg qd for 52 weeks; the durability of VAT reduction after discontinuation of tesamorelin; and further assessment of whether initiation of tesamorelin in previously untreated patients (placebo in Main Phase) had similar efficacy and findings as those randomized to tesamorelin in the Main Phase. Interpretation of data from the Extension Phase is somewhat limited by the absence of an appropriate comparator. Furthermore, patient discontinuations or enrollment of only patients who have shown efficacy or tolerability to tesamorelin in the initial 26 weeks results in an enriched population for both safety and effectiveness. Despite this, the following figure illustrates some evidence of durability of

effect in patients receiving tesamorelin out to 52 weeks. A more important observation is that for patients discontinuing tesamorelin, there was no durability of effect. Patients switched to placebo had increases in VAT to levels that were similar to those measured at Baseline or even higher (see Figure 2 below).

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



In order to maintain any reduction in VAT with Egrifta, a patient would therefore require chronic therapy, as discontinuation of treatment results in reaccumulation of VAT.

Because assessment of VAT requires assessment through routine CT scans, the applicant is proposing, as an alternative, monitoring of drug effect based on waist circumference. Waist circumference was a secondary assessment in both trials and the mean change from Baseline relative to placebo was approximately 1.5 cm and found to be statistically significant in both trials.

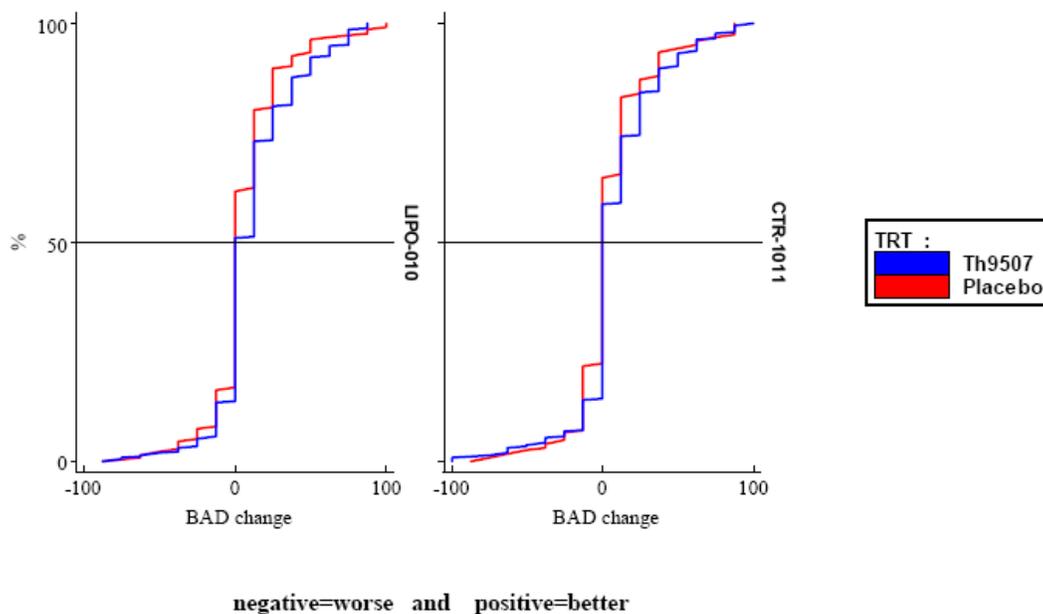
Dr. Mohamadi has clearly explained the hierarchy for analysis of the multiple secondary endpoints under Section 6.1.5 of his review. In both trials, evidence of significant effect of Egrifta on many of these endpoints is lacking or inconsistent. An expectation that reducing VAT with Egrifta would also lead to improve dyslipidemia was not fulfilled. Significant reductions in TGs, TC/HDL-C and non-HDL-C were observed in one study but not the other. Even the statistically significant changes for some of these parameters are modest compared to what can be achieved with available therapies to treat dyslipidemia. For example, Study 10 resulted in a median percent change from Baseline in TG of -13%. Reductions of 20-50% can be achieved with statins and fibrates, hence Egrifta should not be considered primary therapy for treating dyslipidemia in HIV patients. At best, one can only conclude that there were no adverse changes in lipid profiles associated with Egrifta therapy.

