

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**22-505**

**OTHER REVIEW(S)**

**MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

**DATE:** November 10, 2010

**TO:** NDA File

**THROUGH :** Mary Parks, M.D. and Amy Egan, M.D., M.P.H., Division of Metabolism and Endocrinology Products (DMEP)

**FROM:** Jennifer Johnson, Regulatory Project Manager

**SUBJECT:** Documentation of Agreement by Sponsor to Timelines for Postmarketing Requirements (PMRs)

**APPLICATION/DRUG:** NDA 022505, Egrifta (tesamorelin) for Injection

Please see attached email, which documents the sponsor's agreement to timelines set forth for three postmarketing requirements, a condition of approval of Egrifta.

**Johnson, Jennifer**

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**From:** wilson.michelle@kendle.com  
**Sent:** Wednesday, November 10, 2010 12:35 PM  
**To:** Johnson, Jennifer  
**Cc:** Martine Ortega; Nadine Bouchard  
**Subject:** Fw: NDA 22505: Egrifta Postmarketing Requirements Timelines  
**Importance:** Low

Jennifer,

Please see Thera's response below.

Best wishes,

Michelle

---

**From:** Nadine Bouchard [nbouchard@theratech.com]  
**Sent:** 11/10/2010 12:26 PM EST  
**To:** Michelle Wilson  
**Cc:** Martine Ortega <mortega@theratech.com>  
**Subject:** RE: NDA 22505: Egrifta Postmarketing Requirements Timelines

Hello Michelle,

by this email we confirm that we are OK with the proposed timelines.

Thanks,

Nadine

---

**De :** wilson.michelle@kendle.com [mailto:wilson.michelle@kendle.com]  
**Envoyé :** mercredi 10 novembre 2010 12:04  
**À :** Martine Ortega  
**Cc :** Nadine Bouchard  
**Objet :** Fw: NDA 22505: Egrifta Postmarketing Requirements Timelines

FYI. Please review and let me know if you have changes. Thanks! Michelle

---

**Michelle Wilson, Ph.D.** | Principal Consultant | Global Regulatory Consulting & Submissions  
**Kendle International, Inc.** | 441 Vine Street | Suite 500 | Cincinnati, Ohio 45202 | Ph (513) 829-1108; Mobile (513) 578-5671 (NEW) | Fax (513) 763-7628

----- Forwarded by Michelle Wilson/CIN/Kendle on 11/10/2010 12:03 PM -----

From: "Johnson, Jennifer" <Jennifer.Johnson@fda.hhs.gov>  
To: "wilson.michelle@kendle.com" <wilson.michelle@kendle.com>  
Date: 11/10/2010 11:57 AM  
Subject: NDA 22505: Egrifta Postmarketing Requirements Timelines

Reference ID: 2862972

11/10/2010

Dear Michelle,

This email is to summarize the timelines for the postmarketing requirements (PMR) we have requested.

1. PMR #1: Single vial presentation for tesamorelin for injection.

Final protocol submission date: 5/5/2011

Study completion date: 7/5/2012

Final report submission date: 9/5/2013

2. PMR #2: Long-term observational safety study of at least 10 years duration comparing patients with HIV-associated lipodystrophy and excess abdominal fat treated with Egrifta (tesamorelin) compared to a similar group of patients not treated with Egrifta.

Final protocol submission date: 5/30/2011

Study completion date: 12/31/2024

Final report submission date: 8/30/2025

3. PMR #3: Prospective, randomized, placebo-controlled clinical trial to evaluate if Egrifta increases the risk of development and/or progression of retinopathy when administered to HIV-infected patients with lipodystrophy and concomitant diabetes.

Final protocol submission date: 4/30/2011

Study completion date: 5/30/2016

Final report submission date: 11/30/2016

Before we can take an action, we will need agreement on these timelines, which will be specified in the action letter. A response to this email will be sufficient. Note that the action letter will specify only month and year, and not the date.

Let me know if you have any questions.

Kind Regards,  
Jennifer

**Jennifer Johnson**  
**Regulatory Project Manager**  
**Division of Metabolism & Endocrinology Products**  
**Center for Drug Evaluation and Research**  
**Food & Drug Administration**  
**301-796-2194 phone**  
**301-796-9712 fax**  
[jennifer.johnson@fda.hhs.gov](mailto:jennifer.johnson@fda.hhs.gov)

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Confidentiality Notice

This email and any files transmitted with it are confidential and intended solely for the use of the individual or entity to whom they are addressed. If you are not the named addressee, you should not copy, transfer, save or otherwise disseminate this email. Please notify the sender immediately by email if you have received this email by mistake and delete it and any file transmitted with it from your system.

Reference ID: 2862972

11/10/2010

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JENNIFER L JOHNSON  
11/10/2010

## Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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PMR/PMC Description: Single vial presentation for Tesamorelin acetate for injection.

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PMR/PMC Schedule Milestones: Final protocol Submission Date: 05/05/2011  
Study/Clinical trial Completion Date: 07/05/2012  
Final Report Submission Date: 09/05/2013  
Other: \_\_\_\_\_

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The applicant's clinical development program used tesamorelin acetate in two vials with 1.1 mg of product rather than a single vial with 2.2 mg of product. The approved dose will be 2 mg of product injected sub-cutaneously daily. This requires that patients reconstitute 2 vials of tesamorelin acetate with a single vial of diluent (sterile water) for the single injection. The two vial presentation increases the risk that microbiological contamination could occur during product reconstitution, and thus there is the potential for an unexpected serious risk of soft tissue infections. Additionally, the risk for such infections in the HIV+ population may be higher than in the general population. There were, however, no such infections or other adverse effects of the 2-vial system seen in the clinical trials. Therefore, the sponsor is being required to develop a single vial presentation for tesamorelin acetate for injection as a post-marketing requirement. This will require sufficient time to select an appropriate vial, implement validated fill and lyophilization processes, and conduct stability testing. There are currently no other products approved for the treatment of this condition.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The two vial presentation increases the risk that microbiological contamination could occur during product reconstitution, and thus there is the potential for an unexpected serious risk of soft tissue infections. The risk for such infections in the HIV+ population may be higher than in the general population.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Manufacturing studies to determine a process for providing a daily dose (2 mg) of lyophilized product in a single vial. This single vial would replace the container-closure system described in the original application in which the daily dose is provided in two separate vials each containing 1.1 mg of lyophilized powder.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
  - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
  - Thorough Q-T clinical trial
  - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
  - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)  
Manufacturing process study.
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

---

**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

## Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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PMR/PMC Description: Prospective, randomized, placebo-controlled clinical trial to evaluate if Egrifta increases the risk of development and/or progression of retinopathy when administered to HIV-infected patients with lipodystrophy and concomitant diabetes.

---

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>04/30/2011</u>
	Study/Clinical trial Completion Date:	<u>05/30/2016</u>
	Final Report Submission Date:	<u>11/30/2016</u>
	Other:	_____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

A favorable risk/benefit profile has been established for Egrifta in patients with HIV lipodystrophy in the Phase III clinical program. Patients who exhibit concomitantly diabetes and HIV-lipodystrophy represent a subgroup of the total number of patients with HIV lipodystrophy. There is a theoretical risk (currently labeled) that long-term IGF-1 elevations associated with Egrifta treatment may increase the risk of diabetic retinopathy in this subpopulation. Confirmation and conceivably quantification of such risk will create a more accurate label and will permit a better definition of the risk/benefit profile in this subgroup of HIV patients with lipodystrophy.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The primary objective of the clinical trial is to evaluate if Egrifta increases the risk of diabetic retinopathy when administered to HIV-infected patients with lipodystrophy and concomitant diabetes (Egrifta increases IGF-1 serum concentrations significantly relative to baseline, and IGF-1 is known to increase the risk of progression of diabetic retinopathy in non-HIV diabetics). Secondly, the study will evaluate the long-term effect of Egrifta on glucose metabolism. Although short-term administration of Egrifta to patients with HIV-lipodystrophy and excess abdominal fat was associated with a small increase in risk of developing diabetes, it is not known if this undesired effect persists with long-term administration or, contrary to short-term observations, the Egrifta-mediated reduction in visceral adipose tissue results in long-term improvements in glucose metabolism (i.e. reduction in insulin resistance). Long term data will also be gathered, through a blinded adjudication process, on the risk of major adverse cardiovascular events (MACE) in patients treated with Egrifta relative to placebo.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)  
 Animal Efficacy Rule  
 Pediatric Research Equity Act  
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?  
 Assess signals of serious risk related to the use of the drug?  
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A placebo-controlled clinical trial is the most desirable clinical trial design to address primarily the potential risk of diabetic retinopathy and secondarily the long-term effect of Egrifta on markers of glucose metabolism.

Based on the literature, we estimate that the prevalence of patients with HIV lipodystrophy is approximately 200,000 in the United States, of which roughly 10% (20,000) may have diabetes melitus. This represents a sizeable enough population to conduct a prospective, randomized, placebo-controlled study. Study participants would include any patient with HIV lipodystrophy and diabetes eligible for Egrifta treatment. The primary objective would include comparing the percentage of subjects with a 3-step or greater progression in the Early Treatment Diabetic Retinopathy Study (ETDRS) scale after treatment with Egrifta compared with placebo.

Concomitantly, other secondary endpoints could be evaluated such as markers of glycemic control (i.e., fasting blood glucose and hemoglobin A1c), and occurrence of MACE.

Required

- Observational pharmacoepidemiologic study
- Registry studies

*Continuation of Question 4*

- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
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---

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(signature line for BLAs)

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---

PMR/PMC Description: Long-term observational safety study of at least 10 years duration comparing patients with HIV-associated lipodystrophy and excess abdominal fat treated with Egrifta (tesamorelin acetate) compared to a similar group of patients not treated with Egrifta.

---

PMR/PMC Schedule Milestones: Final protocol Submission Date: 05/30/2011  
Study/Clinical trial Completion Date: 12/31/2024  
Final Report Submission Date: 08/30/2025  
Other: \_\_\_\_\_

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
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- Theoretical concern
- Other

In its Phase 3 studies, the Sponsor has demonstrated a reasonable safety profile for Egrifta for its use up to one year's duration; however, there are a number of potential concerns that may arise with long-term administration of a growth hormone releasing hormone analog, such as worsening glucose intolerance and risks associated with prolonged elevations in IGF-1. While these could not be assessed in the framework of the Phase 3 studies, a postmarketing study would reliably address such concerns.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

As this is a first-in-class drug, there is no available long-term safety data on GHRH analogs. The Agency's review of the Phase 3 data revealed a number of potential safety concerns that are appropriate for postmarketing review, including possible worsening of glucose tolerance and prolonged elevations in IGF-1. Furthermore, such a study would provide insight into the risk of certain targeted adverse events such as development of cancer and hypersensitivity reactions that may be associated with long-term use of Egrifta. Finally, since the primary endpoint (decrease in visceral adipose tissue) has not been validated, members of an EMDAC panel suggested that the sponsor study the effect of Egrifta on the occurrence of major acute cardiovascular events (MACE).

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
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- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Long-term observational study of at least 10 years duration. Eligible study participants would include any patient prescribed Egrifta, as well as a matched, but untreated observation group who meet the criteria for Egrifta treatment. Objectives would include:

- Collection of data on long term safety including targeted adverse events (e.g. occurrence of cancer, hypersensitivity reactions, liver and/or kidney abnormalities, diabetic retinopathy)
- Collection of long-term data on the occurrence of MACE
- Collection of long-term data on different markers directly impacted by increases in GH, including IGF-1, IGF-BP3, fasting blood glucose, and hemoglobin A1c

Patients would be assessed at the time of enrollment, then semi-annually until the cessation of treatment, with the requested data recorded at each visit. All patients would be followed for at least 10 years, and specific analyses will be performed when an adequate sample size is attained.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
  - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
  - Thorough Q-T clinical trial
  - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
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  - Other (provide explanation)
- 

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/  
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AMY G EGAN  
11/09/2010



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: November 5, 2010

To: Mary Parks, M.D., Director, Division of Metabolic and  
Endocrinological Drug Products, OND

Thru: Gwen Zornberg, M.D., Sc.D., Team Leader, Division of  
Epidemiology, OSE  
FOR: Judy Staffa, R.Ph., Ph.D., Acting Director, Division of  
Epidemiology, OSE

From: Diane K. Wysowski, M.P.H., Ph.D., Epidemiologist, Division  
of Epidemiology, OSE

Subject: A review of a proposal for a PMR study for a long-term  
observational safety study of tesamorelin acetate (Egrifta)

Drug Name(s): Tesamorelin (Egrifta)

Submission Number:

Application Type/Number: NDA 22-505

Applicant/sponsor: Theratechnologies Inc.

OSE RCM #: RCM 2010-2291

## CONTENTS

EXECUTIVE SUMMARY .....	3
1 BACKGROUND .....	4
2 MATERIALS REVIEWED.....	5
3 RESULTS .....	5
3.1 Synopsis of proposed study.....	5
3.2 Critique of proposed study.....	6
4 SUMMARY.....	9
5 REFERENCE.....	10

## **EXECUTIVE SUMMARY**

DMEP plans to approve tesamorelin acetate (Egrifta), a growth hormone releasing factor analog indicated for the reduction of excess abdominal fat in HIV-infected patients with lipodystrophy. Because of the potential of this drug to be used off-label in people with excess abdominal fat without HIV infection and in those who use human growth hormone and IGF-1 for “body building” (1) and because the drug is associated with increases in glucose and IGF-1 possibly resulting in adverse long-term consequences, I recommend that DMEP:

-add information to the Warnings and Precautions section of the product information regarding the potential for inappropriate use and also that the consequences of long-term use have not been studied and are unknown.

Although DMEP asked the sponsor, Theratechnologies Inc., to conduct a postmarketing clinical trial of cardiovascular outcomes, the company enumerated a number of concerns including the feasibility of conducting such a study. As an alternative, they submitted a proposal “to collect long-term safety information related to treatment with Egrifta in adult HIV patients with lipodystrophy.” However, many of the reasons for not performing a clinical trial also will be challenges for performing observational studies.

I have concerns about whether an observational study will be feasible because, for comparability’s sake, unexposed patients should be selected from the same database as exposed subjects (not from an opportunistic external database as planned by the company), and I believe that unless patients are very ill or financially unable to afford Egrifta, it may be difficult to obtain a large enough sample of HIV patients with lipodystrophy who choose not to take the drug. Therefore, I believe the company should address whether an observational study will be feasible.

In addition, a number of other challenges and study limitations should be addressed in any submitted protocol. I suggest that the company:

- specifically state that a comparison will be made between Egrifta-exposed and unexposed;
- include diabetes mellitus as a primary outcome;
- include a calculation of sample size; consider a greater ratio of unexposed to exposed (e.g., 4:1) to increase statistical power;
- include a statistical analysis plan; consider time to event analyses and control for covariates;
- select unexposed controls (usually from the same database or source as the exposed) having comparability to exposed subjects; consider matching and use of propensity scores;
- increase the study period to 10 years to identify possible drug-related cancer cases;
- include a plan to enroll adequate numbers of non-exposed subjects;
- include a plan for tracking physicians and patients (including those who drop out, are lost to follow-up, and who die) over a 10-year period;

- include a plan to use the National Death Index since mortality and cause of death in patients who discontinue Egrifta, drop out, or are lost to follow-up will not be known;
- include a plan to increase physician enrollment and to address dwindling physician participation over time;
- standardize all data entry forms;
- address the issue of missing data;
- address privacy issues since health data will be transferred via the Internet; and
- collect data on lipid parameters and hypertension and any other covariates known risk factors for outcomes, and
- include information on hospitalizations and emergency department visits in Egrifta–exposed and unexposed subjects.

Finally, in this study or a separate one, I recommend that the sponsor collect data on unapproved use and any safety issues that result from that use.

## **1 BACKGROUND**

The Division of Metabolic and Endocrinological Drug Products (DMEP) plans to approve tesamorelin acetate (Egrifta), a growth hormone releasing factor analog indicated for the reduction of excess abdominal fat in HIV-infected patients with lipodystrophy. The medication is a first-in-class drug and, therefore, no long-term safety data on GHRH (growth hormone releasing hormone) analogs are available. The DMEP’s review of the Phase 3 clinical trial data was conducted by Ali Mohamadi, M.D., and it revealed a number of *known and potential* safety concerns including:

- worsening of glucose tolerance,
- elevations in insulin-like growth factor-1 (IGF-1), and
- increases in the risk of diabetes mellitus, cancer, and cardiovascular outcomes.

There is also a potential for considerable off label use, misuse, and abuse of this drug in individuals *without HIV infection* who have excess abdominal fat. Because of the very high prevalence of overweight and obesity in the U.S. with people having excess abdominal fat, it seems likely that there will be considerable off-label use of this drug. Furthermore, like other human growth hormone products, it may also appeal to body builders and result in illegal “black market” sales. The company submitted a risk evaluation and mitigation strategy (REMS) proposal, including a restricted distribution plan, Medication Guide, and a communication plan to “health care professionals who prescribe or dispense antivirals,” but a review by the Office of Surveillance and Epidemiology’s Division of Risk Management dated September 3, 2010, did not agree that such a plan was warranted apparently primarily because of the absence of serious adverse events in the clinical trials. However, the review also expressed a concern about the potential for inappropriate use of Egrifta “for muscle enhancement or weight loss” and non-opposition to the “sponsor employing methods to decrease inappropriate prescribing as they deem necessary.”

The Endocrinologic and Metabolic Drugs Advisory Committee for Egrifta held in May, 2010, unanimously voted in favor of drug approval; however, there was a consensus that postmarketing studies or a registry was needed to answer questions about Egrifta's cardiovascular benefit versus risk, glucose control, elevated IGF-1 levels and malignancy, and identification of non-responders.

According to a sponsor's submission, in an email dated June 23, 2010, DMEP staff asked the sponsor, Theratechnologies Inc., to conduct a clinical trial to assess the benefit (or non-inferiority) of a reduction in visceral adipose tissue on major adverse cardiovascular events (MACE) and to include adequate numbers of women, racial subgroups, and subjects with diabetes. DMEP asked for assessment of other safety endpoints in the trial such as IGF-1 levels, malignancies, liver and/or kidney abnormalities, and in a subset of diabetic patients, retinopathy.

Theratechnologies Inc. responded with a "Proposal for a Long-Term Safety Observation Study of Tesamorelin Acetate (Egrifta)" dated July 26, 2010. In an attachment, entitled "Challenges of Conducting a MACE Trial of Tesamorelin in HIV-Infected Patients," the company concluded that "the conduct of a randomized placebo-controlled superiority MACE trial is not feasible in this specific population (HIV-infected patients with lipodystrophy) and will in all likelihood not succeed in addressing the questions raised by the Agency as to whether or not tesamorelin can reduce MACE in HIV-infected patients with abdominal lipohypertrophy." The reasons the company provided for lack of feasibility included:

1) Sample size issues

Based on an estimated U.S. population of 200,000 HIV-infected patients with lipodystrophy and excess abdominal fat, proof of superiority of reduction in visceral abdominal tissue on cardiovascular outcomes would require 16,000 patients per treatment group for a potential reduction in MACE of 15% and 43,000 patients per treatment group for a potential reduction of 7%.

2) Length of follow-up issues

The sponsor stated that the number of cardiac events in the HIV infected population is lower than in other populations at risk, and patients would need to be followed up for a long period of time since the incidence of cardiac events is associated with increasing age in both HIV-infected and HIV-uninfected subjects.

3) Anticipated inadequate enrollment in the placebo arm because of tesamorelin availability outside the trial

4) Ethical issues involved with withholding tesamorelin

5) Issues involved with changes in risk factors over time

6) Differences in cardiovascular risk by antiretroviral drug treatment

7) Increased dropout rates in the placebo group

However, instead of a synopsis for a protocol for the clinical trial, the sponsor submitted a proposal for a long-term safety observation study for tesamorelin. It is worth noting

that several of the challenges given by the sponsor for not doing a clinical trial also would be challenges for conducting an observational study.

A synopsis of the study and a critique are provided in the Results section below.

## 2 MATERIALS REVIEWED

The materials reviewed included Theratechnologies Inc. "Proposal for a Long-Term Safety Observation Study of Tesamorelin Acetate (Egrifta)" dated July 26, 2010, the Egrifta proposed labeling information, and the Review of Safety written by Ali Mohamadi, M.D.

## 3 RESULTS

### 3.1 Synopsis of proposed study

The sponsor is proposing a longitudinal observational long-term safety study with a control arm in collaboration with participating physicians to collect long-term safety information related to treatment with Egrifta in adult HIV patients with lipodystrophy and excess abdominal fat. Participating physicians will be asked to report information on key safety parameters and electronic data entry will facilitate data collection.

