

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-505

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	November 1, 2010
From	Dragos Roman, MD, Team Leader, Division of Metabolism and Endocrinology Products
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	22-505/N000
Applicant	Theratechnologies Inc.
Date of Submission	May 29, 2009
PDUFA Goal Date	April 22, 2010
Proprietary Name / Established (USAN) names	Egrifta (tesamorelin acetate)
Dosage forms / Strength	Injectable 1 mg vial to be administrated once a day at a dose of 2 mg subcutaneously in the abdomen
Proposed Indication(s)	To induce and maintain a reduction of excess abdominal fat in HIV-infected patients with lipodystrophy
Recommended:	Approval

1. Introduction

Egrifta is a synthetic analog of human growth hormone-releasing hormone (GHRH); it is to be administered once daily via subcutaneous injections in the abdomen at a dose of 2mg. The drug substance in Egrifta is tesamorelin acetate, a GHRH analog which contains the entire 44 amino acid sequence of human GHRH to which an additional hexenoyl moiety is attached creating a product that preserves the function of endogenous GHRH while extending its half-life 15-fold. When assessed in an *in vitro* assay, the binding affinity of tesamorelin was comparable to that of endogenous GHRH. Egrifta is a new molecular entity; it has not been approved to date by any regulatory agency outside the US.

Egrifta, like GHRH, stimulates the secretion of endogenous GH via binding to the GHRH receptor (by definition Egrifta will only function in patients with an intact pituitary). Once coupling to the GHRH receptor occurs, GH is released from the pituitary and stimulates anabolic processes (via the GH receptor and subsequent IGF-1 production) and lipolysis (GH receptor mediated but IGF-1- independent). Lipolysis results in a reduction in subcutaneous fat and visceral (mostly abdominal) fat.

Theratechnologies, which manufactures Egrifta, has developed Egrifta for the following indication: induction and maintenance of a reduction in abdominal fat in HIV-infected patients with lipodystrophy. A recombinant human GH (rhGH) clinical program sought this indication in 2006 (Serostim, NDA 20-604, Supplement 40) but was turned down primarily on the basis of not being successful in establishing a favorable risk-to-benefit profile (although the

Serostim dose that was investigated reduced VAT by about 15%, it was also associated with marked increase in insulin resistance and diabetes and also considerably raised IGF-1 levels).

HIV-associated lipodystrophy is a medical condition that has been identified in HIV-infected patients after the introduction of highly active anti-retroviral therapies (HAART) in the mid 1990s. Although such therapies resulted in a dramatic decline in HIV-related mortality and morbidity, they were also linked with changes in body composition (loss of subcutaneous adipose tissue in the limbs and face coexisting with regional fat accumulation in the form of “buffalo hump” and abdominal visceral fat tissue excess), as well as metabolic changes of which the most important are dyslipidemia and insulin resistance. The exact prevalence of HIV-associated lipodystrophy is not known. Estimates vary widely: in the US 200,000 to 800,000 HIV-infected patients may show some manifestations of the syndrome depending on the case definition used and about 50% of such patients have central adiposity; as such, the prevalence of the disease may be as low as 100,000 (a prevalence consistent with an orphan indication) and as high as 500,000. There is some evidence that HIV lipodystrophy is more likely to be seen with older protease inhibitors rather than newer ones, raising the question whether the prevalence may even decline in the future.

There are no approved therapies in the US for the treatment of HIV-lipodystrophy although some of the metabolic manifestations, such as dyslipidemia and insulin resistance, benefit from treatment with approved lipid lowering therapies or insulin sensitizers. The Egrifta NDA is submitted under Section 505(b)(1) of the Food, Drug, and Cosmetics Act.

2. Background

The regulatory history of Egrifta is long and complex. The Agency met with representatives of Theratechnology Inc. multiple times and provided extensive guidance in the design of the Phase III trials, choice and hierarchy of endpoints, statistical analysis plan, patient reported outcome development, etc. A major challenge that the Agency has faced with the Egrifta clinical program was the selection of Phase III clinical trial endpoints. Generally speaking, in doing this, the Agency has drawn from knowledge accumulated in adult GH deficiency trials for a variety of endpoints (total body fat, trunk fat - which includes the visceral fat compartment, lean body mass, serum IGF-1, serum lipids, quality of life questionnaires, etc.), and to some extent from obesity trials. In addition, some features of the Egrifta Phase III clinical program were adapted from the Serostim HIV lipodystrophy program (NDA 20-604). In the Serostim Phase III clinical trials visceral adult fat (VAT) was the primary efficacy endpoint.