The secondary endpoint that requires more discussion is the patient-reported outcome (PRO). As noted in the Introduction/Background, this was the only secondary endpoint identified by the Agency for which the applicant needed to show a positive effect on to support the primary endpoint of VAT reduction. In particular, the applicant had to demonstrate an improvement on belly appearance distress (BAD), as this was considered a consequential component of PRO,

whereas other PRO measures (belly size evaluation or belly profile) were considered supportive.

Please see the Appendix to Dr. Pian’s review for a complete summary of PRO results. Neither of the supportive PRO measures (BSE and belly profile) was significantly different between Egrifta and placebo. Belly appearance distress scores improved at Week 26 in both treatment groups with no significant difference in one study (Study 10  $p=0.076$ ) and significant in the other (Study 11  $p=0.022$ ). Overall, these results are not robust and from the cumulative distribution curves generated by Dr. Pian and provided below one might conclude the results are superimposable between the two treatments. Nonetheless, the overall curve for tesamorelin is shifted slightly to the right of the placebo curve and as evidenced by several patient testimonials at the advisory committee, might represent a small subset of patients who derived a benefit on body image to warrant the drug’s availability.

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



There were several reviews conducted by the Study Endpoint and Labeling Development (SEALD) team on the PRO instruments and endpoints. Overall, SEALD objects to the conclusion that the PRO endpoints relied upon in this NDA have content validity and recommends that the tool used to assess PROs (the Body Image Impact Module or BIIM) not be utilized by FDA in future drug development. However, Dr. Papadopoulos does make a similar observation that there is a slight separation between the curves which might indicate a benefit in only a subset of patients. I agree with her concerns about labeling these results as based on a “validated” tool that would be relied upon by other clinical development programs. I also agree that the above graphical presentation is an appropriate descriptive display of the findings in labeling that would not support the applicant’s claim of superiority on patient

reported outcomes but at the same time, convey that some patients may experience a better self-image with Egrifta.

## 8. Safety

As summarized under Section 7.0 the applicant was clearly able to demonstrate efficacy on a biomarker but clinical benefit of a reduction in VAT remains uncertain and if present is likely realized in only a subset of HIV patients with lipodystrophy. In the setting of modest clinical benefit, the threshold for serious toxicity is very low.

In this development program, the incidence of serious adverse events was comparable between the two treatment groups: 3.7% in tesamorelin and 4.2% in placebo. Dr. Mohamadi summarized the deaths in the tesamorelin program involving both HIV and non-HIV studies. There were 4 deaths in the HIV program (3 on tesamorelin and 1 on placebo) and 6 in the non-HIV program (5 on tesamorelin and 1 on placebo). With exception for post-tonsillectomy/adenoidectomy hemorrhage resulting in asphyxiation and metastatic lung cancer, the remaining deaths were cardio-pulmonary events in patients with multiple medical problems and elderly (range 49-95 yrs) and there were too few deaths overall to make any definitive conclusions.

As stated in the Introduction/Background, our experience with Serostim in patients with HIV-lipodystrophy guided the focus of this review on glucose intolerance/diabetes and excess GH stimulation. In addition, an assessment of hypersensitivity/immune-related adverse events was conducted given that this is a peptide. These safety concerns were also emphasized at the Advisory Committee in the FDA presentations given by Drs. Mohamadi and Roman.