The specific study objectives are to collect long-term safety information related to treatment with Egrifta in adult HIV patients with lipodystrophy including:

- cancers during and following Egrifta treatment
- hypersensitivity reactions
- liver and/or kidney abnormalities
- retinopathy in diabetic patients
- MACE during treatment with Egrifta
- serious or unexpected (not listed in the full prescribing information) adverse events likely to be related to the drug
- fasting blood glucose, HbA1c, and other glucose parameters
- serum IGF-1 and IGF-1 SDS (if obtained)
- serum IGFBP-3 (if obtained)

Other study objectives are to collect long-term data on adherence to antiretroviral treatment regimens during treatment with Egrifta and to provide safety data on a broad population (i.e., female patients and patients of different ethnic origins).

The company plans to ask participating physicians (prescribers of Egrifta in adult HIV patients with lipodystrophy) to report information on key safety parameters. Electronic data entry will be via the Internet using a secure website. The company states that "eligible investigators who are willing and qualified to conduct clinical research according to Good Clinical Practice, will be the prescribers of Egrifta."

Patients with HIV-associated lipodystrophy treated with Egrifta apparently will be compared with "a similar group of patients followed without treatment with Egrifta from an existing HIV cohort." Specifically, these unexposed patients will be adult HIV patients

in an external database who meet the criteria for Egrifta use with no prior exposure to any experimental or marketed GH-related product, including any form of GH, GRF/GHRH, GH secretagogues, or IGF-1. “Additionally, these patients should not receive any of the above mentioned agents.”

The patient’s medical record will be used as source documentation although additional information “could be requested regarding family history of cancer, diabetes, and CVD.” Specific data, including a number of risk factors for MACE (e.g., smoking status, body mass index) will be collected at each visit including an enrollment visit, semi-annual follow-up visits, the last visit, and a post-treatment visit.

Blood samples will be analyzed by local laboratories “according to the clinical judgment of the physicians.” If a patient or physician chooses to withdraw participation in the study, the company states that “appropriate notification of exit or treatment discontinuation should be submitted to the registry database.”

The sponsor did not provide sample size estimates for this study. They state that “all patients (including the observation group) should be follow-up for at least 5 years.” A scientific committee, composed of independent experts, or a DSMB will oversee the scientific/safety aspects. Important findings will be shared with participating physicians, the FDA, and the general endocrine community at scientific meetings and through journal publications and reports.

### 3.2 Critique of proposed study

Although the company’s proposal is preliminary, it contains enough information to comment upon major challenges and likely limitations, including the following:

1) Study objectives do not specifically state a comparison will be made between Egrifta-exposed and unexposed

The study proposal states that long-term data will be collected for Egrifta in adult HIV patients with lipodystrophy and for an untreated observation group from an existing HIV cohort in an external database. In a formal protocol, the study objectives should explicitly state that long-term safety data collected for Egrifta in adult HIV patients with lipodystrophy will be compared to long-term safety data for adult HIV patients with lipodystrophy without Egrifta exposure for increased risks of cancer, MACE, hypersensitivity reactions, liver and kidney abnormalities, and retinopathy in diabetic patients.

2) Study objectives should include diabetes mellitus as a primary outcome

In the proposal, diabetes mellitus is not included as a clinical outcome. I recommend that diagnosis and treatment of diabetes be included as one of the primary outcomes in any submitted protocol. In addition, the protocol should pay particular attention to identifying and following patients prescribed Egrifta who have pre-existing diabetes.

3) Sample size must be calculated

In the proposal, the sample size is not calculated. The formal protocol must contain a calculation of the estimated sample size needed to conduct the study. The protocol should state plans to enroll adequate numbers of women and racial subgroups.

#### 4) Statistical analysis plan not included

In the proposal, statistical analyses are not mentioned. The formal protocol must include a section on planned statistical analyses including control for covariates. Survival analyses that take into consideration time to event and censoring (due to discontinuation of the study drug, death, losses to follow-up, etc.) would be preferred.

#### 5) Lack of comparability of exposed and unexposed subjects

The proposal states that the source of the unexposed group is “from an external database.” The protocol must provide information about the source of the unexposed group. In most observational studies, controls are chosen from the *same databases* as the cases, (e.g., patients who do not elect Egrifta from the same physician practices as the Egrifta-exposed subjects) and are matched on calendar time, age, sex, and possibly other demographic variables. This is done in an attempt to obtain comparable demographics and follow-up between exposed and unexposed subjects. Propensity scores should also be considered to adjust for possible selection bias between exposed and unexposed subjects.

In addition, to increase statistical power, the researchers should consider matching more than one unexposed subject to each exposed subject (e.g., 4:1).

#### 6) Length of follow-up likely too short

The proposal states that “all patients (including the observation group) should be followed for at least 5 years.” I recommend that both the exposed Egrifta subjects and the unexposed Egrifta subjects be followed for 10 years. This is important for determinations of the relative risk of any drug-related cancer incidence and mortality.

#### 7) Enrolling non-exposed subjects and feasibility of an observational study

The proposal does not address the problems with enrolling patients and the feasibility of conducting an observational study of Egrifta. Once the drug becomes available, it seems likely that many patients with lipodystrophy (with the exception of those very ill and financially unable to afford it) will want to take it. The proposal does not address the difficulties of finding non-exposed subjects to enroll; rather, it states that an external database will be used to capture non-exposed subjects. However, comparability may be compromised by the use of an external database. On the other hand, non-exposed subjects are expected to be difficult to find. This presents a conundrum for conducting an observational study.

For this reason, I believe that conducting this study using observational data may not be feasible. Potential adverse drug reactions of a serious nature may be more easily and adequately addressed in a clinical trial or by a clinical study.

#### 8) Losses to follow-up and mortality not addressed

If the study is conducted for 5 years or as long as 10 years, there will be many changes that occur during this period. All subjects would have to be followed for the length of the study period. This will be a very difficult challenge. The protocol should address this issue.

In addition, names and identifiers of all patients lost to follow-up should be entered into the National Death Index to identify subjects who have died and to obtain causes of death.

Many, if not most, patients who die of cancer and many who die from heart disease do not die within hospital settings. Unless there is physician follow-up of all patients in the study, the fact of death and the causes of death will not be known unless the NDI is accessed.

#### 8) Physician enrollment and dwindling physician participation over time

The proposal states that “eligible investigators, who are willing and qualified to conduct clinical research according to guidelines of Good Clinical Practice, will be prescribers of Egrifta.” In any long-term safety study, it is a challenge to find physicians willing to participate as investigators. Over a 10-year study, physicians will die, patients will switch physicians, and it will be difficult to keep physicians participating in the study. The protocol should address these issues.

#### 9) Standardization of data, missing data, and privacy issues

The proposal states that physicians will enter data on subjects over the Internet; however, it does not specify if there will be a standardized form for them to fill in.

Also, the company will need to track each physician entry for timeliness and incomplete information, and they will need to develop methods and approaches for contacting physicians who do not provide any data or incomplete data.

All forms filled out by physicians will need to be standardized. There should be options for physicians who do not choose to use the Internet. Finally, the ethics and legality of sending private health information over the Internet will have to be addressed and methods to maintain privacy developed.

#### 10) Lack of collection of data on lipid parameters and hypertension

The proposal does not mention that measurements of lipid parameters or blood pressure measures and hypertension will be captured. Since hypercholesterolemia and hypertension along with smoking are primary risk factors for MACE, the investigators would need to capture these data.

#### 11) No mention that information on hospitalizations and emergency department visits will be collected

The proposal does not mention that data on hospitalizations and emergency department visits will be collected. To assess if the drug is related to unlabeled adverse events, this information will need to be collected for exposed and unexposed subjects.

#### 12) No data available on inappropriate use

The proposal is for the study of patients with HIV-associated lipodystrophy treated with Egrifta and a similar group of patients without treatment with Egrifta. The proposal does not address this drug’s potential for significant off-label use in patients without HIV who have excess abdominal fat. Since a high prevalence of overweight and obesity exist in the U.S., it is likely that his drug would have considerable off-label use. Furthermore, like human growth hormone, it may also appeal to abuse by body builders. Given that

Egrifta has the potential for significant off-label use and abuse and because it increases glucose and IGF-1 levels that may lead to adverse clinical outcomes, it seems important that any protocol of the long-term safety of this drug should assess (in the same protocol or another one) the drug's inappropriate use, misuse, and abuse and safety consequences.

#### 4 SUMMARY

DMEP plans to approve tesamorelin acetate (Egrifta), a growth hormone releasing factor analog indicated for the reduction of excess abdominal fat in HIV-infected patients with lipodystrophy. Because of the potential of this drug to be used off-label in people with excess abdominal fat without HIV infection and in body builders who use human growth hormone and IGF-1 (1) and because the drug is associated with increases in glucose and IGF-1 possibly resulting in adverse long-term consequences, I recommend that DMEP:

-add more information to the Warnings and Precautions section of the product information regarding the potential for inappropriate use and also that the consequences of long-term use have not been studied and are unknown.

Although DMEP asked the sponsor, Theratechnologies Inc., to conduct a postmarketing clinical trial of cardiovascular outcomes, the company enumerated a number of concerns including the feasibility of conducting such a study. They submitted a proposal "to collect long-term safety information related to treatment with Egrifta in adult HIV patients with lipodystrophy." I have concerns about whether an observational study will be feasible because, for comparability's sake, unexposed patients are usually selected from the same database as exposed subjects (not from an opportunistic external database as planned by the company), and I believe that unless patients are very ill or financially unable to afford Egrifta, it may be difficult to obtain a large enough sample of HIV patients with lipodystrophy who choose not to take the drug. Therefore, I believe the company should address whether an observational study will be feasible.

In addition, a number of other challenges and study limitations must be addressed in any submitted protocol. They are described in detail in the Results section of the text and outlined in the Executive Summary.

Finally, in this study or a separate one, I recommend that the sponsor collect data on inappropriate prescribing and use of Egrifta and any safety issues that result from that use.

Diane K. Wysowski, Ph.D.

#### 5 REFERENCE

1. IGF-1-The Hormone: Insulin-like Growth factor-1.  
<http://articles.muscle-talk.co.uk/article-igf-1.aspx> Accessed 10/29/10.

cc: MohamadiA/RomanD/EganA/BishaiJ/ParksM/DMEP  
TossaM/WysowskiD/VegaA/StaffaJ/ZornbergG/DEPI  
KarwoskiC/WillyM/LaCivitaC/DempseyM/DRISK

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DIANE K WYSOWSKI  
11/05/2010

GWEN L ZORNBERG  
11/05/2010

I concur with Dr. Wysowski's conclusions and recommendations in concurrence with our Acting DEPI Division Director, Dr. Judy Staffa.

**DIVISION OF PULMONARY, ALLERGY, and RHEUMATOLOGY**  
**PRODUCTS MEDICAL OFFICER CONSULTATION**

Date: October 29, 2010  
To: Jennifer Johnson, Regulatory Project Manager, Division of Metabolic and Endocrine Products (DMEP)  
From: Sofia Chaudhry, MD, Medical Officer,  
Through: Susan Limb, MD, Medical Team Leader  
Through: Badrul Chowdhury, MD, PhD, Division Director  
Subject: EGRIFTA™ hypersensitivity reactions

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**General Information**

NDA/IND#: NDA 22505  
Sponsor: Theratechnologies Inc.  
Drug Product: EGRIFTA™ (tesamorelin) for subcutaneous injection  
Request From: Jennifer Johnson, Regulatory Project Manager, DMEP  
Date of Request: October 27, 2010  
Date Received: October 27, 2010  
Materials: Immunogenicity Report—Amendment I, patient narratives, case  
Reviewed: reports, proposed labeling

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**Executive Summary**

This is a medical officer consultation review requested by the Division of Metabolic and Endocrine Products (DMEP) for tesamorelin (Egrifta™). Tesamorelin is proposed for the reduction of excess abdominal fat in HIV-infected patients with lipodystrophy at a recommended dose of 2 mg injected subcutaneously once daily. DMEP has requested DPARP's input on hypersensitivity reactions reported in the tesamorelin development program.

Tesmorelin is a synthetic growth hormone releasing factor (GRF) analog comprised of the 44-amino-acid sequence of hGRF on which a hexenoyl moiety has been anchored near the N-terminus to increase resistance to enzymatic degradation. It is supplied as a sterile lyophilized powder for SC injection with mannitol as an excipient then reconstituted in sterile water for injection.

The safety database is comprised of 1419 patients, 798 of whom were HIV patients, who received at least 1 dose of tesamorelin. A total of 740 HIV patients were evaluated in the pivotal Phase 3 trials, which included two 26-week placebo-controlled efficacy and safety trials followed by an additional 26-week open-label extension phase.

The sponsor identified 4 cases of hypersensitivity from the Phase 1 and 2 trials. In the pivotal Phase 3 trials, there were 27 (27/740; 3.6%) cases of hypersensitivity reactions in the tesamorelin treatment arm compared to 1 case in the placebo arm. A total of 21 patients discontinued early from the trial secondary to the hypersensitivity reactions. A review of the patient narratives and case report forms indicates that the majority of the reactions were localized injection reactions characterized by the immediate onset of pruritus, erythema, irritation, rash, and urticaria. There were a few cases of generalized urticaria and other rash, indicative of a systemic hypersensitivity reaction. In addition, several patients experienced increases in eosinophils that recovered following tesamorelin discontinuation. Interestingly, there were multiple reports of patients who noted a local injection reaction in conjunction with pruritus, wheals, or other rash formation at prior sites of injection. A couple of the cases had signs or symptoms of more systemic involvement such as dyspnea, tachycardia, sweating, or dizziness. However, in all cases the symptoms were transient (few minutes or less) and self-limited, making a diagnosis of anaphylaxis unlikely.

A relatively high rate of anti-drug antibody development was observed in the trial and was more pronounced in the patients with hypersensitivity reactions. At baseline prior to treatment, 98% of patients were seronegative. Of the 27 tesamorelin-treated HIV patients with hypersensitivity, 23 (23/27, 85%) patients tested positive for anti-drug IgG antibodies, compared to a seropositive rate of approximately 50% for the pivotal trial population as a whole. Of the 23, 13 had high titers  $\geq 400$  at some point in the trial, and 2 patients tested positive for anti-tesamorelin IgE antibodies. IgE was not consistently sampled in the general patient population so rates for comparison are not available. While the higher rate of immunogenicity observed in the hypersensitivity patients implies an immune-based mechanism for the reactions, the presence or titer of anti-tesamorelin antibodies did not appear to correlate with the clinical severity of the hypersensitivity reaction. In addition, there were several individuals with high titers who did not experience a hypersensitivity reaction. The absence of a correlation may be secondary to the technical limitations of the immunoassays used in the trials. Therefore, the immunoassays that are currently available do not appear to be predictive of individual risk.

### **Conclusions and recommendations:**

The nature of the hypersensitivity events implies an immune-mediated pathophysiology, potentially IgE-mediated. The risk of more severe systemic reactions, such as anaphylaxis, is assumed, and cases of more severe reactions might be anticipated with broader use upon approval of the product. As such, DPARP agrees with the inclusion of hypersensitivity reactions in the Warnings and Precautions section of the product label. However, DPARP recommends labeling for hypersensitivity reactions with a specific description of the more common reactions observed in the clinical program, which did not include anaphylaxis. Also, based on the case narratives reviewed, DPARP does not see a need for further clinical characterization of the hypersensitivity risk as a post-marketing requirement beyond routine surveillance.

DPARP suggests the following language for the label regarding the hypersensitivity risk for DMEP's consideration:

- DPARP recommends striking the following statement in the Contraindications section, which minimizes the risk of hypersensitivity reactions:

### 4.3 Hypersensitivity

EGRIFTA™ is contraindicated in patients with known hypersensitivity to tesamorelin and/or mannitol (an excipient)- (b) (4)  
see Warnings and Precautions (5.5)].

- DPARP recommends the following wording for the Warnings and Precautions section to reflect the nature of hypersensitivity events observed in the clinical program:

### 5.5 Hypersensitivity Reactions

Hypersensitivity reactions (b) (4) may occur in patients treated with EGRIFTA™. Hypersensitivity reactions occurred in 3.6% of patients with HIV-associated lipodystrophy treated with EGRIFTA™ in the Phase 3 clinical trials. These reactions included pruritus, erythema, flushing, urticaria, and other rash. (b) (4)

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

- As noted above, the utility of immunogenicity data for evaluating an individual patient's risk for a hypersensitivity reaction is limited. However, healthcare professionals may still find the information useful in the context of the other immunogenicity data available. DPARP suggests the following changes to the Immunogenicity section:

### 6.2 Immunogenicity

As with all therapeutic proteins and peptides, there is a potential for in vivo development of anti- EGRIFTA™ antibodies. In the combined Phase 3 clinical trials anti-tesamorelin IgG antibodies were detected in 49.5% of patients treated with EGRIFTA™ for 26 weeks and 47.4% of patients who received EGRIFTA™ for 52 weeks. In the subset of patients with hypersensitivity reactions, anti-tesamorelin IgG antibodies were detected in 85.2%. (b) (4)

Cross-reactivity to endogenous growth hormone-releasing hormone (GHRH) was observed in approximately 60% of patients who developed anti-tesamorelin antibodies. Patients with and without anti-tesamorelin IgG antibodies had similar mean reductions in visceral adipose tissue (VAT) and IGF-1 response suggesting that the presence of antibodies did not alter the efficacy of EGRIFTA™. In a group of patients who had

antibodies to tesamorelin after 26 weeks of treatment (56%) and were re-assessed 6 months later, after stopping EGRIFTA™ treatment, 18% were still antibody positive. Neutralizing antibodies to tesamorelin and hGHRH were detected in vitro at Week 52 in 10% and 5% of EGRIFTA™-treated patients, respectively. They did not appear to have an impact on efficacy, as evidenced by comparable changes in VAT and IGF-I level in patients with or without in vitro neutralizing antibodies.

The observed incidence of antibody positivity in an assay is highly dependent on several factors including assay sensitivity and specificity, methodology, sample handling, timing of sample collection, concomitant medication and underlying disease. For these reasons, comparison of the incidence of antibodies to EGRIFTA with the incidence of antibodies to other products may be misleading.

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SOFIA S CHAUDHRY  
11/02/2010

SUSAN L LIMB  
11/02/2010

BADRUL A CHOWDHURY  
11/03/2010  
I concur

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications**

**\*\*\*Pre-decisional Agency Information\*\*\***

## Memorandum

**Date:** October 25, 2010

**To:** Jennifer Johnson, Regulatory Project Manager  
Division of Metabolism and Endocrinology Products (DMEP)

**From:** Sam Skariah, Regulatory Review Officer  
Kendra Jones, Regulatory Review Officer  
Division of Drug Marketing, Advertising, and Communications (DDMAC)

**CC:** Lisa Hubbard, Professional Group Leader, DDMAC  
Shefali Doshi, Acting DTC Group Leader, DDMAC

**Subject:** NDA #022505 Egrifta<sup>™</sup> (tesamorelin for injection) for subcutaneous use  
DDMAC Labeling Comments for Egrifta

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DDMAC has reviewed the proposed prescribing information (PI), patient labeling (PPI), Instructions for Use (IFU), and carton/container labeling for Egrifta submitted for consult on April 9, 2010, and offers the following comments.

The versions of the proposed PI, PPI, and IFU used in this review were sent via email from Jennifer Johnson (Project Manager) on 10/14/10.

### **General Comment**

DDMAC's comments are provided directly on the marked up version of this document, attached below. DDMAC does not have any comments at this time regarding the draft carton/container labeling.

Thank you for the opportunity to comment on these proposed materials.

If you have any questions on the PI, please contact Samuel Skariah at 301.796.2774 or [Sam.Skariah@fda.hhs.gov](mailto:Sam.Skariah@fda.hhs.gov).

If you have any questions on the PPI or IFU, please contact Kendra Jones at 301.796.3917 or [Kendra.Jones@fda.hhs.gov](mailto:Kendra.Jones@fda.hhs.gov).

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SAMUEL M SKARIAH  
10/25/2010

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**CONSULTATION**

**Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research**

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**DATE:** October 19, 2010

**FROM:** Ali Mohamadi, MD, Division of Metabolism and Endocrinology Products

**THROUGH:** Dragos Roman, MD, Clinical Team Leader  
Mary Parks, MD, Director, Division of Metabolism and Endocrinology Products

**TO:** Samuel M. Skariah, Regulatory Review Officer, Division of Drug Marketing, Advertising, and Communications

**SUBJECT:** Egrifta draft launch core visual aid and print advertisement directed to healthcare professionals

**I. Background and basis for consult**

On September 16, 2010, the Division of Metabolism and Endocrinology Products (DMEP) received a consultation request from the Division of Drug Marketing, Advertising, and Communications (DDMAC) on the draft visual aid and healthcare professional (HCP)-directed print advertisement submitted by Kendle International for Egrifta (NDA #22-505). Egrifta (tesamorelin acetate) is a human growth hormone releasing factor (GRF) analog that has been developed by Theratechnologies for the indication of reducing excess abdominal fat in HIV-infected patients with lipodystrophy. The proposed clinical dose is 2 mg once daily. These promotional launch materials were submitted to DDMAC on September 3, 2010 and received on September 7, 2010.