The Division accepted the applicant’s proposal that an 8% reduction in VAT can be considered a “clinically meaningful difference” for the purpose of powering the Phase III studies (this clinical difference was used previously for power calculations in the Serostim clinical program). Acceptance of VAT as a primary endpoint in both the Serostim and Egrifta clinical programs was based on a substantial body of evidence that links visceral (mostly abdominal) adiposity to insulin resistance, atherogenic dyslipidemia, hypertension, impaired fibrinolysis, increased risk of thrombosis, and inflammation, all cardiometabolic risk factors. However,

despite the close connection of VAT to cardiometabolic risk, the Division also expressed reservations on the confidence that can be placed on VAT reduction alone (i.e. without evidence of additional clinical benefit) since there are no clinical trials that demonstrate that pharmacological reductions of VAT improve cardiovascular outcomes. The Division did not ask for a cardiovascular outcome study as a prerequisite for a successful registration trial (such a trial is not feasible based on the low prevalence of HIV-lipodystrophy with excess abdominal fat). In this context the Agency recommended that the sponsor identify or develop adequate patient reported outcomes (PROs) to demonstrate an additional clinical benefit of Egrifta beyond VAT reduction. In the end the Agency accepted the sponsor's proposal to include several PROs as secondary endpoints in the Phase III trials and include them in a hierarchical statistical plan.

3. CMC/Device

There are no CMC approvability issues. Several chemistry reviews address different aspects of the Egrifta application and are archived in DARRTS (12/16/2009; 10/21/2009; 1/22/2010; 2/6/2010). In final analysis the CMC reviewer recommends approval of Egrifta without additional postmarketing requirements (12/16/2009).

Egrifta is manufactured as a lyophilized powder containing in each vial 1 mg of tesamorelin free base and (b) (4) mg of mannitol as the only excipient; no preservatives are included since the product is intended for immediate use. The Egrifta vial is to be reconstituted in Sterile Water for Injection at a concentration of 1 mg/ml. Since the daily dose of Egrifta is 2 mg, two vials are needed to be reconstituted for each use and injected once-a-day subcutaneously.

The release specifications for the drug substance and drug product were found to be acceptable to the CMC reviewer. All impurities were adequately qualified at their respective proposed acceptable limit. One process related impurity (b) (4) and one degradant (b) (4) are identified in the drug substance specifications. During stability testing no additional impurities have been identified in the drug product. Since Egrifta is photosensitive, Egrifta vials are immediately labeled and placed in secondary containers, which provide protection from light. Based on the supporting stability data, a shelf-life of 24 months at 2° – 8°C has been granted.

According to the CMC reviewer, acceptable cGMP recommendations have been received from the Office of Compliance for each of the seven manufacturing and testing facilities.

4. Nonclinical Pharmacology/Toxicology

There are no nonclinical pharmacology/toxicology approvability issues. The nonclinical pharmacology/toxicology review, archived in DARRTS (3/2/2010 with additional Memos to the File on 3/11/2010, 8/27/2010), concludes that the sponsor has provided an adequate set of toxicity studies and recommends approval.

The reviewer indicates that the toxicology studies did not show a mutagenic effect of tesamorelin in bacteria or in mammalian cells grown *in vitro*. There was no evidence of chromosomal damage *in vivo* (as judged by the examination of bone marrow cells in mice). In addition, no evidence of clastogenicity was found in both a mammalian chromosome aberration assay and an *in vivo* assay (murine micronucleus induction). These findings are consistent with the current understanding of the physiology of GH which is neither mutagenic nor clastogenic. The review also notes that, although a lifetime carcinogenicity study was not conducted with tesamorelin, in a six-month study in rats there was no increase in cell proliferation markers in tissues of the gastrointestinal tract, liver, pituitary, adrenal glands, and testes (the exposure was 1.5X to 26X the maximum recommended human dose based on AUC calculations). These animal data provide a lot of reassurance regarding the theoretical concern that Egrifta may increase the risk of malignancies. Particularly, it provides strong evidence that Egrifta does not cause *de novo* malignancies. However, these observations do not provide the same level of evidence against a potential growth promoting effect that Egrifta may have on already existing tumors who express GH receptors. This issue will be further addressed in the Safety section in the context of IGF-1 elevations observed in the Phase III clinical trials.