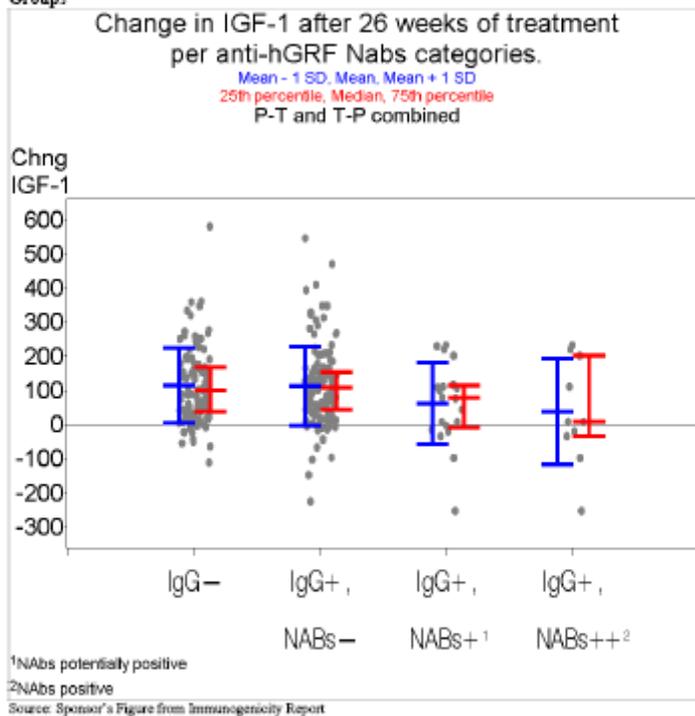
There is no doubt that more patients treated with tesamorelin developed glucose intolerance and had a higher risk of developing diabetes (defined by HbA1c > 6.5%) than placebo-treated patients (4.5% vs 1.3%, respectively). However, the overall mean increase in HbA1c from Baseline to Week 26 was small. Baseline mean HbA1c was 5.26 and 5.28 in the tesamorelin and placebo groups, and increased 0.14% and 0.02% in the two groups, respectively, with the highest HbA1c measured in the tesamorelin group being 8.1. Since patients with T2DM who were treated with oral antidiabetic agents or insulin were excluded, the impact of tesamorelin on the control/management of a broader population of patients with T2DM who are more likely to have higher HbA1c values is not known.

Similarly, there is no doubt that IGF-1 levels are increased to a greater extent with tesamorelin than placebo. Dr. Roman has succinctly summarized the findings at the end of the Main Phase, particularly highlighting the fact that 1/3<sup>rd</sup> of patients treated with tesamorelin have elevations > 3 SDS. Even though there is a decline in completers during the Extension Phase (which is limited by the discontinuation), 1/5 of these patients still have IGF-1 levels > 3 SDS. The concern is not one of acute toxicity, as most patients with acute problems discontinue due to symptoms of excess GH (e.g., joint pain, swelling, carpal tunnel), but long-term exposure to the growth potential of IGF-1, particularly on cancer risk. This long-term concern could not

be addressed feasibly by the applicant in its clinical trials although an Advisory Committee member also raised the concern of retinopathy with increased IGF-1 levels, especially in patients with impaired glucose tolerance or diabetes.

Treatment with tesamorelin resulted in a higher percentage of patients developing anti-tesamorelin antibodies, a subset of whom also had cross-reactivity with human GH-releasing factor (hGRF) or evidence of neutralizing Abs. Development of anti-tesamorelin Abs did not appear to affect efficacy or safety. The applicant also summarized efficacy by the presence or absence of neutralizing Abs to tesamorelin or hGRF. There is a slight trend towards an attenuated mean and median IGF-1 response in the Main Phase of the study but sample sizes are quite sparse in those with neutralizing Abs to hGRF.