Following its review of these promotional materials, DDMAC has requested the Division's input on several of the claims made in this piece. DDMAC's specific questions are listed in Section III of this consultation, followed by the Division's responses.

**II. Materials reviewed for consult**

1. DDMAC request for consultation
2. Sponsor's draft launch core visual aid and print advertisement directed to healthcare professionals for Egrifta

**III. DMEP Comments and Recommendations**

**Question 1.**

(b) (4)

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ALI MOHAMADI  
10/19/2010

DRAGOS G ROMAN  
10/19/2010

MARY H PARKS  
10/19/2010



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: September 15, 2010

To: Mary Parks, M.D., Director  
**Division of Metabolism and Endocrinology Products**

Through: Mary Willy, PhD, Deputy Director  
**Division of Risk Management (DRISK)**

LaShawn Griffiths, MSHS-PH, BSN, RN  
Senior Patient Labeling Reviewer, Acting Team Leader  
**Division of Risk Management**

From: Latonia M. Ford, RN, BSN, MBA  
Patient Labeling Reviewer  
**Division of Risk Management**

Subject: DRISK Review of Patient Labeling (Patient Package Insert  
and Instruction for Use)

Drug Name(s): Egrifta (tesamorelin acetate) Injection

Application  
Type/Number: NDA 22505

Applicant/sponsor: Theratechnologies Inc.

OSE RCM #: 2009-1555

## 1. INTRODUCTION

This review is written in response to a request by the Division of Metabolism and Endocrinology Products (DMEP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for Egrifta (tesamorelin acetate) Injection.

On May 29, 2009, Theratechnologies Inc. submitted a New Drug Application (NDA) 22505 for Egrifta (tesamorelin acetate) Injection. Egrifta is indicated for the reduction of excess abdominal fat in HIV-infected patients with lipodystrophy. Kendle International Inc is the designated agent for NDA 22505.

Please send these comments to the Applicant. DRISK spoke with DMEPA and a separate DMEPA review of the IFU was completed on March 1, 2010. Let us know if DMEP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant.

### MATERIAL REVIEWED

- Draft Egrifta (tesamorelin acetate) injection Prescribing Information (PI) received May 29, 2009 and revised by the Review Division throughout the current review cycle, and sent to DRISK August 31, 2010.
- Draft Egrifta (tesamorelin acetate) injection Patient Package Insert (PPI) and Instructions for Use (IFU) received on May 29, 2009 and revised by the review division throughout the review cycle, and sent to DRISK August 31, 2010.

## 2. RESULTS OF REVIEW

In our review of the PPI and IFU, we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the PI
- removed unnecessary or redundant information
- reformatted the PPI to be consistent with other patient labeling
- where appropriate, made the PPI consistent with the March 2010 approved Norditropin patient labeling
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

Our annotated PPI and IFU is appended to this memo. Any additional revisions to the PI should be reflected in the PPI and IFU.

Please let us know if you have any questions.

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22505	ORIG-1	THERATECHNOLOGIES INC	Egrifta

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/s/

LATONIA M FORD

09/15/2010

Egrifta (tesamorelin acetate) PPI and IFU DRISK Final Review.

MARY E WILLY

09/15/2010

I concur



## **INTRODUCTION**

Theratechnologies, Inc. submitted a New Drug Application (NDA) 22-505, on May 29, 2009, for Egrifta (tesamorelin) for injection, which is indicated to induce and maintain a reduction of excess abdominal fat in HIV-infected patients with lipodystrophy. On August 2, 2010, the Division of Metabolic and Endocrine Products (DMEP) consulted the Maternal Health Team (MHT) to review and comment on the proposed revised pregnancy and nursing mothers subsections of labeling.

## **BACKGROUND**

### **Egrifta (tesamorelin) for injection**

Egrifta (tesamorelin) for injection, a Growth Hormone Releasing Factor (GRF) analog, is a hypothalamic peptide that acts on the pituitary somatotroph cells to stimulate the synthesis and pulsatile release of endogenous growth hormone (GH). Growth hormone is both anabolic and lipolytic. It exerts its effects by interacting with specific receptors on a variety of target cells, including chondrocytes, osteoblasts, myocytes, hepatocytes, and adipocytes, resulting in a host of pharmacodynamic effects. Some, but not all these effects, are primarily mediated by insulin-like growth factor 1 (IGF-1) produced in the liver and in peripheral tissues.<sup>1</sup>

### **Endocrinologic and Metabolic Drugs Advisory Committee Meeting**

Egrifta was discussed at an Endocrinologic and Metabolic Drugs Advisory Committee Meeting on May 27, 2010. Committee members voted unanimously to approve the product because of demonstrated efficacy in the indicated population and the lack of other drugs to reduce excess visceral abdominal fat in HIV-infected patients. In addition, the committee recommended postmarketing studies for follow-up on cardiovascular outcomes, increased risk for diabetes, and increases in IGF-1, which may promote tumor growth.

### **Nonclinical Reprotoixcty Studies**

In developmental and reproductive toxicity studies in rats, hydrocephaly occurred in pups of pregnant rats that received tesamorelin from organogenesis through lactation. Based on AUC, animal doses were less than two times the maximum recommended human dose (MRHD) of tesamorelin, and there were no signs of maternal toxicity. Hydrocephaly did not occur in pups exposed to tesamorelin during organogenesis at a maternal dose less than the MRHD (based on AUC); however, pups had decreased skull ossification. Because of dosing differences in these studies, it is not possible to determine whether tesamorelin induces hydrocephaly during the period of organogenesis, during the peri/post natal period, or during both periods.

### **Pregnancy and Nursing Mothers Labeling**

FDA currently classifies the reproductive and developmental risk of drugs for use during pregnancy into five categories (A, B, C, D, and X)<sup>2</sup> using available animal and/or human data. Some of the categories require consideration of both the potential risks (to mother and fetus) and the potential benefits (to the mother) if the drug is used during pregnancy. The classification system does not define a linear increase in fetal risk from pregnancy category A to pregnancy category X (see Appendix A for a description of each pregnancy category). The MHT notes that the pregnancy category classification will be eliminated when the Final Pregnancy and Lactation

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<sup>1</sup> See draft revised labeling, July 29, 2010

<sup>2</sup> See Appendix A for pregnancy category definitions table

Labeling Rule (PLLR) publishes (Proposed Pregnancy and Lactation Labeling Rule published May 29, 2008).<sup>3</sup> When the final regulations publish, the PLLR will complete the requirements on content and format of labeling for human prescription drug and biological products (Physician Labeling Rule, January 24, 2006, 71 FR 3922) by revising the content and format requirements for the pregnancy, labor and delivery, and nursing mothers subsections of labeling. The proposed changes to prescription drug labeling will provide prescribers with clinically relevant and more comprehensive information for making prescribing decisions and for counseling women who are pregnant, breastfeeding, or of childbearing age about using prescription medications.

During the past few years, the Maternal Health Team has developed a more consistent and clinically useful approach to the Pregnancy and Nursing Mothers subsections of labeling. This approach complies with current regulations, including the assignment of pregnancy categories, but incorporates “the spirit” of the Proposed Pregnancy and Lactation Labeling Rule (published on May 29, 2008). The MHT reviewer ensures that the appropriate regulatory language is present and that available information is organized and presented in a clear and useful manner for healthcare practitioners. Animal data in the pregnancy subsection is presented in an organized, logical format that makes it as clinically relevant as possible for prescribers. This includes describing animal data in terms of species exposed, timing and route of drug administration, dose expressed in terms of human exposure or dose equivalents (with the basis for calculation), and outcomes for dams and offspring. For nursing mothers, when animal data are available, only the presence or absence of drug in milk is considered relevant and presented in the label, not the amount, as this can vary significantly from species to species.

This review provides MHT’s suggested revisions to the proposed pregnancy and nursing mothers labeling for Egrifta (tesamorelin) for injection.

**SPONSOR PROPOSED LABELING (dated May 29, 2009)**

**USE IN SPECIFIC POPULATIONS**

**8.1 Pregnancy**

[Redacted text block] (b) (4)

**8.3 Nursing mothers**

[Redacted text block] (b) (4)

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<sup>3</sup> See Proposed Pregnancy and Lactation Labeling Rule, 73 FR 30831, May 29, 2008

## **DISCUSSION AND CONCLUSIONS**

Theratechnologies, Inc. submitted a New Drug Application, NDA 22-505, on May 29, 2009, for Egrifta (tesamorelin) for injection, a Growth Hormone Releasing Factor (GRF) analog indicated to induce and maintain a reduction of excess abdominal fat in HIV-infected patients with lipodystrophy. Egrifta (tesamorelin) is a hypothalamic peptide that acts on the pituitary somatotroph cells to stimulate the synthesis and pulsatile release of endogenous growth hormone (GH). Growth hormone is both anabolic and lipolytic. It exerts its effects by interacting with specific receptors on a variety of target cells, including chondrocytes, osteoblasts, myocytes, hepatocytes, and adipocytes, resulting in a host of pharmacodynamic effects.

### **Pregnancy**

The Sponsor did not provide a pregnancy category classification in their proposed labeling for Egrifta (tesamorelin) for injection. Choice of pregnancy category and inclusion of required risk statements are defined by the current labeling regulations at 21 CFR 201.57. Each category is defined by the availability of findings from reproductive and developmental toxicity studies in animals and studies of drug use during human pregnancy. The pregnancy category definitions for pregnancy categories C, D, and X require consideration of both the potential risks and benefits of maternal drug use during pregnancy. The acceptability of clinical benefit to a woman for using a drug for a particular indication during pregnancy is weighed against the known and potential embryo-fetal risks associated with drug exposure and those associated with untreated maternal disease.

Hydrocephaly occurred in offspring in nonclinical developmental and reprotoxicity studies; however, due to the study methodology, it was not possible to determine if tesamorelin induced hydrocephaly during the period of organogenesis, during the peri/post natal period, or during both periods. Based on these positive animal reprotoxicity findings, Egrifta could be classified with a pregnancy category of C or X. However, the MHT recommends a pregnancy category X classification based on a lack of potential clinical benefit to reducing excessive maternal visceral abdominal fat with Egrifta treatment during pregnancy. Intra-abdominal visceral adipose tissue normally increases throughout pregnancy due to the metabolic and hormonal changes that occur with pregnancy.<sup>4</sup> It is unknown what the potential maternal and/or fetal effects would be from reducing the visceral fat accumulation that occurs normally in pregnancy. In addition, if Egrifta crosses the placenta, it is unknown as to the effect it would have on fetal visceral adipose deposition or whether there would be other unexpected impacts on normal fetal growth through Egrifta's effects on growth hormone secretion. Given the potential increased risk for hydrocephaly in an infant exposed to Egrifta prenatally and a lack of apparent clinical benefit, pregnancy category X is most appropriate.

In non-pregnant people, visceral adiposity is associated with adverse metabolic and cardiovascular outcomes.<sup>5</sup> Despite the reduction in visceral adipose tissue in HIV-infected

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<sup>4</sup> Kinoshita A, Itoh M. Longitudinal variance of fat mass deposition during pregnancy evaluated by ultrasonography: the ratio of visceral fat to subcutaneous fat in the abdomen. *Gynecol Obstet Invest.* 2006;61(2):115-8

<sup>5</sup> Moyle G, Moutschen m, et al. Epidemiology, assessment, and management of excess abdominal fat in persons with HIV infection. *AIDS Rev.* 2010 Jan-Mar;12(1):3-14

patients with lipodystrophy from Egrifta use; impaired glucose tolerance increased with Egrifta use and cardiovascular outcomes and safety is unknown.

**Nursing Mothers**

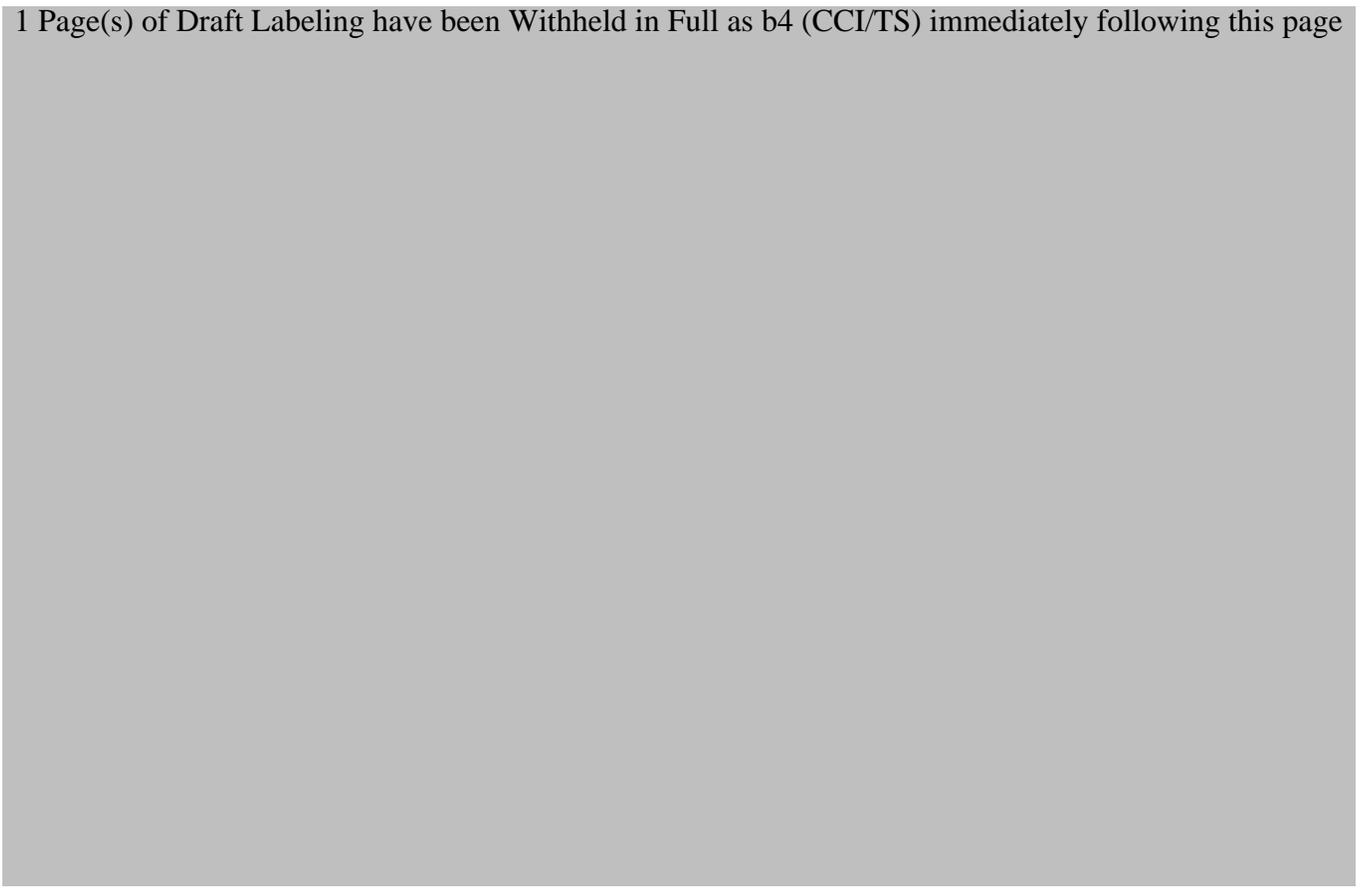
The nursing mothers section of labeling should reflect the CDC recommendation against human milk-feeding by HIV-1 infected mothers in the United States. This measure is to avoid the risk of postnatal HIV-1 transmission.

**Labeling**

The MHT is structuring the Pregnancy and Nursing Mothers labeling information in a way that complies with current regulations but incorporates “the spirit” of the Proposed Pregnancy and Lactation Labeling Rule (published on May 29, 2008). The goal of this restructuring is to make the pregnancy and lactation sections of labeling a more effective communication tool for clinicians.

MHT’s recommended labeling revisions for Egrifta (tesamorelin) for injection labeling are provided below. These recommendations were conveyed to DMEP on September 1, 2010.

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**APPENDIX A:  
FDA Pregnancy Category Definitions**

<b>Table 1. FDA Pregnancy categories (language summarized from 21 CFR 201.57)</b>	
<b>Category</b>	<b>Definition</b>
<b>A</b>	Adequate and well-controlled (AWC) studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters).
<b>B</b>	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no AWC studies in pregnant women, OR animal studies demonstrate a risk and AWC studies in pregnant women have not during the first trimester (and there is no evidence of risk in later trimesters).
<b>C</b>	Animal reproduction studies have shown an adverse effect on the fetus, there are no AWC studies in humans, AND the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks. OR animal studies have not been conducted and there are no AWC studies in humans.
<b>D</b>	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, BUT the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks (for example, if the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective).
<b>X</b>	Studies in animals or humans have demonstrated fetal abnormalities OR there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, AND the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit (for example, safer drugs or other forms of therapy are available).

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/s/

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JEANINE A BEST  
09/14/2010

Karen B FEIBUS  
09/14/2010  
I agree with the content and recommendations contained in this review.

LISA L MATHIS  
09/20/2010



**Department of Health and Human Services**  
**Public Health Service**  
**Food and Drug Administration**  
**Center for Drug Evaluation and Research**  
**Office of Surveillance and Epidemiology**

Date: March 1, 2010

To: Mary Parks, MD, Director  
Division of Metabolism and Endocrinology Products

Through: Kellie Taylor, Pharm D, MPH, Team Leader  
Denise Toyer, Pharm D, Deputy Director  
Carol Holquist, RPh, Director  
Division of Medication Error Prevention and Analysis

From: Cathy A. Miller, BSN, MPH, Safety Evaluator  
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Egrifta (Tesamorelin Acetate) for Injection  
1 mg per vial

Application Type/Number: NDA # 22-505

Sponsor: Kendle International, Inc.

OSE RCM #: 2009-1163

## CONTENTS

EXECUTIVE SUMMARY .....	3
1 BACKGROUND .....	3
1.1 Introduction .....	3
1.2 Product Information .....	3
2 METHODS AND MATERIALS .....	4
2.1 Labels and Labeling .....	4
3 RESULTS .....	5
3.1 Labels and Labeling .....	5
4 DISCUSSION .....	7
4.1 General Comments .....	7
4.2 Strength Presentation on Container Labels and Insert Labeling .....	7
4.3 Egrifta Packaging Configuration (1 mg per vial) .....	8
4.4 Container label .....	8
4.5 Egrifta Medication Box (Box 1 of 2) Carton Labeling .....	8
4.6 Egrifta Injection Kit Box (Box 2 of 2) Carton Labeling .....	9
4.7 Package Insert Labeling Patient Counseling Information .....	10
5 CONCLUSIONS AND RECOMMENDATIONS .....	10
5.1 Comments to the Division .....	10
5.2 Comments to the Applicant .....	11
5.3 Package Insert Labeling Comments Proposed to DRISK .....	14
6 REFERENCES .....	14
APPENDICES .....	15

## **EXECUTIVE SUMMARY**

Egrifta (Tesamorelin Acetate) for Injection is currently under review for the proposed indication of inducing and maintaining a reduction in excess abdominal fat in HIV-infected patients with Lipodystrophy. As such, the Division of Medication Error Prevention and Analysis (DMEPA) utilized Failure Mode and Effects Analysis<sup>1</sup> to evaluate the packaging, container labels, carton and insert labeling submitted by the Applicant to identify additional areas of vulnerability that could lead to medication errors.

Our Label and Labeling Risk Assessment findings indicate the proposed two-box kit design and a single dose that requires two vials (1 mg each) to achieve the 2 mg dose, may contribute to medication errors. A redesign to a single vial and diluent that could be stored in the same location (i.e. room temperature or refrigerator) and deliver the recommended 2 mg dose would minimize some of the potential failures identified with the proposed design. Additionally, improvements can be made to the presentation of the strength (presented as 1.1 mg including the 0.1 mg overfill amount), as well as the prominence of the proprietary and established name on the container label and carton labeling for the Egrifta Injection Kit (Box 2 of 2).

DMEPA also believes that improvements can be made to the Patient Counseling Information section of the insert labeling, however, we defer final comments to the Division of Risk Management (DRISK), who have been consulted to review this information from a patient comprehension and safety perspective (pending OSE Review 2009-1555).

If marketed as currently proposed, DMEPA seeks clarification from the Applicant on the proposed design, in terms of their plans for distribution of the Egrifta kits to retail pharmacies, hospital pharmacies and mail-order pharmacies, since the product contains several elements and the Egrifta medication box requires refrigeration. DMEPA is concerned that elements of the kit will be misplaced (not dispensed) or fail to be refrigerated as directed during storage of the kit.