The human dose has large margins of safety when compared to the doses that show toxicity in animals. Minimum lethal doses of Egrifta were established for mice and rats at 240X and 975X the maximum recommended human dose (MRHD), respectively, on a body surface area basis. For dogs, despite doses of up to 1600X MRHD, no single lethal dose was established. In animal toxicology studies (rats and dogs) tesamorelin demonstrated effects that were consistent with overproduction of growth hormone; they included weight growth, diabetogenic effect, tissue hypertrophy, and canine acromegaly. Impurities in Egrifta that reached relevant threshold levels were qualified in 28-day rat studies and genetic toxicity studies.

A risk of hydrocephaly or altered intracranial pressure was observed in the offspring of animals that were given doses that provide exposures that are 1-2X the MRHD on an AUC basis. On the basis of this observation, the pharmacology/toxicology review team recommends that Egrifta should not be used during pregnancy and that a Pregnancy Category X designation should be given to Egrifta. This recommendation, along with descriptive data of these findings was included in the label.

5. Clinical Pharmacology/Biopharmaceutics

There are no nonclinical clinical pharmacology approvability issues. The clinical pharmacology review (archived in DARRTS on 08/02/2010) recommends approval of Egrifta. The tesamorelin clinical pharmacology program included 10 studies: 6 single- or multiple-dose PK or PK/PD studies conducted in healthy volunteers and HIV-infected patients; 2 bioavailability studies; and 2 drug-drug interaction studies which demonstrated the absence of a clinically significant impact on the metabolism of simvastatin and ritanovir.

In healthy volunteers, the 2mg Egrifta dose had a T_{max} of approximately 9 minutes and an elimination half-life of 13.2 min. No tesamorelin accumulation was observed following

multiple dose administration. The absolute bioavailability of a 2 mg Egrifta subcutaneous injection was <4% in healthy volunteers. No formal metabolism studies were performed in humans. From a pharmacodynamic standpoint, Egrifta induced a clear dose response with respect to both GH and IGF-1. The pharmacokinetics and pharmacodynamics of Egrifta were similar in HIV-infected patients to those observed in healthy volunteers, as was the IGF-1 response. Two drug-drug interactions were conducted: one with simvastatin (a CYP 3A substrate) and another with ritonavir (a CYP 3A inhibitor). In either study the interaction was not significant. There were no PK studies conducted in patients with renal or hepatic impairment. The age effect was studied in non-HIV patients only in whom a lower IGF-1 response was observed relative to younger patients for a comparable tesamorelin dose.

6. Clinical Microbiology

There are no microbiology issues that preclude approval. While the microbiology review (archived in DARRTS as of 6/11/2010) recommends approval of Egrifta, the microbiology reviewer recommends that the applicant commit to providing the tesamorelin daily 2mg dose in a single vial and that this recommendation be made a postmarketing requirement. The microbiology review provides a description of the postmarketing study and a timeline for conducting it. With respect to the timeline, the reviewer recommends that 1) the studies should be initiated no later than 1 month following the NDA approval; 2) the sponsor must submit a summary of stability data collected during the first year no later than 15 months after NDA approval; and 3) if a single vial containing the entire single dose can be manufactured, the sponsor must submit no later than 31 months after NDA approval a supplement that proposes the use of this process for drug product manufacture.

7. Clinical/Statistical- Efficacy

While in final analysis there are no clinical approvability issues in the view of the primary reviewer (Dr. Ali Mohamadi) and myself, it should be noted that the Egrifta application has raised complex scientific issues that required extensive internal discussions and outside advice from an Endocrinologic and Metabolic Drugs Advisory Committee held on May 27, 2010. These issues will be detailed in this section, as well as in the risk/benefit section. They relate, among others, to the choice of the primary endpoint and the lack of a robust link between the primary efficacy endpoint and cardiovascular outcomes, the benefit and limitations of patient reported outcomes in the clinical studies, and some specific safety observations.