Figure 34 Change in IGF-1 After 26 Weeks of Treatment Based on hGRF NAb Status – T-P and P-T Groups



Dr. Mohamadi reviewed reports of hypersensitivity reactions (See section 7.3.5.4 of his review). There were clearly more hypersensitivity reactions in tesamorelin-treated patients compared to placebo (27 vs 1). The majority of these cases resolved spontaneously or resolved with anti-histamines. Of the 27 tesamorelin-treated patients who had a hypersensitivity reaction, 23 (85.2%) had positive anti-tesamorelin Abs at one or more visits. Of these, 13/23 (56.5%) had high titer anti-tesamorelin Abs ( $\geq 400$ ) at least once during the study. There was one patient who experienced injection site reactions during the first month of the study which progressed to more systemic symptoms of swollen tongue/sweating 15 weeks later. This patient had low-level anti-tesamorelin Abs at Week 13 and at the extension

phase and was negative for hGRF Abs. Dr. Mohamadi summarized the overall findings of anti-tesamorelin Abs in the NDA and noted that approximately 50% of patients developed anti-tesamorelin Abs at the end of the Main Phase with 9.3% developing high titers. The observation that 85.2% of patients having a hypersensitivity reaction had positive antibodies and 56.5% were high titer Abs would suggest an association between the development of these antibodies and such reactions.

A consult was placed with the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) to ensure that the hypersensitivity cases that might be anaphylaxis were not miscoded. They did not identify any cases that could be classified as such but stated that the events were immune-mediated and the risk of more severe systemic reactions, including anaphylaxis, may be observed with broader use after approval. They have provided labeling recommendations which have been incorporated.

In addition to the above-mentioned safety issues, it should be noted that patient discontinuation due to an AE during the Main Phase of the trials was higher in the tesamorelin group than placebo (9.6% vs 6.1%). From Table 51 in Dr. Mohamadi's review, the more common AE resulting in discontinuation are similar AEs seen with rhGH therapy (arthralgia and headache). More patients experience injection site reactions with tesamorelin than placebo.

Overall, the safety concerns identified in this NDA 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. Like the efficacy findings, the long-term consequences of these safety concerns are not known and should clearly be evaluated in postmarketing studies.

The effect of VAT reduction on CV risk reduction was not a requirement for approval of Egrifta and given the prevalence of HIV-lipodystrophy, it is unlikely that such a trial can be required to validate VAT as a biomarker of clinical benefit under a subpart H approval. The applicant has proposed a long-term observational study that will assess some of the safety concerns identified in this NDA including occurrence of cancer, hypersensitivity reactions, and retinopathy in diabetic patients. With exception for retinopathy, this proposal might yield useful information similar to the long-term registries established for rhGH in children and adults, and FDA should work with the applicant to design an observational study that would accurately collect information on several of these safety concerns.

Assessing risk for retinopathy in the observational study is unlikely to yield meaningful clinical information for several reasons aside from the voluntary nature of obtaining safety information. The selection of a control group in this observational study will unlikely match for all characteristics which might impact the outcome of interest. Furthermore, detection of retinopathy requires a standardized assessment with scheduled visits to an ophthalmologist. The likelihood that similar scales of reporting retinopathy, similar follow-up of patients, or consistent reporting of these events will occur to provide us with accurate data to make any conclusions on risk of Egrifta on diabetic retinopathy. As such, the FDA will require a clinical

trial be conducted to assess this risk for retinopathy. Section 13 below will describe the basis for this PMR in greater detail.

## 9. Advisory Committee Meeting

This application was discussed at a public advisory committee on May 27, 2010 to the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) supplemented with members from the Antiviral Drugs Advisory Committee, including consumer representatives involved with HIV patient advocacy. Transcripts of this meeting can be found at <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM224181.pdf>. There was one voting question which asked the following:

*Does the overall risk-benefit assessment of a fixed-dose regimen of Egrifta 2 mg/day support its approval for the treatment of excess abdominal fat in HIV-infected patients with lipodystrophy? All 16 voting members voted 'yes' to this question. There were no abstentions.*

Prior to this voting question, the Chair of the committee requested that members discuss several critical points of efficacy and safety leading up to the voting question (starting at page 272 in transcript). Reviewing the discussion of the members has helped place into perspective the safety concerns and whether they could be mitigated enough through labeling and risk management tools to support approval.