We believe the risks we have identified can be addressed and mitigated prior to drug approval, and provide recommendations in Section 5.2.

## **1 BACKGROUND**

### **1.1 INTRODUCTION**

This review was written in response to a request from the Division of Metabolism and Endocrinology Products (DMEP) for an assessment of the proposed packaging, container label, carton and inset labeling for Egrifta (Tesamorelin Acetate), for evaluation to identify areas that could lead to medication errors potential to contribute to medication errors.

### **1.2 PRODUCT INFORMATION**

Egrifta (Tesamorelin Acetate) for injection is being developed for the indication of induction and reduction of excess abdominal fat in HIV-infected patients with Lipodystrophy. Egrifta is a synthetic human Growth Hormone-Releasing Factor analogue that comprises the 44-amino acid sequence of human Growth Hormone-Releasing Factor (hGRF) with a binding affinity to hGRF receptors comparable to that of natural hGRF and an increased stability and half-life in humans.

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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Egrifta is designed for self-administration by the patient. The recommended dose of Egrifta is 2 mg injected subcutaneously once daily, preferably in the morning. Egrifta is supplied in a vial containing 1.1 mg of Tesamorelin Acetate and 55 mg of Mannitol as a lyophilized powder (1 mg/mL). The diluent (Sterile Water for Injection, USP) is provided in a separate vial for reconstitution. To mix Egrifta for administration, 2.2 mL of Sterile Water is first injected into Egrifta vial #1, mixed and drawn up into a syringe, and then injected into Egrifta vial #2. After mixing, 2 mL should be withdrawn for a final concentration of 2 mg/2 mL. If not used immediately, Egrifta should be discarded and should not be frozen or refrigerated after reconstitution. Egrifta should be administered subcutaneously and the recommended injection site is the abdomen, with injection sites rotated to different areas of the abdomen. Egrifta should not be injected into scar tissue, bruises or the navel.

Egrifta is supplied as a kit with two boxes of material. Box #1 (called the Medication Box) contains 60 Egrifta vials. Box #2 (called Injection Kit Box) contains (30) 10 mL vials of Sterile Water for Injection, USP, (30) syringes with needles already attached, (30) 1 1/2" 18-gauge reconstitution needles and (30) injection needles (b) (4) and (30) injection needles 1/2" 27-gauge. Non-reconstituted vials of Egrifta should be refrigerated at 2°C to 8°C (36°F to 46°F).

The proposed proprietary name "Egrifta" was reviewed without objection in OSE Review #2009-1162 on August 13, 2009.

## **2 METHODS AND MATERIALS**

### **2.1 LABELS AND LABELING**

This section describes the methods and materials used by DMEPA to conduct a label, labeling, and packaging risk assessment. The primary focus of the assessments is to identify and remedy potential sources of medication error prior to drug approval. DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.<sup>2</sup>

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container labels and carton labeling communicate critical information including proprietary and established name, strength, form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.<sup>3</sup>

Because our staff analyze reported misuse of drugs, we are able to use this experience to identify potential errors with all medication similarly packaged, labeled or prescribed. DMEPA uses Failure Mode and Effects Analysis (FMEA) and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provided recommendations that aim at reducing the risk of medication errors.

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<sup>2</sup> National Coordinating Council for Medication Error Reporting and Prevention. <http://www.nccmerp.org/aboutMedErrors.html>. Last accessed 10/11/2007.

<sup>3</sup> Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

For this product the Applicant submitted labels and labeling on June 17, 2009 for review (See Appendix A through C). Additionally, DMEPA requested a mock sample kit of the Egrifta product on August 10, 2009 which was submitted to the Agency on September 2, 2009:

- Container Label for Egrifta vial (1 mL per vial)
- Carton Labeling for Medication Box (Box 1 of 2)
- Carton Labeling for Injection Kit Box (Box 2 of 2)
- Mock Egrifta Kit (no images available)

### **3 RESULTS**

#### **3.1 LABELS AND LABELING**

Our review of the labels and labeling of Egrifta noted the following vulnerabilities that may contribute to medication errors:

##### ***3.1.1 Container Label***

- A. As indicated in the DMEP filing communication dated August 10, 2009 by the Division's Microbiology disciplines for this application, Egrifta is currently packaged in 1 mg per vial strength glass vials (1.1 mg Tesamorelin Acetate and 55 mg of Mannitol) for reconstitution. This requires that the patient reconstitute two vials in order to prepare the recommended 2 mg dose per administration. The Division Metabolism and Endocrinology Products (DMEP) commented that the Applicant may have originally chosen this vial design because, at that time dosing (1 mg versus 2 mg) was not definitively determined since some of the earlier studies included 2 mg dosing. A request was made by DMEP to provide justification for proposed dosing that requires two vials of 1 mg each rather than a single vial containing 2 mg of product. DMEPA concurred with the request and asked that the applicant revise the dosage so that the complete 2 mg dose be packaged in one vial. However, to date, the Applicant has not provided additional data regarding this request nor have the suggested that the current design (1.1 mg per vial) would be revised.
- B. As indicated in the DMEP filing communication dated August 10, 2009 by the Division's Chemistry, Manufacturing and Controls disciplines for this application, the strength is presented on the Egrifta as 1.1 mg, representative of the overfill amount, rather than the proposed strength of 1 mg. Additionally, it is not clear whether the dosage strength denotes the free base or the salt form of the peptide because the established name of the product should correlate with the dosage strength (i.e., 1.1 mg Tesamorelin or 1.1 mg Tesamorelin Acetate). DMEPA concurs with the Divisions recommendation and also agree that the product labels and labeling should indicate in some manner, the strength in the vial is 1.1 mg prior to reconstitution and administration.
- C. The proprietary and established name are small and difficult to read on the principal display panel of the container label. In accordance with Code of Federal Regulation CFR 201.10(i), the Egrifta container label bears information that can be removed to allow for a larger, prominent display of the proprietary and established name.

##### ***3.1.2 Carton Labeling for Egrifta Medication Box 1 of 2***

- A. The proprietary name (Egrifta) and the established name (Tesamorelin Acetate) are small and difficult to read on carton labeling.

- B. The reconstitution statement “Must be reconstituted before use” should be expanded upon to better inform patients that the final dose of 2 mg requires two vials of the product.
- C. Although the carton labeling includes a statement regarding storage “Store at 2°C to 8°C (36°F to 46°F)”, the statement does not include information directing the patient to refrigerate the medication box containing Egrifta until administration.

### **3.1.3 Carton Labeling for Egrifta Injection Kit Box 2 of 2**

- A. The information provided on the outside of the individual boxes included in the Injection Kit Box 2 of 2, which contains the (30) sterile 3-cc syringes and (30) 1 1/2” 18 gauge sterile needles does not correspond verbatim to the language used to identify these items on the Injection Kit (Box 2 of 2) Labeling and, there is no identifying information on the outside of the box containing the thirty (30) individual (b) (4) or 1/2” 27 gauge sterile injection needles. Additionally, DMEPA believes that improvement can be made to better identify and link each individual item included in the kit to correspond to the item listed on the Egrifta Injection Box Kit (Box 2 of 2) labeling.
- B. The language describing the Thirty (30) syringes includes the use of the abbreviation ‘cc’ (3-cc syringes) rather than the widely recognized unit of measure milliliter (mL) abbreviation which is used throughout insert labeling. The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) has identified a list of dangerous abbreviations that have historically contributed to medication errors.<sup>4</sup> The abbreviation ‘cc’ can often times be misinterpreted as ‘U’ or ‘units’ and can lead to confusion that could cause a medication error in the correct interpretation of the unit of measure and subsequently, the correct dose.
- C. The (30) 10-milliliter vials of Sterile Water for Injection, USP are intended for single-use administration of one dose. However, there is no information on the labeling for the Sterile Water packaging or the individual container labels of Sterile Water alerting patients to dispose of unused portion after daily administration.
- D. The presentation of the proprietary name (Egrifta) and the established name (Tesamorelin Acetate) are large and too prominent on the carton labeling for the Egrifta Injection Kit Box in comparison to the words ‘Injection Box Kit’. Additionally, there is no language that alerts the patient that the box does not contain the drug product.

### **3.1.4 Other General Labeling Comments**

DMEPA has additional questions and concerns about the intended distribution of the Egrifta product kit including the following:

- Will the Egrifta kit be stocked in retail pharmacies only or will the Egrifta kit be available in hospital pharmacies as well?
- If the Applicant’s planned distribution does not include hospital pharmacies, how will patients who are on an Egrifta regimen who are admitted to the hospital receive their drug?

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<sup>4</sup> National Coordinating Council for Medication Error Reporting and Prevention, Council Recommendations, “Recommendations to Enhance Accuracy of Prescription Writing”. Revised June 2, 2005. [www.nccmerp.org/council/council 1996-09-04.html](http://www.nccmerp.org/council/council%201996-09-04.html).

### 3.1.5 Package Insert Labeling

See comment 3.1.1, B. above

## 4 DISCUSSION

### 4.1 GENERAL COMMENTS

Because the Egrifta product includes a kit with multiple parts, DMEPA has concerns about the Applicant's plans for distribution of the product (retail pharmacies only, hospital pharmacies and/or mail-order pharmacies). DMEPA believes that the Applicant's current proposed package design of the kit creates the potential for medication errors due to the variety of elements in the package and the different storage requirements of each (e.g. Egrifta vials must be stored at 36°F to 46°F while the remaining items packaged in separate boxes of the kit do not require refrigeration). DMEPA continues to have concerns about the two-vial package design of Egrifta that is required for one single dose, and the potential medication errors that could occur if the patient fails to reconstitute two vials of the product (e.g., wrong dose-under dose medication error). Additionally, the Egrifta kit includes two boxes (Medication box 1 of 2 and Injection kit box 2 of 2), DMEPA has concerns about the patient appropriately receiving all necessary elements of the kit during pharmacy dispensing, especially since the Egrifta Medication Box 1 of 2 requires refrigeration.

Additionally, if the Applicant's planned distribution does not include hospital pharmacies, and a patient is admitted to the hospital on an Egrifta regimen, DMEPA is concerned about the provision of all the necessary elements of the Egrifta kit to the patient for administration as well as the proper refrigerated storage of the Egrifta vials when not being used by the patient.

### 4.2 STRENGTH PRESENTATION ON CONTAINER LABELS AND INSERT LABELING

On July 15, 2009, the Division of Metabolism and Endocrinology Products (DMEP) convened the internal filing meeting for new drug application (NDA 22-505) for Egrifta (Tesamorelin Acetate) for injection. The Division identified several review issues and requests for information, that were subsequently communicated to the Applicant in the August 10, 2009 filing communication, including issues also identified by DMEPA. The Chemistry, Manufacturing and Controls discipline stated: "*the proposed labeling states '1.1 mg' as the dosage strength to include the overfill amount of 0.1 mg. The proposed dosage strength is not acceptable because it should not include the overfill amount. Revise the dosage strength to state '1 mg. In addition, clarify whether the dosage strength denotes the free base or the salt form of the peptide because the established name of the product should correlate with the dosage strength (i.e., 1 mg Tesamorelin or 1 mg Tesamorelin Acetate)*".

DMEPA agrees that there is incongruence in the presentation of the strength on the container label and in the insert labeling (1.1 mg) compared to the actual product strength (1 mg) and this inconsistency is a potential source of confusion that could lead patients who are reconstituting and self-administering the drug. Additionally, the U.S. Pharmacopeia (USP) provides guidance on injection products stating "each container of an injection is filled with a volume in slight excess of the labeled 'size' or that volume that is to be withdrawn. The USP excess volumes recommended are usually sufficient to permit withdrawal and administration of the labeled volumes (e.g. for 1 mL labeled size, the recommended excess volume is: for mobile liquids 0.1 mL, and for viscous liquids it is 0.15 mL)"<sup>5</sup> DMEPA also believes, however, that the total

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<sup>5</sup> U.S. Pharmacopeia <1151> Pharmaceutical Dosage Forms, Injections.

volume (strength), including overage (1.1 mg) should be expressed in some manner on the container label of the vial and the carton labeling for the vials. Because CMC and DMEPA have expressed concerns with the presentation of the drug strength on labels and labeling, we believe that a consensus can be reached on the most appropriate presentation of this information, and our collective comments can be forwarded to the Applicant.

#### **4.3 EGRIFTA PACKAGING CONFIGURATION (1 MG PER VIAL)**

In DMEP's August 10, 2009 filing communication to the Application, the Division's Microbiology discipline requested that the Applicant "*provide a justification for why dosing is proposed with two vials containing 1 mg of product each rather than a single vial containing 2 mg of product.*" DMEPA agrees that the current packaging configuration creates the potential for wrong dose medication errors if the patient reconstitutes the wrong number of vials (too few or too many) resulting in underdosing or overdosing of the product. The reconstitution and administration of this product requires many steps and because this product is self-administered by the patient, it is important to provide both clarity as well as simplicity, wherever possible in the administration process. Additionally, the two-vial reconstitution process requires additional manipulation of the product vial and associated needles that also introduces the opportunities for contamination that could lead to patient infections.

#### **4.4 CONTAINER LABEL**

The proprietary and established name presentation is small on the Egrifta container label. DMEPA acknowledges the small size of the container label but notes that CFR 201.10(i) allows for the omission of certain information in cases where the drug is packaged in a container too small or otherwise unable to accommodate a label with sufficient space to bear this information.<sup>6</sup> If some of the non-required information were deleted from the container label, the extra space could allow for a significantly larger and prominent presentation of the proprietary name (Egrifta) and the established name (Tesamorelin Acetate).

#### **4.5 EGRIFTA MEDICATION BOX (BOX 1 OF 2) CARTON LABELING**

The current presentation of both the proprietary name (Egrifta) and the established name (Tesamorelin Acetate) are small in proportion to the total size of the carton labeling and the available space on labeling. It is important that patients using this product readily identify each element of the Egrifta kit in order to prepare the required materials for reconstitution and administration. A more prominent presentation of the product name will help facilitate the accurate identification of the product, Egrifta (Tesamorelin Acetate), during the administration process.

Additionally, the carton labeling for the Egrifta Medication Box (Box 1 of 2) contains the statement "Must be reconstituted before use". Given the current packaging configuration for Egrifta requires that two vials be reconstituted to achieve the '2 mg' dose, DMEPA recommends added language that informs the patient to use two vials per administration. This added language may help inform the patient during the reconstitution phase of the drug administration, and serve to avert medication errors involving wrong dose (wrong number of vials used to reconstitute the vial).

DMEPA notes that while product storage for Egrifta requires that non-reconstituted vials be refrigerated at 2°C to 8°C (36°F to 46°F) and this information appears on the side panel of carton

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<sup>6</sup> Code of Federal Regulation Title 21, Volume 4, Revised April 1, 2009 21CFR201.1

labeling; the information does not clearly direct the patient to ‘refrigerate unused vials until use’. It is important that the patient clearly understand the correct storage procedure for the product to assure that product stability is maintained for safe and effective use. DMEPA acknowledges that this information is included in the insert labeling Patient Counseling Information, however, it is important that patients be alerted to refrigerate the product when they initially receive the product.

## **4.6 EGRIFTA INJECTION KIT BOX (BOX 2 OF 2) CARTON LABELING**

### ***4.6.1 Labeling of Items in Egrifta Injection Kit (Box 2 of 2)***

The Egrifta Injection Kit Box (Box 2 of 2) displays carton labeling on the outside of the box that itemizes each element included inside the box in a bulleted list manner. Included inside the large injection kit box is one box containing (30) thirty 3-cc syringes mounted with needles, one box containing thirty (30) individual 1 1/2” 18 gauge reconstitution needles, one box containing thirty (30) (b) (4) or 1/2” 27 gauge sterile injection needles, one sealed package of thirty (30) 10 mL bottles of sterile water, and the patient instructions (Patient Counseling Information). The labels on the outside of each box containing the elements for injection do not correspond verbatim to the way the items are listed on the Injection Kit box labeling. Because there are multiple elements included in the Egrifta kit that are required for the self-administration of the product, it is feasible that confusion may occur by the patient when gathering all the elements to administer the product (i.e. which needle to use to reconstitute versus which needle to use for injecting the product subcutaneously). DMEPA believes that the labeling language on the outside of the box of each element included in the injection kit should correspond verbatim to the presentation of each element listed on the injection box kit carton labeling, along with a clear, corresponding identification of each item. For example, instead of listing the items included in the injection kit box using bullet points, use alpha letters (A through E) along with the current language used to describe each item. This could also be added to the outside of each individual box along with the verbatim language used to describe each item, so there is no ambiguity about the identification of each item by the patient.

### ***4.6.2 Labeling for 30 mL Sterile Water Vials***

DMEPA notes that while the (30) vials of Sterile Water for Injection, USP are intended for single-use only per daily Egrifta administration, no information is included on the outer labeling of the (30) packaged Sterile Water alerting the user to dispose of the unused portion. Because only 2.2 mL of Sterile Water is required to reconstitute a daily dose of Egrifta, patients may assume they can reuse the same vial until it is empty. Such reuse without proper sterilization of the vial stopper could be a source of contamination that could lead to patient infection. Additional warning information on the carton labeling for the (30) vials of Sterile water may help avert such misuse of the product. DMEPA notes that the Patient counseling information section of the insert labeling “What to Do with Used Injection Materials” makes reference to empty vials of Egrifta and Sterile Water, there are no instructions regarding disposing of the unused portion of the Sterile Water after each administration.

### ***4.6.3 Differentiation of Egrifta Product Vials from Sterile Water Vials***

We note that the proprietary and established names on the carton labeling of the injection kit appears very large and prominent, creating the potential for confusion that could lead to the assumption that the vials included in this box (Sterile Water) are actually the active drug product. DMEPA is concerned about the potential for confusion between the (30) Egrifta active ingredient vials and the (30) Sterile Water vials. Post-marketing experience of products that are packaged in

kits such as Egrifta that require dilution and/or reconstitution has shown that medications errors have occurred due to the inadvertent administration of the inactive ingredient rather than the actual drug product. DMEPA has historically provided recommendations aimed at maximizing the product name on the active ingredient while minimizing the product name on the diluents/reconstitution solutions. Decreasing the prominence of the proprietary and established names on the carton labeling of the injection box kit could help minimize the potential for such confusion.

#### ***4.6.4 Units of Measure on Egrifta Carton Labeling (cc versus mL)***

DMEPA also notes the use of the error-prone unit of measure abbreviation ‘cc’ on the injection box carton labeling for the injection syringes instead of ‘mL’. The abbreviation ‘mL’ is the widely recognized symbol for milliliters when used to indicate this unit of measure in dosing of products. Additionally, because the unit of measure abbreviation on the syringes included in the Egrifta injection kit is ‘mL’ all reference to this unit of measure should consistently correlate to avoid confusion in the patient’s interpretation of the correct dose that could subsequently lead to a medication error.

### **4.7 PACKAGE INSERT LABELING PATIENT COUNSELING INFORMATION**

In Section 4.5, the patient counseling information section under Step 6 “What to do with used injection materials” does not provide directives specific to the disposal of the unused portion of the Sterile Water vials after each administration. As discussed above, the reconstitution of Egrifta requires only 2.2 mL of Sterile water however, the vials are packaged in volume sizes of 10 milliliters designed for single-use administration. DMEPA is concerned that the patient will reuse the opened Sterile Water vials for multiple administrations, thereby introducing opportunities for contamination. The Division of Risk Management (DRISK) has been consulted to review the Medication Guide patient labeling for the Egrifta application. DMEPA staff met with DRISK staff on September 24, 2009 to review the Egrifta product labeling and sample Egrifta kit provided by the Applicant at which time we discussed the concern regarding the sterile water vials, along with other carton and container labeling concerns we had identified in this review. DMEPA defers to DRISK’s full review of the product labeling patient counseling information provided in the package insert labeling for comments and recommendations.

## **5 CONCLUSIONS AND RECOMMENDATIONS**

The Label and Labeling risk assessment noted several areas of needed improvement. These revisions can be made prior to approval.

### **5.1 COMMENTS TO THE DIVISION**

At the July 15, 2009 the internal filing meeting for new drug application (NDA 22-505) Egrifta (Tesamorelin Acetate, three of the issues identified were also identified during DMEPA’s labeling review. These issues include the alignment of the strength to the active salt in the active ingredient, the discordance in the presentation of the strength on container labels (1.1 mg) versus the product strength (1 mg) to include the 0.1 mg overfill amount, and the product packaging configuration of 1 mg per vial when the recommended dose is 2 mg, requiring that two vials be reconstituted for a single dose. These concerns were communicated to the sponsor in the Division’s August 10, 2009 Filing Communication letter.