The Egrifta clinical program was extensive and included in addition to the above-mentioned 10 clinical pharmacology studies, several studies in non-HIV patient populations, a Phase II dose searching study in HIV patients with lipodystrophy, and two Phase III “pivotal trials”. The clinical review, conducted by Dr. Ali Mohamadi (archived in DARRTS on 9/15/2010) has focused, appropriately so, on the two Phase III clinical trials, as did the statistical review (archived in DARRTS on 09/07/2010). Generally speaking, the statistical reviewer confirms most of the sponsor’s analyses, in particular applicant’s analyses for the primary efficacy endpoint demonstrating the superiority of Egrifta over placebo in VAT reduction after 6

months of treatment. The statistical reviewer also confirms applicant's analysis with respect to IGF-1, total and trunk fat, lean body mass (all superior to placebo) and indicates that changes in triglycerides and patient reported outcomes were not consistently statistically different from placebo across the two Phase III trials. Specific references to the findings of the statistical review will be made in the clinical review section.

7.1 Pivotal trials

7.1.1 The Phase III clinical program (general comments on trial design, patient exposure, endpoint selection, and efficacy results)

In support of the proposed indication Theratechnologies has submitted the results of two Phase III clinical trials which were almost identical in design, duration, inclusion criteria, number of patients, and Egrifta dose (of note, although the application refers to three trials, one of them is in fact an extension trial). For simplicity, while maintaining consistency with applicant's terminology, these trials will be referred to in this memorandum as Study 10, Study 11, and Study 12 (extension to Study 11); the latter two will also be referred to as Study 11/12.¹

Both Study 10 and Study 11/12 were randomized, double-blind, placebo-controlled, multicenter (US, Canada, EU) Phase III clinical trials that evaluated the efficacy and safety of the same 2 mg daily dose of tesamorelin in patients with HIV lipodystrophy and excess abdominal fat. They included a 6-month placebo-controlled Main Phase followed by a 6-month Extension Phase. Drug-to placebo randomization for the Main Phase was 3:1 in Study 10 and 2:1 in Study 11. At the end of the Main Phase, completers who received tesamorelin were re-randomized to either a 2mg drug arm (referred to as the tesamorelin-tesamorelin or T-T group) or to a placebo arm (referred to as the tesamorelin-placebo or T-P group)². Patients who received placebo during the Main Phase were switched to the 2 mg tesamorelin dose in an open-label extension phase (placebo-to-tesamorelin or P-T group). This study design allowed for an assessment of maintenance of drug effect (T-T group) and reversibility of such effects after drug discontinuation (T-P group). In addition, the P-T group provided additional confirmation to the efficacy and safety results observed in the Main Phase.

The similarities between Studies 10 and 11/12 did not stop at dose and study design. Both studies included virtually identical inclusion/criteria and mostly the same efficacy and safety assessments. They enrolled adult patients with HIV-associated lipodystrophy who were stable on antiretroviral therapy and who had evidence of abdominal fat accumulation by anthropometric measurements³. Another important characteristic of the clinical trials was the fact that they did not exclude patients with glucose intolerance and diabetes. In fact, patients with diabetes were included as long as they were not treated with insulin, oral antihyperglycemic drugs or insulin-sensitizing agents, and as long as their fasting blood

1 Study 10 stands for Study TH9507/III/LIPO/010. Study 11 stands for Study TH9507-CTR-1011. Study 12 stands for TH9507-CTR-1012.

2 Drug to placebo randomization was 3:1 in Study 10 Extension and 1:1 in Study 12.

3 Lemieux S et al: A single threshold value of waist girth identifies normal-weight and overweight subjects with excess visceral adipose tissue. *Am. J Clin. Nutr.* 1996; 64:685-93.

glucose was not ≥ 150 mg/dL. Allowing patients with glucose intolerance in the Phase III trials helped to better define the effect of Egrifta on glucose metabolism in these patients at risk.