For glucose intolerance and diabetes, the majority of the members felt the risk was real but small and manageable with currently available anti-diabetic agents. The company had proposed a contraindication for the drug's use in the diabetic population; however, several members did not support such a restriction and some encouraged further clinical trials in the diabetic population. Noteworthy was a point made by Dr. Thomas on his concerns of diabetic retinopathy (page 260) and that a clinical trial should be conducted to prospectively perform fundoscopic exams of study subjects. Such a proposal has merit and is being discussed with the company as a postmarketing requirement. I would add that such a trial would be of an enriched patient population for CV risks and a secondary endpoint should include assessment of CV events by a blinded adjudication committee.

The majority of the panel members felt that there were inadequate data to comment on whether elevations in IGF-1 levels would increase risk of malignancies, although some felt that risk would be remote (Molitch 285...."I think the risk for cancer is actually quite low, although it's probably finite.....it certainly deserves long-term surveillance....). Dr. Burman suggested time limits on use (pg 301). Many of the comments and recommendations from the panel member are reflected in labeling (monitoring and recommendations for discontinuation of use with persistent IGF-1 increases in the absence of efficacy) and the applicant's proposed observational study.

Similarly, the majority of the panel members felt that there were inadequate data to comment on long-term CV benefits/risk of Egrifta. Several members recommended a CV outcomes trial but no one outlined a design or argued that such a trial was feasible. On the contrary, several

members felt that such a trial would be impractical given the reluctance of patients to be randomized to placebo or the low event rates in the setting of other approved therapies to manage competing CV risk factors. Post AC, the FDA and applicant considered the estimated population size and event rates and deemed a prospective CV outcomes trial to be infeasible. The applicant has proposed a prospective observational study that would include collection of MACE events. This would be considered a postmarketing requirement.

## **10. Pediatrics**

A full waiver for pediatric studies under PREA was recommended by the Division because of concerns that use of this product in the pediatric patient population with open epiphyses would result in excessive linear growth in the absence of a clear benefit. This recommendation was discussed with and agreed to by the Pediatric Review Committee (PeRC) on June 30, 2010.

## **11. Other Relevant Regulatory Issues**

Drs. Mohamadi and Roman have fully discussed in their reviews.

## **12. Labeling**

### **Issues Identified by Division of Medication Error Prevention and Analysis (DMEPA) and Division of Risk Management (DRISK)**

The proposed tradename of Egrifta® was found acceptable by DMEPA on August 13, 2009

DRISK has concluded that a Risk Evaluation and Mitigation Strategy (REMS) is not warranted as their review of available safety information for Egrifta did not identify safety concerns not already known with growth hormone products, none of which has a REMS. As a REMS is not supported by the available data, neither would it be appropriate to require an ETASU for fear that patients would be using Egrifta off-label for cosmetic purposes or weight loss. At present, there is no legislation prohibiting the off-label use of IGF-1 similar to rhGH. While I question the scientific rationale for why such legislation exists for rhGH when that drug product carries no addictive potential such as opioids, I recognize that the availability of Egrifta may be viewed as an alternative for unsound medical practice as it shares a similar mechanism of action to rhGH. In addition to the voluntary restricted distribution plan from the applicant, the FDA labeling will specifically state under the Limitations of Use the following three points:

- Long-term CV benefit and safety of EGRIFTA have not been studied
- Not indicated for weight loss management (weight neutral effect)
- There are no data to support improved compliance with anti-retroviral therapies in HIV-positive patients taking EGRIFTA

Such specific language will only affect what the company can promote and hopefully curb statements made by investigators. Such labeling would not necessarily deter the off-label use of this product, especially by those who are intent on experimenting products for cosmetic and recreational purposes. FDA will request that the company monitor prescription practices of Egrifta and provide this information in its annual report to the NDA.

Both DRISK and DMEPA raised concerns regarding the packaging of two 1-mg vials requiring reconstitution to achieve the single 2-mg dose for injection as a potential for medication error. They have recommended that the applicant develop a single vial kit as a postmarketing requirement.