DMEPA agrees with the Division’s recommendations regarding the presentation of the salt and the packaging configuration (1 mg vial versus 2 mg vial). However, with regards to the labeling of product strength to include the 0.1 mg overfill, we note that the Division of Metabolism and

Endocrinology Products recommended that the Applicant revise the container label product strength to '1 mg'. DMEPA agrees that the strength expression of 1 mg may minimize confusion for patients who will be reconstituting and administering the product, however, we also believe that a clarifying statement should also appear on the label indicating that an overfill exists, since the total drug quantity is 1.1 mg rather than 1 mg, (i.e. each vial contains 1.1 mg of Egrifta before reconstitution).

Additionally, DMEPA has also identified other vulnerabilities in labels and labeling and have provided recommendations to the Applicant in Section 5.2 that aim to minimize these issues and the potential for medication error occurrence.

The Division of Risk Management (DRISK) has been consulted (OSE #2009-1155) to review the Egrifta Medication Guide patient labeling. DMEPA defers comments and recommendations for revisions to the Patient Counseling Information to the DRISK team. Our concerns are listed in Section 5.3.

Additionally, we request that you convey our additional recommendations in Section 5.2 to the Applicant. We would be willing to meet with the Division for further discussion, if needed. Please copy us on any communication to the sponsor with regard to this review. If you have further questions or need clarifications, please contact Millie Wright, OSE Project Manager at 301-796-1027.

## **5.2 COMMENTS TO THE APPLICANT**

We have evaluated your proposed labels and labeling and request that you revise the following prior to approval:

### ***A. Product Design***

- 1) In accordance with the request from the Division of Metabolism and Endocrinology Products in the August 10, 2009 filing communication, provide justification for the product's packaging configuration of 1 mg per vial (total of 1.1 mg Tesamorelin Acetate) when the recommended dose is 2 mg. The current packaging configuration requires the reconstitution of two separate vials of product and introduces the opportunity for wrong dose and wrong strength medication errors during the reconstitution process by the patient, as well as introducing additional opportunities for contamination that may lead to infections. DMEPA believes that this product design has a high potential to contribute to medication errors in the real-world setting if patients fail to reconstitute TWO vials, leading to wrong dose (underdose) medication errors and subsequent lack of effect from the product.

### ***B. Container Label***

- 1) Additionally, as indicated by the Agency, clarify whether the dosage strength denotes the free base or the salt form of the peptide because the established name of the product should correlate with the dosage strength (i.e., 1 mg Tesamorelin or 1 mg Tesamorelin Acetate).
- 2) Increase the size of the proprietary name (Egrifta) and the established name (Tesamorelin Acetate) on the principal display panel of the container label. Per 21 CFR 201.10(i) pertaining to small labels, information can be removed from the principal display panel of the container label to allow for a more prominent presentation of the proprietary name and the established name.

### ***C. Carton Labeling for Egrifta Medication Box (Box 1 of 2)***

1. Increase the size of the proprietary name (Egrifta) and the established name (Tesamorelin Acetate) on the Medication Box (Box 1 of 2) carton labeling. It is important that patients using this product readily identify each element of the Egrifta kit in order to prepare the required materials for reconstitution and administration. A more prominent presentation of the product name will help facilitate the accurate identification of the product, Egrifta (Tesamorelin Acetate), during the administration process.

2. Revise the reconstitution statement to alert the patient that the reconstitution process requires the use of TWO VIALS of product to achieve a 2 mg dose. For example:

Must be reconstituted before administration using **TWO VIALS** of Egrifta to achieve the required **2 mg** dose.

3. Add a statement to the principal display panel of the Egrifta Medication Box 1 of 2 alerting the patient to refrigerate the medication box until use. We recommend:

Keep Egrifta Vials Refrigerated Until Reconstitution and Administration

### ***D. Carton Labeling for Egrifta Injection Kit (Box 2 of 2)***

1. Revise the Egrifta Injection Kit Box (Box 2 of 2) Carton labeling by itemizing the box contents in a format that corresponds to each item contained inside the box, including a large and prominent presentation of the identifiers (A through E) for easy identification. For example:

- A. Thirty (30) sterile 3 mL syringes mounted with individual reconstitution needles
- B. Thirty (30) individual 1 1/2" 18 gauge sterile reconstitution needles
- C. Thirty (30) individual [REDACTED]<sup>(b) (4)</sup> or 1/2" 27 gauge sterile injection needles
- D. Thirty (30) 10 mL bottles of sterile water for Injection, USP
- E. Patient Instructions

2. Revise the labeling language displayed on each of the boxes included inside the Egrifta Injection Kit (Box 2 of 2) to correspond, verbatim, to the list (above) on the carton labeling, including a large and prominent presentation of the identifiers (A through E) for easy identification:

- A. Thirty (30) sterile 3-cc syringes mounted with individual reconstitution needles
- B. Thirty (30) individual 1 1/2" 18 gauge sterile reconstitution needles
- C. Thirty (30) individual [REDACTED]<sup>(b) (4)</sup> or 1/2" 27 gauge sterile injection needles
- D. Thirty (30) 10 mL bottles of sterile water for Injection, USP
- E. Patient Instructions

3. Revise the unit of measure presented as 'cc' for the thirty (30) syringes on the labeling of the injection kit box 2 of 2 to the unit of measure 'mL'. The 'mL' presentation corresponds to the unit of measure that appears on each syringe as well as the presentation in the product insert labeling. The unit of measure presentation should align consistently throughout Egrifta labeling to provide clarity to the patient during reconstitution and administration of the product and minimize confusion that could lead to wrong dose medication errors.

4. Add a statement to the outer package labeling of the thirty (30) vials of Sterile Water, USP alerting the patient that each vial is for single-use administration only. Because each Egrifta dose requires only 2.2 mL of Sterile Water, and the Sterile Water vial volume is 10 mL, patients may assume they can reuse vials for future doses. DMEPA is concerned that reuse of vials could introduce opportunities for contamination of the Sterile water that could lead to patient infections. Adding a warning statement to the labeling of the Sterile Water Packaging will alert the patient before use. We recommend a statement such as:

“For Single-Use Only – Dispose of Unused Portion After each Administration”.

5. Decrease the size of the proprietary name (Egrifta) and the established name (Tesamorelin Acetate) on the Egrifta Injection Kit Box 2 of 2 labeling. Post-marketing experience of products that are packaged in kits such as Egrifta that require dilution and/or reconstitution has shown that medication errors have occurred due to the inadvertent administration of the inactive ingredient rather than the actual drug product. The proprietary and established names on the carton labeling of the injection kit appears very large and prominent, creating the potential for confusion that could lead to the assumption that the vials included in this box (Sterile Water) are actually the active drug product. Decreasing the prominence of the proprietary and established names on the carton labeling of the injection box kit could help minimize the potential for such confusion. We recommend increasing the size of the words “Injection Kit Box 2 of 2” while decreasing the size of the proprietary name (Egrifta) and established name (Tesamorelin Acetate) so that the words “Injection Kit Box (Box 2 of 2) are larger and appear more prominent.

### ***E. Package Insert Labeling***

As indicated previously by the Agency, clarify whether the dosage strength denotes the free base or the salt form of the peptide because the established name of the product should correlate with the dosage strength (i.e., 1 mg Tesamorelin or 1 mg Tesamorelin Acetate).

### ***F. Egrifta Packaging and Distribution***

Provide a description of your intended plan for distribution of the Egrifta product kit, with regard to whether distribution will include retail pharmacies, hospital pharmacies and mail-order pharmacies. Because the Egrifta kit includes two boxes (Medication box 1 of 2 and Injection kit box 2 of 2), we are concerned about the patient appropriately receiving all necessary elements of the kit during pharmacy dispensing, since the Egrifta Medication Box 1 of 2 requires refrigeration.

Additionally, if your planned distribution does not include hospital pharmacies, and a patient is admitted to the hospital on an Egrifta regimen, how will the necessary elements of the Egrifta kit be provided to the hospitalized patient for administration as well as the proper refrigerated storage of the Egrifta vials when not being used by the patient.

### 5.3 PACKAGE INSERT LABELING COMMENTS PROPOSED TO DRISK

The Division of Risk Management (DRISK) will be performing an evaluation of Egrifita product labeling, Risk Evaluation and Mitigation Strategies (REMS) and Medication Guide included with this product in a separate OSE review (OSE #2009-1555). DMEPA identified the following issues below that we will communicate to DRISK for consideration in their review:

1. Revise Section 17 Patient Counseling Information's 'How to Mix Egrifita' Step 9 that reads (b) (4) by restating Steps 3, 4 and 5. DMEPA believes that given the multi-step processes involved in the preparation, reconstitution and administration of this product by a lay person (non-healthcare professional), it is important that the step-by-step process is spelled out with abbreviated steps such as (b) (4) to avoid confusion by the user that may lead to medication errors in the preparation process (i.e. withdrawal of the wrong volume). The Step 9 instruction (repeating Steps 3 to 5) may be more thoroughly explained if each step is provided again in an with the same instructional text used in Steps 3 to 5.

2. Add a statement in the Patient Counseling Information section (b) (4)

(b) (4)

3. We note that the current draft of the Patient Instructions Step-By-Step Guide contains a picture of each element included in the Egrifita kit. This illustration shows a (b) (4)

(b) (4). We are concerned that because reconstitution of the recommended 2 mg dose of Egrifita requires two vials, that the illustration showing (b) (4) may be misleading or confusing to patients. We recommend that the illustration display two Egrifita vials in this presentation.

## 6 REFERENCES

### 1. *Reviews*

*OSE Review #2009-1162 Proprietary Name Review for Egrifita (Tesamorelin Acetate) Injection, Miller, C.; August 13, 2009.*

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22505	ORIG-1	THERATECHNOLOGIES INC	Egrifta

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/s/

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CATHY A MILLER  
03/01/2010

KELLIE A TAYLOR  
03/02/2010

DENISE P TOYER  
03/05/2010

CAROL A HOLQUIST  
03/05/2010

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**CLINICAL INSPECTION SUMMARY**

DATE: January 11, 2010

TO: Jennifer Johnson, Regulatory Project Manager  
Robert Perlstein, M.D., Medical Officer  
Division of Metabolic and Endocrine Products (DMEP)

FROM: Susan Leibenhaut, M.D.  
Good Clinical Practice Branch II  
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.  
Branch Chief  
Good Clinical Practice Branch II  
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: #22-505

APPLICANT: Theratechnologies Inc.

DRUG: Egrifta (tesamorelin acetate) for Injection

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard

INDICATION: To induce and maintain a reduction of excess abdominal visceral adipose tissue (VAT) in HIV-infected AIDS patients with HIV-associated adipose redistribution syndrome (HARS)

CONSULTATION REQUEST DATE: July 23, 2009

DIVISION ACTION GOAL DATE: March 29, 2010  
PDUFA DATE: March 29, 2010

**I. BACKGROUND:**

Theratechnologies Inc. submitted NDA 22-505 for Egrifta (tesamorelin acetate) for Injection for the indication of reduction of excess abdominal visceral adipose tissue (VAT) in HIV-infected AIDS patients with HIV associated adipose redistribution syndrome (HARS). This was a routine audit request to assess data integrity and human subject protection for clinical trials submitted in support of this application. The efficacy results of the studies are important in making a regulatory decision with regard to drug approval. Selection of sites was based on numbers of subjects enrolled at the site. Perceptive Informatics was inspected because this CRO performed the readings of primary endpoint data concerning CT scan results. Quintile was inspected because this CRO monitored the clinical trials for this new molecular entity.

The protocols inspected included:

- A. Protocol TH9507/III/LIPO/010 entitled “A Phase 3, Multicenter, Double-blind, Randomized, Placebo - Controlled Study Assessing the Efficacy and Safety of a 2 mg Dose of TH9507, a Growth Hormone Releasing Factor Analog, in HIV Patients with Excess of Abdominal Fat Accumulation” and
- B. Protocol TH9507-CTR-1011 entitled “A Multicenter, Double-blind, Randomized, Placebo - Controlled Study Assessing the Efficacy and Safety of a 2 mg Dose of TH9507, a Growth Hormone Releasing Factor Analog, in HIV Patients with Excess of Abdominal Fat Accumulation”

**II. RESULTS (by Site):**

<b>Name of Clinical Investigator (CI) or Contract Research Organization (CRO) and Location</b>	<b>Protocol #/ # of Subjects Randomized</b>	<b>Inspection Dates</b>	<b>Final Classification</b>
CI Daniel S. Berger, M.D. Northstar Medical Center 2835 N. Sheffield Avenue, Suite 500 Chicago, IL 60657	TH9507/III/LIPO/010/ 38 subjects  TH9507-CTR-1011/ 43 subjects	October 21 to November 24, 2009 (not consecutive)	Pending (Preliminary classification VAI)
CI Michael S. Somero, M.D. 1401 N. Palm Canyon Drive Suite 100 Palm Springs, CA 92262	TH9507/III/LIPO/010/ 41 subjects  TH9507-CTR-1011/ 37 subjects	November 2 to 10, 2009	Pending (Preliminary classification NAI)
CRO Quintiles Canada Inc. 100 Alexis Nihon, Saint-Laurent, Canada H4M 2P4	TH9507/III/LIPO/010/ 79 subjects  TH9507-CTR-1011/ 80 subjects	November 16 to 18, 2009	Pending (Preliminary classification NAI)
CRO Perceptive Informatics 2 Federal Street, Billerica, MA 01821	TH9507/III/LIPO/010/ 79 subjects  TH9507-CTR-1011/ 80 subjects	November 3 to 10, 2009	NAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations.

1. Daniel S. Berger, M.D.  
Northstar Medical Center  
2835 N. Sheffield Avenue, Suite 500, Chicago, IL 60657

**Note:** Observations noted for this site are based on communications with the FDA investigator, and review of the Form FDA 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the Establishment Inspection Report (EIR).

- a. **What was inspected:** For Protocol TH9507/III/LIPO/010, a total of 38 subjects were randomized. A complete audit was conducted of 10 subjects' records and 13 subjects' records were audited for eligibility. For Protocol TH9507-CTR-1011, a total of 62 subjects were screened, 41 subjects were randomized, and 27 subjects completed the study. A total of 32 subjects' records were audited.

- b. **General observations/commentary:** There was no under-reporting of adverse events for either protocol. As per protocol, the primary endpoint was verified by inspection of the Perceptive Informatics site as noted below. The inspection was classified as a VAI for regulatory deficiencies concerning test article accountability, failing to adhere to conduct the investigation in accordance with the investigational plan, and failing to maintain adequate and accurate case histories.
1. For Protocol TH9507/III/LIPO/010 the following violations were noted:
    - a. The source documents did not contain the protocol-specified subject diaries used to record daily medication dosing for Subject 42009 (active) and Subject 42031 (placebo). Subject 42009 is listed as having first dose on March 10, 2006 and last dose on May 23, 2006 and withdrawing for an adverse event. Subject 42031 is listed as having first dose on April 13, 2006 and last dose on May 18, 2006 and withdrawing because of an administrative problem.
    - b. The diary for Subject 42012 (placebo-active) indicated that study drug was taken until 7/23/06, CRF indicates study drug was taken until 9/23/06, and line listing in the NDA indicates study drug taken until 10/24/06.
    - c. Subject 42045 (active) has a diary indicating that study drug was taken until 7/23/06, but study documents indicate that subject withdrew on 6/4/06. This withdrawal is reflected in the line listing.
    - d. Concerning eligibility, Subject 42002 (active-placebo) had CD4, CD8, and viral load testing prior to the eight week window allowed for testing, and Subject 42013 (placebo-active) had a change in his testosterone regimen within six months prior to randomization, which were exclusion criteria.
    - e. Quality of life questionnaires were not found for the following subjects:
      1. Subject 42013 (placebo-active) for Visits 1 and 2.
      2. Subject 42038 (active-active) for Visit 6.
  2. For Protocol TH9507-CTR-1011 the following violations were noted:
    - a. Concerning eligibility, Subject 0023 (active) was diabetic on Avandia at the time of screening and randomization, and male Subjects 0038, 0137 and 0138 had waist measurements that were 94 cm instead of the protocol required  $\geq 95$ cm.
- c. **Assessment of data integrity:** At this site, there were violations concerning inaccurate documentation of subject exposure to study drug. The review division may consider an information request to the sponsor concerning this issue and consider removing these subjects in performing a reanalysis of the data. Given that these inspectional findings do not appear to represent a systemic finding, the study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

2. Michael S. Somero, M.D.  
1401 N. Palm Canyon Drive, Suite 100  
Palm Springs, CA 92262

**Note:** Observations noted for this site are based on communications with the FDA investigator, and review of the Form FDA 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

- a. **What was inspected:** For Protocol TH9507/III/LIPO/010, 54 subjects were screened and 28 subjects completed the study. For each study, fifteen subjects' records were reviewed.
- b. **General observations/commentary:** There was no under reporting of adverse events. Primary endpoint data could not be verified at the site, as per protocol, the primary endpoint was verified by inspection of the Perceptive Informatics site as noted below.
- c. **Assessment of data integrity:** No significant issues have been identified based on preliminary communication with the field investigator, and the study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

3. Quintiles Canada Inc.  
100 Alexis Nihon, Saint-Laurent, Canada H4M 2P4

**Note:** Observations noted for this site are based on communications with the FDA investigator, and review of the Form FDA 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

- a. **What was inspected:** The inspection audited monitoring activities of the CRO for both sites for Protocol #TH9507/III/LIPO/010 and Protocol #TH9507-CTR-1011.
- b. **General observations/commentary:** Preliminary communications with the field investigator revealed that the monitoring was adequate for the clinical trials.
- c. **Assessment of data integrity:** The study appears to have been monitored adequately, and the data submitted by the sponsor may be used in support of the respective indication.

4. Perceptive Informatics  
2 Federal Street, Billerica, MA 01821

- a. **What was inspected:** The inspection audited all of the 79 records from both sites for Protocol #TH9507/III/LIPO/010 and all of the 80 records from both sites for Protocol

#TH9507-CTR-1011. A comparison between the source data for each of the protocols with the efficacy data listings submitted in the NDA found no discrepancies.

- b. **General observations/commentary:** A comparison between the source data for each of the protocols with the data listings submitted in the NDA found no discrepancies. The primary endpoint data were verifiable.
- c. **Assessment of data integrity:** The studies appear to have been conducted adequately, and the data submitted by the sponsor may be used in support of the respective indication.

### III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two clinical investigator sites and two CROs were inspected in support of this NDA. There was no under-reporting of adverse events and the primary endpoint was verified by inspection of Perceptive Informatics. As discussed above, audit of the Berger site noted the violations as discussed above including violations concerning inaccurate documentation of subject exposure to study drug for a few subjects. The review division may consider an information request to the sponsor concerning this issue and consider removing these subjects in performing a reanalysis of the data. Other violations of the protocol do not appear to effect data integrity.

Although some regulatory violations were noted as per above, these are considered isolated occurrences and are unlikely to importantly impact data integrity. The data are considered reliable in support of the NDA.

**Note:** The final classifications for the inspections of Drs. Berger and Somero and of Quintiles are pending. An addendum to this clinical inspection summary will be forwarded to the review division if additional observations of clinical and regulatory significance are discovered after reviewing the EIRs for these inspections.

*{See appended electronic signature page}*

Susan Leibenhaut, M. D.  
Good Clinical Practice Branch II  
Division of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

Tejashri Purohit-Sheth, M.D.  
Branch Chief  
Good Clinical Practice Branch II  
Division of Scientific Investigations

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22505	ORIG-1	THERATECHNOLOGIES INC	Egrifta

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/s/

SUSAN LEIBENHAUT  
01/12/2010

TEJASHRI S PUROHIT-SHETH  
01/12/2010

## STUDY ENDPOINT REVIEW

SEALD ACTION TRACK NUMBER	2009.002.A.00067
APPLICATION NUMBER	NDA 22-505
LETTER DATE/SUBMISSION NUMBER	5-29-2009
DATE OF CONSULT REQUEST	8-13-2009
DUE DATE	9-29-2009
PDUFA DATE	3-29-2010
REVIEW DIVISION	DMEP
MEDICAL REVIEWER	Rob Perlstein
REVIEW DIVISION PM	Jennifer Johnson
SEALD REVIEWER	Elektra J. Papadopoulos
REVIEW COMPLETION DATE	1-07-2010
PRODUCT NAME APPLICANT	Egrifta (tesamorelin acetate) for injection Theratechnologies Inc.
ENDPOINT(S) CONCEPT(S)	“Belly distress” (BAD) and “Belly size” (BSE) in patients with HIV associated adipose redistribution syndrome
INSTRUMENT(S)	BAD and BSE of the Body Image Impact module (BIIM)
INDICATION	To induce and maintain a reduction of excess abdominal visceral adipose tissue (VAT) in HIV-infected AIDS patients with HIV- associated adipose redistribution syndrome (HARS)
INTENDED POPULATION	HIV-infected AIDS patients with HIV- associated adipose redistribution syndrome (HARS) <a href="\\CDSESUB1\EVSPROD\NDA022505\0000">\\CDSESUB1\EVSPROD\NDA022505\0000</a>

# STUDY ENDPOINT REVIEW

## 1 EXECUTIVE SUMMARY

This Study Endpoints and Label Development (SEALD) review is provided as a response to a request for consultation by the Division of Metabolic and Endocrine Products (DMEP) regarding the patient-reported endpoint measures used in NDA 22-505 to provide evidence of efficacy for the use of Egrifta to induce and maintain a reduction of excess abdominal visceral adipose tissue (VAT) in HIV-infected AIDS patients with HIV-associated adipose redistribution syndrome (HARS). The Body Image Impact module (BIIM) a patient-reported outcome (PRO) tool was used in the phase 3 studies. The PRO instrument “dossier” containing copyrighted, proprietary, and confidential information supporting this tool was submitted as a Type V Drug Master File (DMF) dated May 21, 2009 by (b) (4) for Agency review.