The number of patients randomized to the Main Phase of each trial was approximately 270 in the tesamorelin group and 130 in the placebo group; thus the Phase III program included approximately 543 patients studied at the to-be-marketed dose for 6 months (of these, 413 were completers). The primary efficacy endpoint for each of the two trials was the percent change from baseline to Week 26 in visceral adult fat (VAT) where VAT change was defined as the cross-sectional area in cm^2 measured by CT scan at the L4-L5 vertebral level. The secondary endpoints for the Phase III clinical trials were total cholesterol/HDL-cholesterol ratio, triglyceride levels, IGF-1 levels, and patient reported outcomes (PROs) related to Body Image (Belly Profile, Belly Size Evaluation and Belly Appearance Distress), all evaluated at Week 26.

Consistent with the uniform criteria used for patient enrollment across the Phase III studies, the baseline patient characteristics were remarkably similar between the two Phase III clinical trials for mean age (approximately 48 years), mean weight (89 kg), BMI (29 kg/m^2), waist circumference (104 cm), waist-to-hip ratio (1). Across both clinical trials patients had a similar mean duration since initial HIV diagnosis (13.5 years), time since lipodystrophy diagnosis (4.8 years), duration of antiretroviral therapy (about 4.5 years), viral load, and CD4 and CD8 cell count. There were only minor imbalances in terms of type of antiretroviral drug combinations used prior to enrollment. Patient discontinuations in the two trials were between 23 and 25% for the tesamorelin group but not very different from the placebo group (16 to 27%). There were some differences in subject disposition between the two trials but they did not indicate a specific pattern.

7.1. 2 Efficacy results

Primary efficacy analysis

The primary efficacy analysis was a drug-to-placebo comparison of the percent change in VAT from baseline to Week 26 using an analysis of covariance. This analysis showed in each study a statistically significant reduction of VAT in the Egrifta group relative to placebo ($p < 0.001$ for the ITT analysis). Interestingly, the placebo-subtracted treatment effect was higher in Study 10 (-19.6%) than Study 11 (-11.7%). Patients entered the trial with VAT levels of 182 cm^2 , high above a 130 cm^2 'threshold' value above which glucose/insulin profile and lipoprotein profile alterations are have been linked to an increased risk of cardiometabolic complications in non-HIV patients. On-treatment absolute reductions in mean VAT were 32 cm^2 and 21 cm^2 in Studies 10 and 11, respectively, approximately half-way between baseline levels and the proposed threshold value of 130 cm^2 . Sensitivity analyses conducted by the statistical reviewer were fully consistent with the ITT analysis. When compared to the ITT results, the % VAT reduction was slightly higher among completers in Study 10 (23%) and Study 11 (13%), not surprisingly, since patients who respond better tend to stay in the trial. There were no disagreements between the FDA and the applicant's primary efficacy analyses. The changes in VAT were observed as early as 13 weeks of treatment (first post baseline assessment of efficacy) and were quantitatively similar to those observed at 6 months. Of

importance, efficacy data from the extension phase clearly demonstrate that the discontinuation of Egrifta results in reaccumulation of VAT to levels close to those recorded at baseline; this was observed 13 weeks after treatment discontinuation (the earliest timepoint of evaluated after discontinuation of treatment). This finding indicates that, in order to maintain VAT reduction, tesamorelin treatment has to be continued long-term, likely indefinitely (data beyond one year are not available). The VAT reductions observed at 6 months were sustained through 52 weeks (last timepoint on trial).

Secondary endpoint and additional efficacy analyses

In contrast to the clear effect on VAT reduction, efficacy analyses of secondary endpoints showed modest and inconsistent changes. For instance, statistical significance was achieved at Week 26 in Study 10 for the mean change in triglycerides (-52.8 mg/dl relative to placebo; $p < 0.0001$) and non-HDL cholesterol (-10.8 mg/dl relative to placebo; $p < 0.001$). In contrast, smaller changes that did not reach statistical significance were noted in Study 11 (triglycerides: -19.9 mg/dl; $p = 0.10$; non-HDL-C +1.1 mg/dl; $p = 0.216$). In general, efficacy appeared to be greater in Study 10 over Study 11, although an explanation for this fact is not evident. Such small changes in serum lipid variables are consistent with observations made in rhGH trials.