Most all comments from DMEPA and DRISK conveyed to the applicant have been adequately addressed in their changes to labeling (container, cartons, and package inserts).

### **Recommendations from Pediatric and Maternal Health Staff**

In their consult dated April 2, 2010, the Maternal Health Team (MHT) recommended Pregnancy Category X for Egrifta. This recommendation was based on findings of hydrocephaly in nonclinical and reprotoxicity studies with no known clinical benefit with the use of Egrifta during pregnancy. Of note, MHT staff concluded that intra-abdominal visceral adipose tissue normally increases during pregnancy such that administration of a drug that reduces VAT during pregnancy would be countering a normal physiologic process. A concern that HIV+ pregnant patients with excess VAT would be at greater risk for insulin resistance and diabetes is not sufficient reason to recommend the use of Egrifta during pregnancy as there is no evidence that HIV+ patients are at greater risk for diabetes during pregnancy than HIV- patients. Furthermore, the increased risk of impaired glucose tolerance observed in the clinical trials with Egrifta makes it difficult to consider the use of this drug in HIV+ pregnant women to reduce the risk of diabetes. The applicant has agreed to this pregnancy category labeling.

## **13. Decision/Action/Risk Benefit Assessment**

- **Regulatory Action**

Approval

- **Risk Benefit Assessment**

Theratechnologies was able to demonstrate a significant reduction in VAT that met the agreed-upon threshold of > 8% reduction with Egrifta in two pivotal studies. However, the significant reductions in VAT were not accompanied by robust or consistent changes in secondary supportive efficacy measures of improved patient's self-perception of body image or lipid abnormalities. Instead, the most compelling evidence of benefit came from patient testimonials during the open public hearing at the advisory committee. Whether these patients represent the small subset of patients showing improvements on the PRO measure of Belly

Apperance Distress is not clear. Regardless, their personal accounts of benefit were sufficient enough to garner a unanimous vote for approval from all 16 voting members at the advisory committee.

Overall, Egrifta is clearly effective on modifying a biomarker but what the clinical benefit is with this degree of VAT reduction is uncertain and benefit based on PRO measures in this population appears modest at best. However, the safety concerns identified in this NDA are not immediately life-threatening or severe enough to reasonably argue against the availability of Egrifta to the HIV population with lipodystrophy who have few to no options.

FDA heard the plea from the medical and patient community on making this therapy available. However, all parties here must be keenly aware that data are absent on the long-term clinical benefits of Egrifta on CV risk reduction, compliance to HAART and the long-term risks of elevated IGF-1 levels. And it is with this understanding that the label for Egrifta must be demarcated for the intended population and clearly states the unknown benefits and potential risks. It should also be clearly conveyed that the approval of Egrifta, based on VAT reduction in this limited patient population with few alternatives, is not an FDA endorsement of this endpoint as a validated surrogate for drug approval in other highly prevalent conditions (e.g., metabolic syndrome, obesity, atherosclerosis). Additional assessment of benefits and risks will be obtained from postmarketing requirements outlined below.

- **Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies**

DRISK has concluded that a REMS is not necessary for the safe and effective use of this product.

- **Recommendation for other Postmarketing Requirements and Commitments**

Postmarketing Requirements will include:

1. Development of a single vial for daily administration of tesamorelin 2 mg

Please see Dr. Steven Fong's microbiology review. I concur with his recommendation.

2. Observational study to further assess long-term risks associated with Egrifta

The observational study proposed by the applicant was reviewed by OSE's DEPI (Division of Epidemiology). Several comments on the preliminary protocol were provided by Dr. Wysowski, which will be conveyed to the applicant. I concur with Dr. Wysowski that the period of observation would need to be longer to assess cancer risk. Dr. Wysowski was also concerned about off-label use of Egrifta, particular for "body building". She acknowledges DRISK's assessment that a REMS and ETASU are not required as this product is similar to GH products which do not have either of these. However, she recommends that the Warnings and Precautions section includes information regarding the potential for inappropriate use and also that the consequences of long-term use have not been studied and are unknown.