The following patient-reported outcome (PRO) endpoints are derived from the BIIM and are described within the sponsor’s proposed labeling: (a) Belly appearance distress (BAD); (b) (4)

This SEALD review concludes that these PRO endpoints have questionable content validity and the current version of the BIIM should not be recommended by FDA for future drug development. The main concern that arose from the review of these instruments is their ability to measure a clinically meaningful effect of treatment or (b) (4). Two items from the BIIM are targeted as key study endpoints for analysis, the (b) (4) and the BAD. (b) (4)

The “belly appearance distress” item (i.e., BAD) may be a valid measure of that concept, but the PRO dossier provided minimal results from qualitative research to address these concerns and support the content validity of the PRO tool. The PRO dossier did not address whether qualitative research was done to evaluate patient understanding of the final instrument (e.g., cognitive interviews). Thus, the information provided does not meet the standards for instrument development as recommended within the FDA PRO Guidance for Industry including evidence of saturation and evidence of patient understanding during the qualitative research process.

This review does not provide a final opinion about whether the submitted clinical trial evidence is adequate to support labeling, i.e., whether the evidence is convincing, clinically meaningful and meets the specified plan for control of Type 1 error. That decision requires clinical and statistical review of the primary data.

## STUDY ENDPOINT REVIEW

Comments on review of PRO endpoints with a focus on interpretation of the BAD data are as follows:

- The treatment effect on the BAD was very modest. The CDF curves showed minimal separation and most of the separation was seen in a subset of the total population. The study design was suboptimal in that the enrollment criteria did not pre-specify a minimum score on the BAD, a key secondary endpoint. As a result, it is possible that a subset of patients may have been enrolled at the milder end of the BAD spectrum making it harder to realize substantial improvement.
- A minimum responder definition for the BAD of a 25-point increase in transformed score (i.e., 2 scale units) was derived based upon calibration of the BAD to the patient-reported BPA responder interval in the clinical trial sample.
- This responder definition (i.e., BAD improvement of 2 scale units) should be applied to the CDF curves to aid in interpretation. Based upon the description provided for the BAD item, which contains 9 response options, any change *less than 2 scale units* (e.g., a 1 scale unit improvement from 0, or “Extremely upsetting and distressing” to 12.5, or “Very upsetting and distressing”) does *not* represent a meaningful responder definition (See section 3.7 below).

## 2 SPECIFIC QUESTIONS TO SEALD

This consult response addresses the following question posed by DMEP to SEALD:

As you requested at the pre-NDA meeting held on September 19, 2008, Ralph Turner's Phase V validation materials have apparently been included in the May 29, 2009 NDA submission. Are these validation materials sufficient for SEALD purposes?

**SEALD has not previously reviewed evidence of content validity of the Body Image Impact Module (BIIM) and we requested documentation of instrument development with the NDA submission. A PRO dossier for the BIIM was submitted in a DMF from the instrument developer, (b) (4)**

**The information provided in the DMF regarding the Body Image Impact Module does not appear sufficient to establish the content validity and other measurement properties of the PRO tool. The qualitative study (n=8) included semistructured interviews with eligible patients and was intended to document self-reported body dysmorphia experiences and perceptions among persons diagnosed with lipodystrophy/HARS.**

**On review of the brief study summary, we found that a limited number of patient interviews (7 male and 1 female) were described and that saturation of the qualitative research to support content validity was not demonstrated. The text of volume IV of the PRO instrument dossier, the qualitative portion, referred to appendices where qualitative summaries were to be located. However, these appendices were not located. The interview guide and qualitative research protocol were not provided. Patient-level data were not provided.**

## STUDY ENDPOINT REVIEW

How the PRO instrument was actually developed was not described and no evidence of cognitive interviewing to test the final version of the instrument was described in the submission. Therefore, we cannot conclude that the instrument adequately captures the most important concerns related to the concept of measurement and that patients understand the items similarly and in the way that is intended.

Although the entire instrument was administered in the studies, only single items of this instrument were designated as endpoints in the phase 3 studies. The two key PRO variables identified for study in the phase 3 program were: (1) belly appearance distress (BAD) and (2) self-reported belly size estimation (BSE). In addition, a belly profile assessment (BPA) was developed to be used as an anchor for BAD and BSE interpretation. It is important to recognize that the study objective of the qualitative study was to document self-reported body dysmorphia experiences and perceptions among persons diagnosed with lipodystrophy/HARS. The main focus for the study was not to document patient experiences and perceptions with belly size and/or distress, specifically.

The reference to “belly size estimation” does not describe the item content of the BSE. On reading the item, it asks the subject to compare his/her current belly size to his/her idea of a “healthy look.” It is questionable whether (a) subjects can rate their belly size in the absence of more specific criteria and (b) whether the term “healthy look” will be interpreted the same way across subjects and within the same subject over time.

According to the DMF submission,

[REDACTED] (b) (4)

We recommend omitting from labeling reference to the instrument name [REDACTED] (b) (4) because the name of this instrument is not helpful to prescribers reading the labeling. Instead, if the product is approved, we recommend that any results that are reported be described in terms of the measurement concept (e.g., “patient-reported belly appearance distress”).

We recommend omitting the term [REDACTED] (b) (4) from labeling, because the [REDACTED] (b) (4) of an instrument is context specific and never complete. Furthermore, the content [REDACTED] (b) (4) and other measurement properties of the PRO tool have not been established.

The patient-reported BPA was to be used as a non-key study endpoint to aid in the interpretation of the BAD and BSE and to identify a responder definition for the BAD and BSE. However, the protocol describes an analysis of means, so we are not sure how this should be used in the interpretation of PRO study results. Therefore, we recommend cumulative distribution function curves (CDFs) be generated for the continuous variables

## STUDY ENDPOINT REVIEW

reported in labeling, if approved. This allows for visualization of the full distribution of subjects' responses (improved, no change and worse). The responder definition can be applied to the CDF curves.

The PRO instrument administered to subjects in the phase 3 studies was not found within the case report forms. Information regarding translation and cultural adaptation of the PRO instrument for use in multinational studies was omitted from the original NDA submission as well as from the DMF. This information was provided subsequently in an amendment to the NDA. Upon review of these instruments, this reviewer noted they were a different version from what was shown in the PRO dossier. However, the difference was in formatting of the tool and was deemed a minor modification.

### 3 ENDPOINT REVIEW

#### Background:

Relevant meetings and correspondence between the FDA and sponsor over the course of IND 61,226 are as follows:

- A Type C meeting (30 March 2005) where the FDA provided the following advice/agreements.
  - The Agency agreed with the primary and secondary endpoints for the Phase 3 program and that an 8% reduction in VAT was appropriate.
  - A clinically meaningful improvement in body self image using a valid instrument would be an essential component of any NDA submission.
  - The sponsor should work with Ralph Turner of Phase V Technologies to identify or develop the PRO instrument.
  - An attempt should be made to correlate improvement of body self-image with enhanced compliance to HART therapy.
  - The two proposed Phase 3 clinical studies should be conducted sequentially and that multiple approaches for determining the Minimal Important Difference (MID) be incorporated, including identifying how much change in patient-reported self image is associated with a clinically meaningful reduction in VAT.
- Amendment SN0047 (25 January 2006): proposal for establishing the MID for the Body Image Impact module.
  - The Agency agreed to the Sponsor's proposal (letter date April 3, 2006).
  - The FDA advised that the patient's view of what was a meaningful improvement in body morphology/belly profile should be used as an anchor (together with the clinician value) for determining the MID for the Body Appearance Distress scale.

## STUDY ENDPOINT REVIEW

- The FDA also indicated that the treatment difference in the change in the Belly Appearance Distress scale after 26 weeks of treatment should be reported in the labeling.
- SPA (June 14, 2006; amendment SN0054): The Phase 3 CTR-1011 study was described.
  - The Agency agreed (August 1, 2006) with the primary and secondary endpoints and provided advice regarding the control of the Type I error.
  - Graphs of cumulative distribution functions were to be generated for all continuous variables.
- Meeting (December 18, 2007) The following rank order was agreed upon:
  - Study CTR-011: change from baseline to week 26 in 1) VAT; 2) triglycerides and belly appearance distress; and 3) total cholesterol/HDL cholesterol ratio.
  - Study LIPO-010: change from baseline to week 26 in 1) VAT; 2) belly appearance distress; 3) total cholesterol/HDL cholesterol ratio; 4) triglycerides.
- PreNDA meeting (September 19, 2008) for TH9507 (tesamorelin acetate) for
  - The Agency requested (May 1, 2009) inclusion of information related to the development and validation of the PRO instruments together with the individual items of the questionnaires/instruments in the Body Image Impact Module.
  - The inclusion of body image secondary endpoints in the labeling would be a review issue.

### 3.1 Instrument

Appended are copies of the PRO instruments (Body Size Scale, Body Image Distress Scale and Body Profile Scale, Belly) obtained from the BIIM PRO dossier submitted in the DMF.

Also appended are copies of the version of the instruments used in the phase 3 clinical studies.

#### Reviewer's Comments:

**The final instrument administered to the patients in the clinical trials was not found in the original NDA submission. This reviewer searched for the PRO instrument as a part of the clinical trial case report forms and the PRO instrument was not there. Copies of the final instrument were submitted in an NDA amendment. Examples of the actual instruments completed by subjects in the clinical studies were submitted in English, French and Spanish. This reviewer focused on the sections that were used in the phase 3 studies as primary or key secondary endpoints to support labeling claims. Upon review of these instruments, this reviewer noted they were a different version from what was shown in the**

## STUDY ENDPOINT REVIEW

**PRO dossier. However, the difference was in formatting of the tool and was deemed a minor modification.**

### 3.2 Claim Structure

The sought indication is as follows: EGRIFTA™ is indicated to induce and maintain a reduction of excess abdominal fat in HIV-infected patients with lipodystrophy.

Proposed labeling includes the following PRO-derived claims related to the concepts of Belly appearance distress (BAD), belly size estimation (BSE) and patient-reported belly profile assessment (BPA) as measured by the PRO instrument, the Body Image Impact Module (BIIM).

*Belly appearance distress, (b) (4) and belly profile assessment (the main PRO secondary endpoints) were measured using a (b) (4) PRO questionnaire, the (b) (4) Belly appearance distress and patient self-reported belly profile significantly improved in EGRIFTA™-treated patients compared to placebo at Week 26 of treatment in both STUDY 1 and STUDY 2. The difference in scores for belly size was not statistically significant between patients treated with EGRIFTA™ and placebo in both studies. Patients who received EGRIFTA™ over 52 weeks experienced sustained improvements in belly appearance distress as well as patient-reported belly profile. On the contrary, patients who discontinued treatment tended to lose improvements seen at Week 26 in these parameters. No statistically significant differences were observed in the change from baseline to Week 52 in belly size scores between the two groups of patients.*

**Comments: This reviewer does not recommend inclusion of the term (b) (4) in labeling because it is not possible to describe an instrument's (b) (4) outside of the context of use. Reference to the specific PRO instrument named (b) (4) is not helpful to prescribers and should be omitted from labeling.**

**The reference to (b) (4) does not describe the item content. The item content is more accurately described as the patient's perception of his/her current belly size in comparison to their idea of a "healthy look." This variable did not demonstrate improvement in the phase 3 studies. As noted in a previous SEALD review by Dr. Paivi Miskala, it is questionable whether (a) subjects can rate their belly size in the absence of more specific criteria and (b) whether the term "healthy look" will be interpreted the same way across subjects and within the same subject over time. It is also possible that while there may have been some decrease in VAT as measured by CAT scan, the degree of this change may not have approached the patient's concept of what looks healthy.**

## 3.3 Endpoint Model

The study endpoints for Study CTR 1011 (October 2007 amendment) were described as follows.

### 3.2. Study Endpoints

#### 3.2.1. Primary efficacy study endpoint

The primary efficacy endpoint is the percent change from baseline to week 26 in VAT.

#### 3.2.2. Secondary efficacy study endpoints

The secondary efficacy endpoints are defined below:

1. Change from baseline to week 26 in total cholesterol/HDL-cholesterol ratio;
2. Change from baseline to week 26 in triglycerides;
3. Change from baseline to week 26 in IGF-1 levels;
4. Change from baseline to week 26 in patient reported outcomes related to Body Image (belly profile, belly size evaluation and belly size distress scales).

**Reviewer's comment:** This does not adequately describe the hierarchy of the three PRO endpoints with respect to each other, because all three PRO endpoints (belly profile, belly size in comparison to "healthy" look and belly size distress) are listed together under item 4. Further, criteria for response are not specified within the clinical protocol. See the background section of this review for a description of the agreed-upon rank order of the secondary endpoints.

## 3.4 Conceptual Framework

(b) (4)

## STUDY ENDPOINT REVIEW

(b) (4)

**Reviewer's comment: The PRO dossier did not describe how the BAD scores were to be transformed. This information was found within the sponsor's submission and is shown in Section 3.7 of this report as well as in the Appendix.**

**A user manual for the instrument was not submitted.**

### 3.5 Content Validity

The key PRO study endpoints were measures of some aspect of the subject's belly:

- (a) Belly size (BSE): Patient perceptions of their current belly size in comparison to their idea of a "healthy" look; and
- (b) Belly appearance distress (BAD): Patient-reported distress concerning the appearance of their belly.

In addition to the PROs described above, there was also a patient-rated belly profile (patient-rated BPA) in which the patient was to choose among six belly profiles, the one that they feel most accurately depicts their actual profile.

**Reviewer's comment: Sources of variability that might affect the assessment of the patient-rated BPA include the subject's posture, the type of clothing worn and whether or not the subject had just eaten a large meal. Such factors were not addressed by the PRO instrument.**

Volume IV of the PRO dossier contains a description of the qualitative research to support the instrument. According to this brief report, sources of information used in instrument development included:

- Expert input elicited from HIV/AIDS specialists;
- Results of a focus group conducted by an outside group (Adult AIDS Clinical Trials Group) concerning body image disturbance among patients receiving combination antiretroviral therapy; and
- HIV/AIDS medical forums available on the web.

Volume IV of the PRO dossier presents a very brief summary of a qualitative report of a series of semi-structured interviews conducted with HIV/AIDS patients diagnosed with lipodystrophy/HARS.

The stated objective of this study was to document self-reported body dysmorphia experiences and perceptions among persons diagnosed with HIV/AIDS.

**Reviewer's comment: The objective of the study was a broad assessment of self-reported body dysmorphia. The main focus for the study was not to document patient experiences and perceptions with "belly size."**

## STUDY ENDPOINT REVIEW

### Eligibility:

Main eligibility criteria were as follows.

- Age 18 years or older
- Laboratory confirmation of HIV infection
- Lipodystrophy with lipohypertrophy
- Evidence of excess abdominal adipose tissue such that  
Men waist circumference > 88.2 cm and waist:hip ratio  $\geq 0.95$   
Women waist circumference > 75.3 cm and waist:hip  $\geq 0.9$

### Results:

Eight subjects (7 men, 1 woman) were interviewed. The mean age was 45 years old (range 39 to 60 years old). Subjects varied with regard to duration of lipodystrophy from 1 year to 18 years, with a mean duration of 6.5 years.

Participants were asked to describe their current look. The responses were summarized in a table as follows.

**Table 1 Qualitative Interviews: “Describe Current Look”**

Category	Number of Responses (%)
Large Belly	7 (88)
Buffalo Hump	3 (38)
Buttocks	2 (25)
Chest	2 (25)
Face	3 (38)

The report provided examples of quotes from participants as follows.

“stomach is really big”

“no neck, fat all the way down”

“buttocks disappeared”

“breasts make me look like a full figure girl”

“face is pretty bad, sunken cheeks”

**Reviewer’s comment: The qualitative report does not include patient-level data, only summary tables. The sample interviewed is very limited and included only one woman out of 8 participants. This reviewer agrees that “large belly” did appear to be the predominant complaint from the summaries. However, the belly was noted in only 4 patients as being “most bothersome” according to the table below.**

**According to the qualitative report, several subjects reported that patients were bothered by the belly in combination with loss of tissue (lipoatrophy) in other areas.**

## STUDY ENDPOINT REVIEW

**Table 2 Qualitative Interviews: “Most Bothersome”**

Category	Number of Responses (%)
Belly	4 (50)
Buttocks	2 (25)
Buffalo Hump	2 (25)
Face	1 (13)
Thin Arms, Legs	1 (13)
Discomfort	1 (13)

The report provided examples of quotes from participants as follows.

“Pants look like hell on me from behind”

“Have to wear a goatee to make it look like I have a chin”

“I look fat”

**Reviewer’s comment: Again, the results of the patient interviews are extremely limited. There is not sufficient evidence for saturation on the basis of these interviews. Only one woman was interviewed. The concept of body image is often viewed differently between men and women and it is important to include an adequate sample of both men and women.**

### **3.6 Other Measurement Properties (reliability, construct validity)**

The instrument’s reliability was assessed in a sample of male and female HIV+ subjects participating in a clinical study of r-hGH treatment for lipodystrophy. A total of 327 subjects were screened and 238 were randomized in this study. A total of 87% of the subjects were male and the mean age was 44 years.

The internal consistency reliability data for the summary scales that were presented in the PRO dossier had limited relevance relevant for this particular application, because single items (not summary scales) from the multi-item BIIM tool were utilized as endpoints in the phase 3 studies.

The PRO dossier states that the test-retest reliability for the BIIM Body Size Scale ranged from 0.602 (arm size) to 0.784 (hump size). The test-retest reliability for the BAD showed a reproducibility coefficient of 0.616. The retest interval was assessed within 14 days (between screening and randomization) with a mean retest interval of 10.5 days.

**Reviewer’s comment: According to the PRO dossier, the “reproducibility sample comprised 182 subjects whose demographic characteristics did not differ from the whole sample.” There were 327 patients screened and 238 randomized. It is unclear why the reliability sample was measured in a subset of 182 out of 238 randomized subjects.**

## STUDY ENDPOINT REVIEW

Correlation of the PRO endpoints with the objective measure of VAT based upon CAT scan measurements was also requested of the sponsor based upon the data from the current NDA submission.

From the NDA amendment dated December 7, 2009 (serial 13), for Study LIPO-010, the correlation between the percent change in VAT and the raw change in patient-assessed BPA for the active group resulted in a correlation coefficient, “r” of 0.33.

The correlation between the raw absolute change in BAD and change in VAT for the active treatment group was resulted in an “r” of 0.26.

The correlation between absolute change in BSE and change in VAT for the active treatment group resulted in an “r” of 0.15.

### 3.7 Interpretation of Scores

The patient-rated belly profile (BPA) (Appendix 3) was used as a non-key study endpoint as an anchor in the development of a responder definition for the key secondary study endpoints, the BAD and the BSE.

In the patient-rated BPA, the patients choose among six images of belly profiles, the one that they feel most accurately depicts themselves.

Using the patient-rated BPA, the selection of the responder interval for patients was a 2.3 unit improvement or more based on a sample mean difference between “current look” minus “smallest benefit” at baseline. The responder criteria for BAD and BSE round off to 2 scale units (i.e., 25 points for BAD and 50 points for BSE).

The method for defining the responder criteria as stated in the December 21, 2009 NDA amendment is as follows:

*Method:*

(b) (4)

## STUDY ENDPOINT REVIEW

(b) (4)

**Reviewer's comment:** As stated elsewhere in this review, to demonstrate treatment benefit, we find it informative to examine the cumulative distribution function (CDF) of responses between treatment groups to characterize the treatment effect. The responder definition agreed upon with the Agency (i.e., 25 points for BAD and 50 points for BSE on a 0-100 scale) should be applied to the appropriate CDF curve.

A responder analysis review document prepared by Dr. Marcia Testa of Phase V Technologies inc. was submitted for Agency review in an NDA amendment dated December 21, 2009 (serial 15). A portion of this document describes data on patient responses on the basis of the patient-reported BPA. As stated above, the consensus of patients on the average was 2.3 units of improvement on the patient-rated BPA (which rounds to 3 whole units).