On the other hand, statistical significance was achieved consistently for increases in total body lean mass and reductions in total body fat, trunk fat (which includes VAT, but not in subcutaneous adipose fat (SAT)). The 2 mg regimen of Egrifta reduced total fat by 1.4 kg relative to placebo, trunk fat by 1.2 kg relative to placebo, and increased lean body mass by 1.4 kg to placebo, all at 6 months. These observations are consistent with body composition changes seen with rhGH. The drug's effect on weight was neutral since the numerical reduction in body weight due to fat reduction was canceled by the increase in lean body mass.

Consistent with the VAT findings, a greater reduction in waist circumference was observed at Week 26 with Egrifta relative to placebo (approximately 1.5 cm; $p < 0.001$) and this difference was statistically significant for each study. The mean waist:hip ratio was also statistically significantly different in Study 11, in Study 10 and in the pooled analysis.

Per FDA's statistical analysis, changes in patient reported outcomes related to body image were relatively modest and showed statistically significant differences relative to placebo only for two of the three secondary endpoint PROs: Belly Appearance Distress and Belly Profile. The absence of a much larger treatment effect should not be surprising in the light of the waist circumference findings (1.5 cm relative to placebo) since these PROs measure the patients' perception and emotional distress in relation to the abdominal size change.

In general, efficacy results for all of the above-mentioned efficacy variables were consistent at Week 52 with the 26-week observations.

7.1.3 Study Endpoints and Label Development (SEALD) consult

The SEALD review provides a critical look of the Body Image Impact Module (BIIM), a patient-reported outcome (PRO) tool that was used in the phase 3 studies (archived in DARRTS 1/13/2010). The consult focuses on the PROs that were evaluated as secondary

endpoints. The reviewer expresses reservations with respect to the content validity of the current version of the BIIM, which does not meet the new standards articulated in the December 2009 guidance for industry entitled “Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims” and states that it should not be recommended by FDA for future drug development. Of note, the PROs evaluated in the Egrifita clinical trials have been incorporated with input from the Agency much in advance of the 2009 guidance. The reviewer notes that Belly Size Estimation is not a valid measure of “belly size” as it asks the subject to compare his/her current belly size to his/her ideal “healthy look” and thus, in the absence of more specific criteria, it is doubtful that the term “healthy look” will be interpreted the same way across subjects and even for the same subject over time. The reviewer also indicates that Belly Appearance Distress may be a valid measure but the data provided in the PRO dossier does not meet the new standards for instrument development recommended within the 2009 PRO guidance. The consult defers to the statistical and clinical team the judgment as to whether the data submitted and critically evaluated methodologically in the consult can be considered clinically meaningful and adequate for labeling. In response to the comments and recommendations made by the SEALD consult, the clinical and statistical team decided to include in the label only the results of the Belly Appearance Distress. It was felt that from a clinical perspective Belly Appearance Distress is an endpoint of higher significance as it does not measure the self-reported perception about changes in the size of the abdomen but rather the emotional impact and distress for the patient, an important proxy for QOL in HIV-patients with lipodystrophy. As recommended by the SEALD consult, the term (b) (4) will no longer be included in Egrifita label description of this PRO since, although developed with advice, it does no longer meet the new standard set by the December 2009 FDA PRO guidance.

7.1.4 Dose Selection

The 2 mg dose was selected on the basis of a single Phase II clinical trial in which a 2 mg dose of Egrifita was superior to placebo, and a 1 mg Egrifita dose was less effective than 2 mg in reducing VAT and showed similar VAT changes as placebo. It is not known if Egrifita doses between 1mg and 2 mg would still be effective, or if a titration regimen would achieve better tolerance, as is the case for rhGH regimens. The Egrifita Phase III clinical trials provide evidence that the proposed 2mg Egrifita dose, if appropriately labeled, is expected to provide a treatment regimen with a favorable risk/benefit profile.