As the Limitations of Use will already describe the following:

- Long-term CV benefit and safety of EGRIFTA have not been studied
- Not indicated for weight loss management (weight neutral effect)
- There are no data to support improved compliance with anti-retroviral therapies in HIV-positive patients taking EGRIFTA

I believe the label has adequately addressed her concerns.

All drugs have potential for off-label use for which FDA labels generally do not advise against because such benefit-risks decisions must be made by the prescribing physician. Dr. Wysowski's recommendation that the Warnings and Precautions section of the label carry language to deter this out of concern of 'black market' sales of Egrifta is not accompanied by any evidence that such FDA labeling would prevent these individuals from seeking out this product for cosmetic or recreational use.

3. A randomized, placebo-controlled, double-blind clinical trial in patients with HIV-lipodystrophy and T2DM to assess risk of retinopathy

The potential role of the GH/IGF-1 axis in diabetic retinopathy dates back to a report of regression of proliferative diabetic retinopathy (PDR) following postpartum pituitary necrosis.<sup>6</sup> Since that time there have been numerous studies published, nonclinical and clinical, observational and interventional, further describing the relationship between IGF-1 and the development of PDR, not all conclusive of a causative effect. Several studies have reported higher levels of IGF-1 in patients with PDR; however, these studies may have been limited in the assay used to measure IGF-1 levels.<sup>7,8</sup> A prospective, 3-year, observational, case-control study involving 42 patients with T2DM which included fundoscopic exams at baseline and at several time points after the initiation of insulin found significantly higher IGF-1 levels at 36 months in those with retinopathy progression  $\geq 3$  levels compared to those at  $\leq 2$  levels.<sup>9</sup> In addition to these studies, a clinical trial of IGF-1 in patients with T1 and T2DM was reported to have been halted due to progression of retinopathy. The evidence here should raise a concern for the potential of Egrifta, which has been demonstrated to increase IGF-1 levels in the HIV trials, to increase the risk of retinopathy in the population being targeted for therapy due to lipodystrophy, as these patients have a greater risk for glucose intolerance and progression to diabetes, exacerbated by Egrifta.

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<sup>6</sup> Poulsen JE. Recovery from retinopathy in a case of diabetes with Simmonds' disease. *Diabetes* 1953;2:7-12.

<sup>7</sup> Grant MB et al. Insulin-like growth factors in vitreous. Studies in control and diabetic subjects with neovascularization. *Diabetes* 1986;35:416-420.

<sup>8</sup> Dills DG et al. Association of elevated IGF-1 levels with increased retinopathy in late onset diabetes. *Diabetes* 1991;40:1725-1730.

<sup>9</sup> Henricsson M et al. Progression of retinopathy in Insulin-treated type 2 diabetic patients. *Diabetes Care*. 2002;25:381-385.

In determining whether a prospective, placebo-controlled clinical trial can be conducted with Egrifta in patients with HIV-lipodystrophy and T2DM to evaluate risk of retinopathy several things were considered:

*Ethics* – Since Theratechnologies excluded the majority of patients with T2DM from their pivotal clinical trials supporting this NDA, it can be argued that effectiveness of this drug has not been established in these patients to raise objection towards a trial that would randomize some patients to no therapy for HIV-lipodystrophy.

*Scientific Justification* – As stated by the applicant in its Clinical Overview, HIV-infected patients receiving ART have a 2 to 3-fold increased incidence of prediabetes and diabetes compared to non-HIV patients. This underlying risk is carried into the HIV-lipodystrophy population. In an article provided by applicant in response to an FDA inquiry, the prevalence of diabetes diagnosed by OGTT in a cohort of subjects with HIV-lipodystrophy was 7%.<sup>10</sup> The prevalence is likely higher as supported by our experience with the HARs trials involving rhGH, which excluded 20% of patients screened from study enrollment due to diabetes at baseline (see product label for Serostim®). As such, it should be expected that a sizeable proportion of patients with HIV-lipodystrophy who will receive Egrifta will be at risk for diabetic retinopathy which may or may not be exacerbated by this drug.