The author notes that all individuals who were at the milder end of the scale of the patient-reported BPA (e.g., D, E or F profiles) at baseline are not able to improve by 3 BPA units, since their disease state at baseline did not allow for this degree of change. Although this is a valid observation, it is important to remember that the purpose of the patient-rated BPA was as an anchor for interpretation of the BAD and BSE endpoints. The patient-rated BPA itself was not a key study endpoint for regulatory purposes.

## STUDY ENDPOINT REVIEW

(b) (4)

**Reviewer's comment: Based upon the descriptions provided above, any change less than 2 scale units (i.e., 1 scale unit from 0, or "Extremely upsetting and distressing" to 12.5, or "Very upsetting and distressing) does not appear to represent a meaningful responder definition for the BAD.**

### 3.8 Language Translation and Cultural Adaptation

The PRO evidence dossier did not contain information regarding translation and cultural adaptation of the PRO instrument for use in multinational studies. Translated PRO instruments (French and Spanish) and translation certificates were requested by the Agency and subsequently provided in an amendment to the NDA received on December 5, 2009.

**Reviewer's comment: Although documentation of translation and cultural adaptation was omitted from the PRO dossier, the evidence for translation was subsequently obtained in an amendment to the NDA and it appears adequate for regulatory purposes.**

### 3.9 Phase 3 Study Design

Study CTR-1011 and the Main Phase (first 26 weeks) of Study LIPO-010 were similarly designed. Both studies were multicenter, randomized, parallel, double-blind, placebo-controlled studies to evaluate the efficacy and safety of tesamorelin (2 mg/day) in HIV subjects with excess abdominal fat. Tesamorelin (or placebo) was administered once daily by subcutaneous injection. Subjects were randomized in a 2:1 (active:placebo) ratio to receive either tesamorelin or placebo daily for up to 26 weeks.

#### Study CTR-1011

The study is a phase 3 multicenter, randomized, double-blind, placebo-controlled study to assess the safety and efficacy of a 2 mg dose of TH9507 in HIV subjects with excess abdominal fat accumulation. The study was a multicenter and took place in 46 sites (25 United-States, 8 Canada, 1 Belgium, 4 France, 3 Spain, and 5 United Kingdom). Patients were screened for study eligibility and randomized in a 2:1 (active: placebo) ratio to receive either tesamorelin or placebo daily for up to 26 weeks.

## STUDY ENDPOINT REVIEW

### Study Endpoints:

Primary: Percent change from baseline to week 26 in VAT.

Secondary:

- (1) Change from baseline (CFB) to week 26 in total cholesterol/HDL ratio
- (2) CFB to week 26 in IGF-1 TGs
- (3) CFB to week 26 in IGF-1 levels
- (4) CFB to week 26 in PROs related to Body Image (belly profile, belly size evaluation, and belly size distress scales).

### Key Eligibility:

- Patients ages 18-65 years (inclusive)
- HIV positive with CD4 count > 100 cells/cubic mm and viral load < 10,000 copies per mL.
- On stable ART regimen for 8 weeks prior to randomization
- Evidence of excess abdominal fat accumulation defined by the following and considered to be part of HIV-associated lipodystrophy syndrome in context of treatment:
  - Males: waist circumference at least 95cm and waist/hip ratio at least 0.94.
  - Females: waist circumference at least 94 cm and waist/hip ratio at least 0.88.

**Reviewer's comments: The enrollment criteria for study CTR-1011 did not pre-specify a minimum score on the BAD, the key secondary PRO endpoint. As a result, it is possible that a subset of patient may have been enrolled at the milder end of the BAD spectrum making it harder to realize substantial improvement.**

Randomization: Patients were to be randomized according to strata for study site and cut-off for fasting blood sugar value greater than 6 mmol/L (108 mg/dL) at screening.

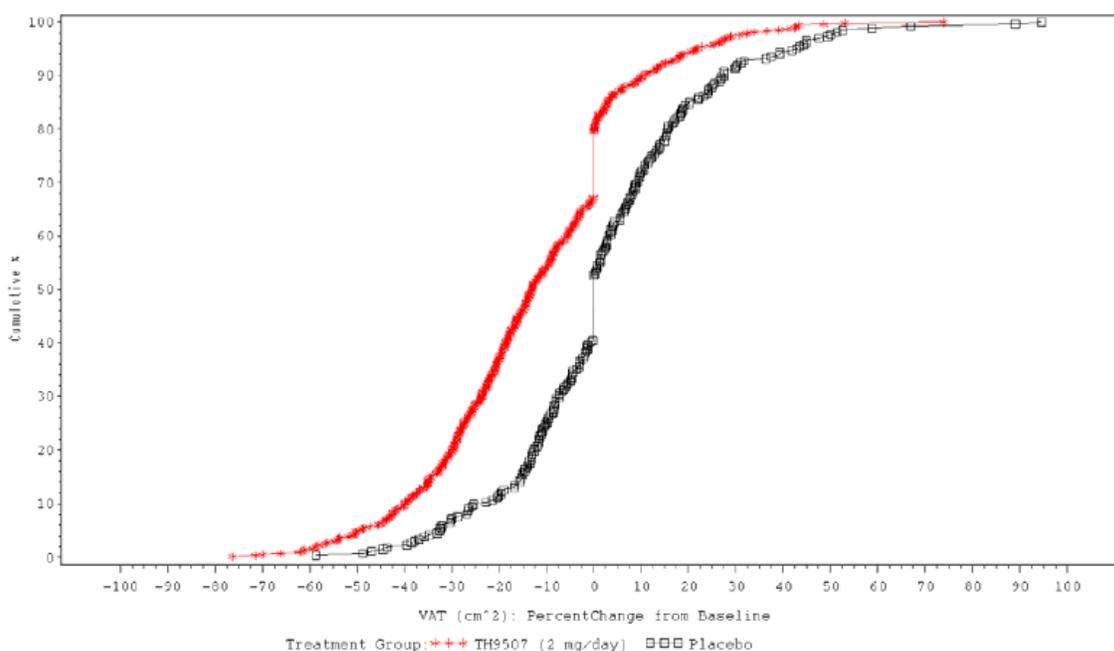
Statistical considerations: A gatekeeper strategy was to be used to control for multiple endpoints (any key secondary endpoints were considered for statistical significance only if the primary endpoint was found to be statistically significant).

Study Assessments: The PROs were to be administered at screening, baseline and at study days 92 and 183.

### 3.10 Efficacy Results

From the Integrated Summary of Efficacy of the sponsor’s submission, the cumulative distribution function of the percent change in VAT from baseline to Week 26 demonstrated that a higher proportion of subjects in the tesamorelin group than in the placebo group showed a decrease in VAT over the 26-Week treatment period (Figure 1).

**Figure 1: Cumulative Distribution Function of the Percent Change in VAT by Treatment Group at Week 26 in the Main Phase - ITT Population**



The curve to the left (red font) represents the Tesamorelin treatment group and the curve to the right (black font) represents the placebo group. Movement from right to left on the x-axis indicates the percentage change from baseline in objectively measured VAT from the CAT scan data. Thus, improvement is indicated by movement from right to left. The cumulative percentage of patients is shown on the y-axis. The CDF on the basis of objectively measured VAT shows a separation between the study arms along nearly the entire curve, with the active treatment group demonstrating higher percentages of patients improved compared with the placebo group.

## STUDY ENDPOINT REVIEW

### Key secondary PRO endpoints:

This review focuses on the key PRO secondary endpoint specified in the endpoint hierarchy, namely “belly distress.”

### CTR-1011:

The table below shows changes from baseline by treatment group in belly appearance distress from the sponsor’s study report for CTR-1011. The ratings are scored on a scale from 0 (extremely upsetting and distressing) to 100 (extremely encouraging). A score of 50 indicated neutral (no feeling either way).

**Table 34: PRO: Belly Appearance Distress - Change from Baseline at Weeks 13 and 26 - ITT Population**

	Tesamorelin (N=269) (n=269)	Placebo (N=126) (n=126)	P-value <sup>1</sup>	P-value <sup>2</sup>
	Mean (SD)	Mean (SD)		
Baseline	22.3 (24.19)	20.2 (22.07)	0.416	
Week 13				
Actual Value	31.7 (26.64)	25.0 (23.77)		
Change from baseline <sup>3</sup>	9.4 (26.34)	4.8 (23.71)	0.004**	0.023*
P-value <sup>4</sup>	<0.001**	0.026*		
Week 26				
Actual value	30.5 (25.40)	25.4 (25.10)		
Change from baseline <sup>3</sup>	8.4 (28.99)	5.2 (26.61)	0.022*	0.083
P-value <sup>4</sup>	<0.001**	0.031*		

References: [Appendix 16.1.9.3](#), Volume II, Part 1, [Table 2k.4](#) and Volume II, Part 2, [Tables 4b.3, 4m.4, 8b.3, and 8h.4](#).

<sup>1</sup> ANOVA for baseline; Ranked ANCOVA including relevant covariates (e.g., gender, age) for change score

<sup>2</sup> Univariate ANCOVA as per supportive analysis; using log transformed data for wk 26

<sup>3</sup> Positive change scores represent improvements in belly appearance distress.

<sup>4</sup> Paired samples t-test for within-group change

\* p<0.05

At baseline, the mean scores were 22.3 for the tesamorelin group and 20.2 for the placebo groups. According to the study report, this indicates feelings about current belly appearance ranged between “Quite Upsetting and Distressing” and “Very Upsetting and Distressing”.

At week 26, the mean score in the tesamorelin group was 30.5 (indicating approximately “a little upsetting”) and the mean score in the placebo group was 25.4 (indicating “quite upsetting and distressing”).

**Reviewer’s comment: This indicates a very modest treatment effect in terms of mean change from baseline (tesamorelin-placebo).**

## STUDY ENDPOINT REVIEW

### LIPO-010:

The table below shows changes from baseline by treatment group in belly appearance distress from the sponsor’s study report for LIPO-010. As stated earlier, the ratings are scored on a scale from 0 (extremely upsetting and distressing) to 100 (extremely encouraging). A score of 50 indicated neutral (no feeling either way).

### BAD (Belly Distress):

**Table 36: PRO: Belly Distress - Change from Baseline at Week 26 (MAIN PHASE) - ITT Population**

		Tesamorelin (N=273)	Placebo (N=137)	P-value <sup>1</sup>	P-value <sup>2</sup>
Baseline	n	272	137	0.431	
	Mean (SD)	22.1 (22.23)	24.0 (25.68)		
	Median	12.5	12.5		
	Range	0.0; 100.0	0.0; 100.0		
Week 26	n	272	137		
	Mean (SD)	33.7 (25.93)	30.2 (27.31)		
	Median	25.0	25.0		
	Range	0.0; 100.0	0.0; 100.0		
Change from baseline	n	272	137	0.076	0.028*
	Mean (SD)	11.6 (26.93)	6.2 (25.82)		
	Median	0.0	0.0		
	Range	-87.5; +87.5	-87.5; +100.0		
	P-value <sup>3</sup>	<0.001**	0.006**		

Reference: [Appendix 16.1.9.5, Week 26 Analysis, Volume II, Part 1, Table 2k.4](#) and [Appendix 16.1.9.5, Week 26 Analysis, Volume II, Part 2, Tables 4b.3 and 4m.4](#)

<sup>1</sup>ANOVA including relevant covariates (e.g., gender, age) at baseline and parametric ANCOVA for change score

<sup>2</sup>Ranked ANCOVA as per supportive analyses

<sup>3</sup>Paired sample t-test

\*p<0.05

\*\*p<0.01

The study results of LIPO-010 were similar to those of CTR-1011 with regard to the BAD endpoint. At baseline, mean scores were 22.1 for the tesamorelin group and 24.0 for the placebo groups, indicating feelings about current belly appearance that were in the range between “Quite Upsetting and Distressing” and “Very Upsetting and Distressing”.

In the tesamorelin group, BAD scores improved from baseline by a mean of +11.6, which is within the range of “A little upsetting” to “No feeling either way”.

In the placebo group, BAD scores increased by a mean of +6.2 from baseline, indicating feelings within the range of “A Little Upsetting” to “Quite Upsetting and Distressing”.

The absolute difference between treatment groups in change was 5.4. This represents, on average, a treatment effect of less than one unit in magnitude using the original response options.

## STUDY ENDPOINT REVIEW

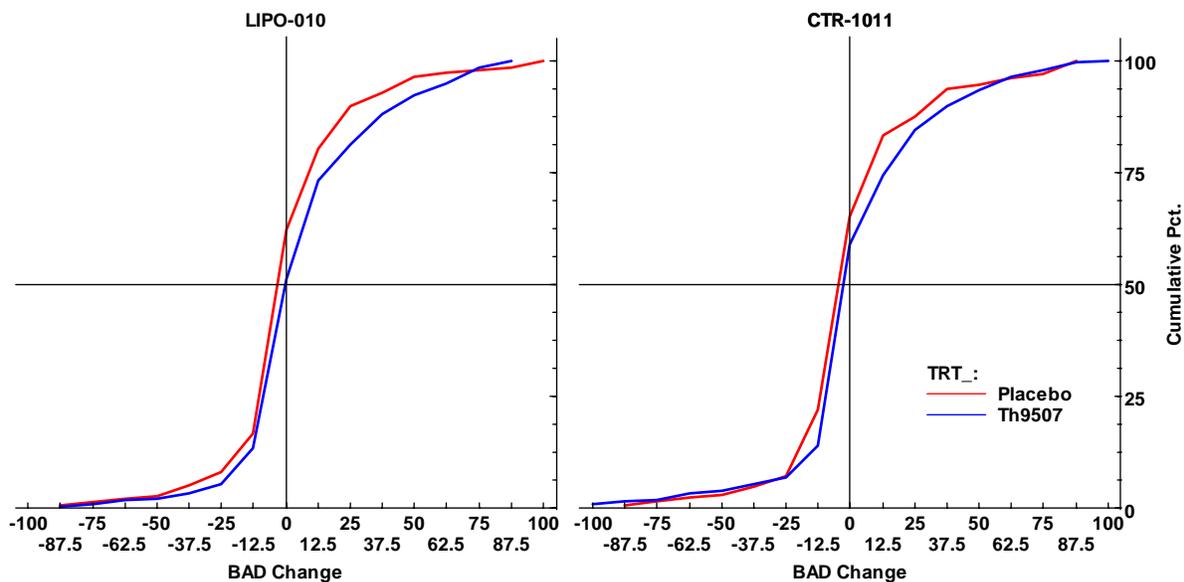
The ANCOVA test for differences in change from baseline to Week 26 scores between treatment groups was not statistically significant ( $p=0.076$ ).

**Reviewer's comment: Similar to CTR-1011, the treatment effect in this study was modest. In this study, the week 26 analysis for the BAD failed to meet statistical significance. If this endpoint is to be considered for inclusion in labeling, this reviewer recommends that CDF graphs be generated illustrating the distribution of responses for the BAD score in each study.**

According to the study report for CTR-1011, a supportive analysis for the key PRO endpoints focused on the responders at Week 26.

The CDF curves for the PRO endpoints were not located in the original NDA submission. The FDA statistician generated CDF graphs for each of the PRO endpoints (BAD, BSE and BPA). The responder definition can then be applied to the CDF curves to assist in interpretation.

The graph of BAD from the FDA statistical review is shown below. Movement toward the right indicates improvement. Recall, the responder definition is a 25-point improvement for BAD.



Similar to the analysis of means, these graphs show a very modest treatment effect as there is very little separation between the curves. Most of the separation is found in the upper right portion of the curve indicating that benefit is found in only a subset of patients and the curves tend to cross at the far right (at higher levels of positive change).

5 pages withheld in full immediately after this page as (b)(4) CCI/TS.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22505	ORIG-1	THERATECHNOLOGIES INC	Egrifta

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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ELEKTRA J PAPADOPOULOS  
01/07/2010

LAURIE B BURKE  
01/13/2010

# REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

## Division of Metabolism and Endocrinology Products

**Application Number:** NDA 22-505

**Name of Drug:** Egrifta (tesamorelin acetate) for Injection, 1 mg/vial

*Note: the proposed labeling states “1.1 mg” as the dosage strength to include the overfill amount of 0.1 mg. The proposed dosage strength is not acceptable because it should not include the overfill amount. The dosage strength should be revised to state “1 mg” instead. This recommendation was provided by CMC reviewer Suong Tran, with concurrence from Ali Al Hakim, and incorporated into the 74-Day filing letter issued by FDA on August 10, 2009. Along with this request, the applicant was also asked in the letter to clarify whether the dosage strength denotes the free base or the salt form of the peptide because the established name of the product should correlate with the dosage strength (1 mg tesamorelin or 1 mg tesamorelin acetate).*

**Applicant:** Theratechnologies Inc. (U.S. Agent: Kendle International Inc.)

### **Material Reviewed:**

**Submission Date(s):** May 29, 2009

**Receipt Date(s):** May 29, 2009

**Submission Date of Structure Product Labeling (SPL):** May 29, 2009

**Type of Labeling Reviewed:** WORD (PLR FORMAT REVIEW #1)

### **Background and Summary**

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

### **Review**

The following issues/deficiencies have been identified in your proposed labeling.

## Recommendations

Please address the identified deficiencies/issues and re-submit labeling by **September 18, 2009**. This updated version of labeling will be used for further labeling discussions.

### General

- Some discrepancies were noted between the Word and SPL versions of the package insert. Where these discrepancies exist, they are noted in the relevant sections below. Please be sure that the content contained in the Word version matches that of the content contained in the SPL version.

### Highlights

#### *Beginning of Highlights*

- Remove the <sup>TM</sup> symbol after EGRIFTA. Do not use the <sup>TM</sup> symbol after the drug name in Highlights or the Table of Contents. Use the <sup>TM</sup> symbol only once in the content of labeling (FPI).

#### *Dosage Forms and Strengths*

- The proposed labeling states “1.1 mg” as the dosage strength to include the overfill amount of 0.1 mg. The proposed dosage strength is not acceptable because it should not include the overfill amount. Revise the dosage strength to state “1 mg”. In addition, clarify whether the dosage strength denotes the free base or the salt form of the peptide because the established name of the product should correlate with the dosage strength (1 mg tesamorelin or 1 mg tesamorelin acetate).

*Note: This deficiency was addressed in the 74-Day filing letter issued by FDA on August 10, 2009, but will also be included with the other revisions identified in this review for the sake of completion.*

- Delete [REDACTED] <sup>(b) (4)</sup> from this section. The [REDACTED] <sup>(b) (4)</sup> should only appear in the Description section of the package insert.

#### *Adverse Reactions*

- Add the numerical reference to the appropriate corresponding section (Adverse Reactions) of the FPI to the end of the summarized statement.

### *Drug Interactions*

- Add the numerical reference to the appropriate corresponding section(s) of the FPI to the end of the summarized statement.

### *End of Highlights*

- Add the phrase “and Medication Guide” to the end of the statement “See Section 17 for PATIENT COUNSELING INFORMATION”. We note that this phrase was present in the SPL version of the package insert, but not in the Word version. The content contained in the SPL version must match that contained in the Word version.

### *Revision Date*

- Add, in bold type, a revision date in the following format: “Revised: Month/Year” (i.e., Revised: August 2009 or Revised: 8/2009). We note that the revision date was present in the SPL version of the package insert, but not in the Word version. The content contained in the SPL version must match that contained in the Word version.

### **FPI: Contents**

- Adjust the formatting of the two columns contained in the Table of Contents so that this section does not exceed ½ page.
- A horizontal line must be located between the Table of Contents and the FPI.
- There should be no periods after the numbers for the section or subsection headings. Remove the periods that follow the subsection numbers for these specific subsections: 2.1, 2.2, 5.1, 5.3, 5.4, 5.5, 6.1 and 6.2. This applies to the corresponding subsections in the FPI as well.

### **FPI**

#### **DOSAGE FORMS AND STRENGTHS**

- The proposed labeling states “1.1 mg” as the dosage strength to include the overfill amount of 0.1 mg. The proposed dosage strength is not acceptable because it should not include the overfill amount. Revise the dosage strength to state “1 mg”. In addition, clarify whether the dosage strength denotes the free base or the salt form of the peptide because the established name of the product should correlate with the dosage strength (1 mg tesamorelin or 1 mg tesamorelin acetate).

*Note: This deficiency was addressed in the 74-Day filing letter issued by FDA on August 10, 2009, but will also be included with the other revisions identified in this review for the sake of completion.*

- Delete (b) (4) from this section. The (b) (4) should only appear in the Description section of the package insert.

#### **WARNINGS AND PRECAUTIONS**

- Change the font from all capital letters to regular font in the subsection “5.4 Laboratory Tests” to match other subsections.

#### **ADVERSE REACTIONS**

- Bold type should not be used within subsections. Use another method to emphasize sub-headings, such as italics or underline.

#### **CLINICAL PHARMACOLOGY**

- Bold type should not be used within subsections. Use another method to emphasize sub-headings, such as italics or underline.