*Feasibility* – In addressing this issue, we drew from our experience with other retinopathy trials. In particular, we evaluated the clinical trial comparing insulin glargine to NPH in T2DM to determine whether there was a difference in risk of retinopathy based on rates of progression in the Early Treatment Diabetic Retinopathy Study (ETDRS) scale.<sup>11</sup> This study provided us with several reasonable estimates of control rate, drop-out rates, and the primary endpoint and non-inferiority margin that have already been accepted by the agency a postmarketing commitment under the insulin glargine NDA.

Assuming a prevalence of 200,000-400,000 patients in the U.S. with HIV lipodystrophy and a conservative 7% prevalence of T2DM, the population from which the applicant can recruit for a clinical trial is ~14,000-28,000. FDA statisticians, Drs. Todd Sahlroot and Lee Pian provided the following sample size calculations based on an ITT analysis (Table 1) and completers analysis assuming a 30% dropout rate (Table 2). Different randomization ratios are proposed to encourage patients to enroll in a placebo-controlled trial.

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<sup>10</sup> Hadigan C et al. Metabolic abnormalities and cardiovascular disease risk factors in adults with HIV and lipodystrophy. *HIV/AIDS*. 2001;32:130-139.

<sup>11</sup> Rosenstock J et al. Similar progression of diabetic retinopathy with insulin glargine and NPH in patients with T2DM: a long-term, randomized, open-label study. *Diabetologia*. 2009;52:1778-1788.

Table 1. Sample size for Egrifta retinopathy study with 2.5% 1-sided type 1 error rate and 90% power in ITT population

		Non-inferiority margin (risk difference)							
		10%		9%		8%		7%	
control rate	Rand ratio	per arm	total	per arm	total	per arm	total	per arm	total
15%	1:1	272	544	335	670	423	846	552	1104
	1:2	182, 364	546	225, 450	675	288, 576	864	380, 760	1140
	1:3	150, 450	600	189, 567	756	242, 726	968	322, 966	1288
20%	1:1	338	676	416	832	526	1052	688	1376
	1:2	233, 466	699	290, 580	870	370, 740	1110	486, 972	1458
	1:3	197, 591	788	246, 738	984	316, 948	1264	420, 1260	1680

Table 2. Sample size for Egrifta retinopathy study with 2.5% 1-sided type 1 error rate and 90% power in Completers

		Non-inferiority margin (risk difference)										
		10%		9%			8%			7%		
control rate	Rand ratio	per arm	total	per arm	total	per arm	total	per arm	total	per arm	total	
15%	1:1	389	778	479	958	605	1210	789	1578			
	1:2	260	520	322	643	965	412	823	1235	543	1086	
	1:3	215	643	858	270	810	1080	346	1038	1384	460	1380
20%	1:1	483	966	595	1190	752	1504	983	1966			
	1:2	333	666	999	415	829	1244	529	1058	1587	695	1389
	1:3	282	845	1127	352	1055	1407	452	1355	1807	600	1800

Using the 10% NI margin (blue highlighted columns in tables above) that has been accepted in other retinopathy trials conducted for regulatory purposes, the sample sizes necessary to conduct this clinical trial are still within a reasonable percentage of the estimated U.S. patients with HIV-lipodystrophy and T2DM.

While this prospective clinical trial will provide valuable safety information on risk of retinopathy, it can also have important secondary objectives including assessing the impact of Egrifta on glycemic control. Furthermore, the HIV-lipodystrophy population with T2DM is an enriched population for CV risks and a prospective adjudication of MACE events should also be incorporated in the conduct of this trial.

Overall, this PMR is not an unreasonable trial to mandate of Theratechnologies and its results will undoubtedly provide prescribers and patients with important information on the benefits and risks of Egrifta.

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/s/  
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MARY H PARKS  
11/09/2010