#### **HOW SUPPLIED/STORAGE AND HANDLING**

- The proposed labeling states “1.1 mg” as the dosage strength to include the overfill amount of 0.1 mg. The proposed dosage strength is not acceptable because it should not include the overfill amount. Revise the dosage strength to state “1 mg”. In addition, clarify whether the dosage strength denotes the free base or the salt form of the peptide because the established name of the product should correlate with the dosage strength (1 mg tesamorelin or 1 mg tesamorelin acetate).

*Note: This deficiency was addressed in the 74-Day filing letter issued by FDA on August 10, 2009, but will also be included with the other revisions identified in this review for the sake of completion.*

- Delete (b) (4) from this section. The (b) (4) should only appear in the Description section of the package insert.

PLR Format Review #1  
NDA 22-505  
Page 5

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Jennifer Johnson  
Regulatory Project Manager

Supervisory Comment/Concurrence:

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Enid Galliers  
Chief, Project Management Staff

Drafted: J.Johnson/08.04.09

Revised/Initialed: E. Galliers/08.7.09, J.Johnson/08.12.09, E.Galliers/08.12.09 and 08.14.09

Finalized: J.Johnson/08.14.09

Filename: Egrifta RPM LABELING REVIEW.doc

**CSO LABELING REVIEW #1 OF PLR FORMAT**

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JENNIFER L JOHNSON

08/25/2009

PLR Format Review #1 (comments to be sent to sponsor with requested response date of 9/18/09)

**NDA/BLA REGULATORY FILING REVIEW**  
(Including Memo of Filing Meeting)

<b>Application Information</b>		
NDA # 22-505	NDA Supplement #: S- N/A	Efficacy Supplement Type SE- N/A
Proprietary Name: Egrifta Established/Proper Name: tesamorelin acetate Dosage Form: Injection Strengths: 1.1 mg/vial		
Applicant: Theratechnologies Inc. Agent for Applicant: Kendle International Inc.		
Date of Application: May 29, 2009 Date of Receipt: May 29, 2009 Date clock started after UN: N/A		
PDUFA Goal Date: March 29, 2010		Action Goal Date: March 26, 2009
Filing Date: July 28, 2009		
Date of Filing Meeting: July 15, 2009		
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed Indication(s): To induce and maintain a reduction of excess abdominal fat in HIV-infected patients with lipodystrophy Indication as modified by clinical reviewer: To reduce abdominal visceral adipose tissue (VAT) in HIV+ AIDS patients with HIV-associated adipose redistribution syndrome (HARS).		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: N/A		<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>Refer to Appendix A for further information.</i>		<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
Review Classification:  <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>  <i>If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.</i>		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority  <input type="checkbox"/> Tropical disease Priority review voucher submitted
Resubmission after withdrawal? <input type="checkbox"/> Resubmission after refuse to file? <input type="checkbox"/>		
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response: <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR	

601.42)	
Collaborative Review Division (if OTC product): N/A	
List referenced IND Number(s): 61,226	
PDUFA and Action Goal dates correct in tracking system?  <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system?  <i>If not, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Application Integrity Policy</b>	
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> <a href="http://www.fda.gov/ora/compliance_ref/aiplist.html">http://www.fda.gov/ora/compliance_ref/aiplist.html</a>  <b>If yes, explain:</b> N/A  <b>If yes, has OC/DMPQ been notified of the submission?</b> N/A  <b>Comments:</b> N/A	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>User Fees</b>	
Form 3397 (User Fee Cover Sheet) submitted	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
User Fee Status  <b>Comments:</b>	<input type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input checked="" type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).</i>	
<b>Exclusivity</b>	

<p>Does another product have orphan exclusivity for the same indication? <i>Check the Electronic Orange Book at: <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a></i></p> <p><b>If yes</b>, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? N/A</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> YES X NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p> <p><b>Comments:</b></p>	<p>X YES # years requested: 5 <input type="checkbox"/> NO</p>
<p>If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>):</p> <p>Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>	<p>X Not applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<b>505(b)(2) (NDAs/NDA Efficacy Supplements only)</b>	
<p>1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p> <p>2. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).</p> <p>3. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))?</p>	<p>X Not applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>

**Note:** If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).

4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? **Check the Electronic Orange Book at:**  
<http://www.fda.gov/cder/ob/default.htm>

YES  
 NO

If yes, please list below:

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

**Format and Content**

**Do not check mixed submission if the only electronic component is the content of labeling (COL).**

**Comments:**

All paper (except for COL)  
 All electronic  
 Mixed (paper/electronic)

CTD  
 Non-CTD  
 Mixed (CTD/non-CTD)

**If mixed (paper/electronic) submission**, which parts of the application are submitted in electronic format?

N/A

**If electronic submission:**  
paper forms and certifications signed (non-CTD) or electronic forms and certifications signed (scanned or digital signature)(CTD)?

**Forms include:** 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); **Certifications include:** debarment certification, patent certification(s), field copy certification, and pediatric certification.

**Comments:**

YES  
 NO

**If electronic submission**, does it follow the eCTD guidance? (<http://www.fda.gov/cder/guidance/7087rev.pdf>)

YES  
 NO

**If not**, explain (e.g., waiver granted):

<p><b>Form 356h:</b> Is a signed form 356h included?</p> <p><i>If foreign applicant, <b>both</b> the applicant and the U.S. agent must sign the form.</i></p> <p>Are all establishments and their registration numbers listed on the form?</p> <p><b>Comments:</b> A signed form 356h was submitted to the original application but did not contain a listing of all establishments and their registration numbers. A requested for a corrected/updated form 356h was requested of the applicant via email on June 15, 2009. The applicant submitted this revised form on June 17, 2009.</p>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><b>Index:</b> Does the submission contain an accurate comprehensive index?</p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:</p> <p><input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p><b>If no, explain:</b></p>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><b>Controlled substance/Product with abuse potential:</b></p> <p>Abuse Liability Assessment, including a proposal for scheduling, submitted?</p> <p>Consult sent to the Controlled Substance Staff?</p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><b>BLAs/BLA efficacy supplements only:</b> N/A</p> <p>Companion application received if a shared or divided manufacturing arrangement?</p> <p><b>If yes, BLA #</b></p>	<p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	
<p>Patent information submitted on form FDA 3542a?</p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<b>Debarment Certification</b>	

<p>Correctly worded Debarment Certification with authorized signature?</p> <p><b><i>If foreign applicant, both the applicant and the U.S. Agent must sign the certification.</i></b></p> <p><b><i>Note:</i></b> Debarment Certification should use wording in FD&amp;C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> YES  <input type="checkbox"/> NO</p>
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	
<p>Field Copy Certification: that it is a true copy of the CMC technical section (<b><i>applies to paper submissions only</i></b>)</p> <p><b><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></b></p>	<p><input checked="" type="checkbox"/> Not Applicable (<i>electronic submission or no CMC technical section</i>)  <input type="checkbox"/> YES  <input type="checkbox"/> NO</p>
<b>Financial Disclosure</b>	
<p>Financial Disclosure forms included with authorized signature?</p> <p><b><i>Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.</i></b></p> <p><b><i>Note:</i></b> Financial disclosure is required for bioequivalence studies that are the basis for approval.</p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> YES  <input type="checkbox"/> NO</p>
<b>Pediatrics</b>	
<p><b><u>PREA</u></b>  <b><i>Note:</i></b> NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</p> <p>Are the required pediatric assessment studies or a full waiver of pediatric studies included?</p> <p><b>If no</b>, is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included?</p> <ul style="list-style-type: none"> <li>• <b><i>If no, request in 74-day letter.</i></b></li> <li>• <b>If yes</b>, does the application contain the</li> </ul>	<p><input type="checkbox"/> Not Applicable  <input type="checkbox"/> YES  <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES  <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES</p>

<p>certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</p> <p><b>Comments:</b> The sponsor submitted a deferral (for postpubertal children)/waiver (for prepubertal children) request in the original application with a commitment to submit the pediatric plan in an amendment to the NDA after the NDA is filed.</p>	<input type="checkbox"/> NO
<p><b><u>BPCA</u> (NDAs/NDA efficacy supplements only):</b></p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<b>Prescription Labeling</b>	
<p>Check all types of labeling submitted.</p> <p><b>Comments:</b></p>	<input type="checkbox"/> <b>Not applicable</b> <input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use <input checked="" type="checkbox"/> MedGuide <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)
<p>Is electronic Content of Labeling submitted in SPL format?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Package insert (PI) submitted in PLR format?</p> <p><b>If no</b>, was a waiver or deferral requested before the application was received or in the submission?  <b>If before</b>, what is the status of the request? N/A</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>MedGuide or PPI (plus PI) consulted to OSE/DRISK? (<i>send WORD version if available</i>)</p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>REMS consulted to OSE/DRISK?</p>	<input checked="" type="checkbox"/> Not Applicable

<p><b>Comments:</b> A REMS will likely be requested from the sponsor soon. Once the submission arrives, the REMS will be consulted to OSE/DRISK.</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP?</p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<b>OTC Labeling</b>	
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<p>Check all types of labeling submitted.</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> <b>Not Applicable</b> <input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)
<p>Is electronic content of labeling submitted?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Are annotated specifications submitted for all stock keeping units (SKUs)?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>If representative labeling is submitted, are all represented SKUs defined?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP?</p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO

<b>Meeting Minutes/SPA Agreements</b>	
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<p>End-of Phase 2 meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p><b>Comments:</b> An EOP2 meeting was never requested by the sponsor; however, a Guidance meeting (at which issues typically discussed during an EOP2 meeting were discussed) was held on December 3, 2007. The meeting minutes were</p>	<input type="checkbox"/> YES Date(s): <input checked="" type="checkbox"/> NO
--	--

issued on December 18, 2007.	
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <i>If yes, distribute minutes before filing meeting.</i>	X YES Date(s): September 19, 2008 <input type="checkbox"/> NO
<b>Comments:</b>	
Any Special Protocol Assessment (SPA) agreements? <i>If yes, distribute letter and/or relevant minutes before filing meeting.</i>	X YES Date(s): August 1, 2006 <input type="checkbox"/> NO
<b>Comments:</b> The sponsor requested a SPA on June 14, 2006, and the Agency issued a response letter on August 1, 2006.	

ATTACHMENT

### MEMO OF FILING MEETING

**DATE:** July 15, 2009

**NDA/BLA #:** 22-505

**PROPRIETARY/ESTABLISHED NAMES:** Egrifta (tesamorelin acetate) for Injection

**APPLICANT:** Theratechnologies Inc. (U.S. Agent: Kendle International Inc.)

**BACKGROUND:**

This is a new molecular entity (NME), a novel GHRH analog, developed to reduce abdominal visceral adipose tissue (VAT) in HIV+ AIDS patients with HIV-associated adipose redistribution syndrome (HARS). This product is a sterile lyophilized powder (1.1 mg/vial) available as a single-unit dose for reconstitution with 1.1 mL of Sterile Water for Injection USP for a final concentration of 1 mg/mL. The drug product is packaged in a stoppered glass vial and co-packaged in a kit that includes the diluent, disposable syringe, and disposable needle. The diluent is 1 mL Sterile Water for Injection, USP. Each 2 mg dose requires reconstitution of 2 vials of drug product and 2 vials of diluent. Immediately after reconstitution, the 1 mg/mL solution is administered subcutaneously.

To assess safety and efficacy of Egrifta (tesamorelin acetate), the sponsor conducted two Phase 3 multi-center, randomized, placebo-controlled parallel group studies using 2 mg subcutaneously administered doses of Egrifta, or placebo:

TH9507/III/LIPO/010: included a main phase and an extension phase

TH9507-CTR-1011: included only a main phase

Completers of TH9507-CTR-1011 went on to complete TH9507-CTR-1012, an extension of CTR-1011.

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Jennifer Johnson	Y
	CPMS/TL:	Enid Galliers	Y
Cross-Discipline Team Leader (CDTL)	Dragos Roman		Y
Clinical	Reviewer:	Robert Perlstein	Y
	TL:	Dragos Roman	Y
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:	N/A	
	TL:	N/A	
Labeling Review ( <i>for OTC products</i> )	Reviewer:	N/A	
	TL:	N/A	
OSE	Reviewer:	Cathy Miller	Y
	TL:	Kellie Taylor Melina Griffis	N
Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:	N/A	
	TL:	N/A	
Clinical Pharmacology	Reviewer:	Ritesh Jain	Y
	TL:	Wei Qiu (Sally Choe effective July 20, 2009)	Y
Biostatistics	Reviewer:	Lee Ping Pian	Y
	TL:	Todd Sahlroot	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Lauren Murphree-Mihalcik	Y
	TL:	Todd Bourcier	Y
Statistics, carcinogenicity	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC)	Reviewer:	Joseph Leginus Suong Tran (filing only)	Y

	TL:	Ali Al Hakim	Y
Facility (for BLAs/BLA supplements)	Reviewer:	N/A	
	TL:	N/A	
Microbiology, sterility (for NDAs/NDA efficacy supplements)	Reviewer:	Steven Fong	Y
	TL:	Stephen Langille James McVey	N
Bioresearch Monitoring (DSI)	Reviewer:	Susan Leibenhaut	Y
	TL:	TBD	
Other reviewers			

**OTHER ATTENDEES:** Mary Parks, Karen Mahoney, Amy Egan, Julie Marchick, Kati Johnson, Daniela Verthelyi, Ginneh Stowe, Tsvi Aranoff

505(b)(2) filing issues? <b>If yes, list issues:</b>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
Per reviewers, are all parts in English or English translation? <b>If no, explain:</b>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<b>Electronic Submission comments</b> <b>List comments:</b> None	<input type="checkbox"/> Not Applicable
<b>CLINICAL</b> <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed? <b>If no, explain:</b></li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed? <b>Comments:</b></li> </ul> <p><b>If no, for an original NME or BLA application, include the</b></p>	<input checked="" type="checkbox"/> YES Date if known: TBD <input type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<p><i>reason. For example:</i></p> <ul style="list-style-type: none"> <li>○ <i>this drug/biologic is not the first in its class</i></li> <li>○ <i>the clinical study design was acceptable</i></li> <li>○ <i>the application did not raise significant safety or efficacy issues</i></li> <li>○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	
<ul style="list-style-type: none"> <li>• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input checked="" type="checkbox"/> Review issues for 74-day letter
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>PRODUCT QUALITY (CMC)</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

<b>Comments:</b>	X Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?  <b>If no</b>, was a complete EA submitted?  <b>If EA submitted</b>, consulted to EA officer (OPS)?  <b>Comments:</b></li> </ul>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ?  <b>Comments:</b></li> </ul>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Sterile product?  <b>If yes</b>, was Microbiology Team consulted for validation of sterilization? (<b>NDAs/NDA supplements only</b>)</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>FACILITY (BLAs only)</b>  <b>Comments:</b>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<b>REGULATORY PROJECT MANAGEMENT</b>	
<b>Signatory Authority:</b> Curtis Rosebraugh, M.D., MPH  <b>GRMP Timeline Milestones:</b> (Tentative - to be revised as needed throughout review cycle)  Filing Meeting: July 15, 2009 Filing Date: July 28, 2009 74 Day Letter due: August 11, 2009 Team meeting: TBD, aiming for mid-September 2009 (if needed) Mid-cycle review meeting: October 16, 2009 Team meeting: TBD, mid-December 2009 Pediatric Review Committee (PeRC): January 13, 2010 Wrap-up meeting: January 29, 2010	

Primary reviews due: January 29, 2010  
 Secondary reviews due: February 5, 2010  
 CDTL review due: February 12, 2010  
 Date to Division Director: February 15, 2010  
 Advisory Committee: aiming for mid-February 2010, awaiting date from Exec Sec  
 Labeling/PMC/PMR discussions to begin: February 15, 2010  
 Pre-approval safety conference (PASC): February 26, 2010  
 Division Director Review due: March 5, 2010  
 Action package/letter to Office Director: March 8, 2010  
 Office Director review/signoff: March 26, 2010  
**PDUFA goal date: March 29, 2010**

**Comments:**

**REGULATORY CONCLUSIONS/DEFICIENCIES**

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input type="checkbox"/>	The application, on its face, appears to be suitable for filing.  <input type="checkbox"/> No review issues have been identified for the 74-day letter.  <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):  <input checked="" type="checkbox"/> Standard Review  <input type="checkbox"/> Priority Review

**ACTIONS ITEMS**

<input checked="" type="checkbox"/>	Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.
<input type="checkbox"/>	If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.
<input type="checkbox"/>	If filed and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	If BLA or priority review NDA, send 60-day letter.
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Other

## Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JENNIFER L JOHNSON  
07/28/2009

# DSI CONSULT: Request for Clinical Inspections

**Date:** July 23, 2009

**To:** Constance Lewin, M.D., M.P.H, Branch Chief, GCP1  
Tejashri Purohit-Sheth, M.D., Branch Chief (Acting), GCP2  
Susan Leibenhaut, M.D., Medical Officer, GCP2  
Division of Scientific Investigations, HFD-45  
Office of Compliance/CDER

**Through:** Robert Perlstein, M.D., Clinical Reviewer  
Dragos Roman, M.D., Acting Clinical Team Leader  
Division of Metabolism and Endocrinology Products

**From:** Jennifer Johnson, Regulatory Project Manager

**Subject:** **Request for Clinical Site Inspections**

## I. General Information

Application: NDA 22-505  
Applicant: Theratechnologies Inc.  
U.S. Agent: Kendle International, Inc.  
Regulatory Point of Contact: Michelle Wilson, Ph.D.  
Phone: 513-258-5766  
Email: [wilson.michelle@kendle.com](mailto:wilson.michelle@kendle.com)  
Drug Proprietary Name: Egrifta (tesamorelin acetate) for Injection  
NME: Yes  
Review Priority: Standard  
Study Population includes < 17 years of age: No  
Is this for Pediatric Exclusivity: No

Proposed New Indication: To induce and maintain a reduction of excess abdominal visceral adipose tissue (VAT) in HIV-infected AIDS patients with HIV-associated adipose redistribution syndrome (HARS).

PDUFA: March 29, 2010  
Action Goal Date: March 26, 2010  
Inspection Summary Goal Date: January 15, 2010

**II. Protocol/Site Identification**

*Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table.*

<b>Site # (Name,Address, Phone number, email, fax#)</b>	<b>Protocol ID</b>	<b>Number of Subjects</b>	<b>Indication</b>
<p><b>Site #42</b> Daniel S. Berger, M.D. Northstar Medical Center 2835 N. Sheffield Avenue Suite 500 Chicago, IL 60657 773-296-2400 phone [REDACTED] (b) (6)</p>	<p>TH9507/III/LIPO/ 010</p>	<p>38</p>	<p>To induce and maintain a reduction of excess abdominal visceral adipose tissue (VAT) in HIV-infected AIDS patients with HIV-associated adipose redistribution syndrome (HARS).</p>
<p><b>Site #203</b> Daniel S. Berger Northstar Medical Center 2835 N. Sheffield Avenue Suite 500 Chicago, IL 60657 773-296-2400 phone [REDACTED] (b) (6)</p>	<p>TH9507-CTR- 1011</p>	<p>43</p>	<p>To induce and maintain a reduction of excess abdominal visceral adipose tissue (VAT) in HIV-infected AIDS patients with HIV-associated adipose redistribution syndrome (HARS).</p>
<p><b>Site #17</b> Michael S. Somero, M.D. 1401 N. Palm Canyon Drive Suite 100 Palm Springs, CA 92262 760-322-2525 phone 760-322-6789 fax</p>	<p>TH9507/III/LIPO/ 010</p>	<p>41</p>	<p>To induce and maintain a reduction of excess abdominal visceral adipose tissue (VAT) in HIV-infected AIDS patients with HIV-associated adipose redistribution syndrome (HARS).</p>
<p><b>Site #224</b> Michael S. Somero 1401 N. Palm Canyon Drive Suite 100 Palm Springs, CA 92262 760-322-2525 phone 760-322-6789 fax</p>	<p>TH9507-CTR- 1011</p>	<p>37</p>	<p>To induce and maintain a reduction of excess abdominal visceral adipose tissue (VAT) in HIV-infected AIDS patients with HIV-associated adipose redistribution syndrome (HARS).</p>

### **III. Site Selection/Rationale**

*Summarize the reason for requesting DSI consult and then complete the checklist that follows your rationale for site selection. Medical Officers may choose to consider the following in providing their summary for site selection.*

#### **Domestic Inspections:**

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify):

#### **International Inspections:**

Reasons for inspections (please check all that apply): **N/A**

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

Should you require any additional information, please contact Jennifer Johnson at 301-796-2194 or Robert Perlstein at 301-796-1270.

Concurrence: (as needed)

Dragos Roman	Medical Team Leader
Robert Perlstein	Medical Reviewer

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this page is the manifestation of the electronic signature.**  
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/s/

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Jennifer Johnson  
7/23/2009 01:27:15 PM