8. Safety

Due to the considerable overlap in the physiology of GHRH and GH, the safety observations made during the Egrifita clinical program in HIV patients with lipodystrophy were expected to be consistent with those observed for rhGH products in adults. Indeed, most of the treatment-emergent adverse events that occurred more frequently with Egrifita relative to placebo were adverse reactions known to occur in association with rhGH therapy (e.g. arthralgia, extremity pain, headache, peripheral edema, paresthesia/hypoesthesia, musculoskeletal stiffness, myalgia, hyperglycemia, joint stiffness, and carpal tunnel syndrome). In addition, injection site reactions (few associated with systemic reactions such as urticaria) were observed or recorded, but none of the systemic adverse reactions required emergency therapy that went beyond the administration of antihistamines, albeit some of them resulted in trial discontinuation.

Dr. Mohamadi's detailed review and safety analysis indicates that there were no imbalances in SAEs between Egrifta and placebo and that the few deaths recorded were due to co-existing morbidities rather than to tesamorelin's known mechanism of action. A small imbalance in patient discontinuation due to adverse events was noted (9.6% Egrifta and 6.1% placebo) but most of these adverse events were attributable to adverse events seen typically with rhGH.

An important observation with potential safety implications was the fact that the 2 mg Egrifta dose resulted in an increase in serum IGF-1 concentrations that was above the upper limit of "normal" in a considerable proportion of patients: by 6 months, almost half of the patients treated with Egrifta had IGF-1 SD scores above the upper limit of normal and more than 1/3 had levels greater than +3 SD (female patients were much less affected). Although by 12 months the mean IGF-1 levels in completers seemed to decline, they still remained over 2 SD in 1/3 of all patients and over 3 SD in about 1/5 of patients. IGF-1 elevation has been a concern for the Division. In adult GHD patients rhGH aims at restoring levels of IGF-1 within the normal statistical range and no greater than + 2SD. The IGF-1 findings in the Egrifta program have been brought to the attention of the Endocrinologic and Metabolic Drugs Advisory Committee Meeting held in May, 2010. The company's outside IGF-1 consulting expert suggested that the higher IGF-1 levels reached with the 2 mg dose of Egrifta may be an overestimate of the real IGF-1 changes. This was based on the fact that the normative data from (b) (4) used for the calculation of IGF-1 SD scores in the clinical trials are derived from a reference population that is numerically smaller than that of the Egrifta program. When the same data were re-analyzed after a logarithmical transformation of the reference values to account for suboptimal distribution of the data, the percentage of patients with SDS scores > 2 and particularly > 3 dropped considerably. Regardless, it is prudent to proceed cautiously and avoid patient exposure to excessive IGF-1 levels particularly in those patients who do not show a good clinical response. The final Egrifta label will include a warning that recommends discontinuation of Egrifta in patients with persistent elevations of IGF-1 levels.

Although the clinical trials did not indicate any clinically meaningful increases in several measures of glucose metabolism (mean fasting blood glucose, fasting insulin, HOMA-IR and HbA1c), an analysis conducted by the statistical reviewer at the request of the clinical team indicated a slight increase in the risk of type 2 diabetes with Odds Ratio of 3.4 or 3.6 relative to placebo depending on whether baseline diabetes cases were excluded or not. Most of the patients who met the criteria of type 2 diabetes and discontinued Egrifta reverted to pre-diabetes glucose values. During the Extension Phase of the trials there were no convincing data to indicate further deterioration in the glucose status in patients who were continued on tesamorelin, while patients who were switched to placebo seemed to remain stable or slightly improve.

The potential immunogenicity of Egrifta was assessed with respect to the presence of anti-Egrifta and anti-endogenous GHRH antibodies, titers of such antibodies (and *in vitro* neutralizing effect), and potential effect on pharmacodynamic endpoints (VAT, serum IGF-1 concentrations). Although 50% of patients developed anti-tesamorelin antibodies at the end of 26-weeks, this percentage remained virtually the same if treatment continued up to 52-weeks or declined if discontinued. There was no evidence that the presence of anti-tesamorelin

antibodies had any clinical effect based on virtually identical reductions in VAT and IGF-1 in antibody-positive and antibody-negative patients. The testing scheme for neutralizing activity *in vitro* was not extremely informative (with very few serial measurements). However, comparisons of VAT and IGF-1 changes between patients with *in vitro* neutralizing antibodies vs. those without neutralizing antibodies, although more limited in size, did not raise a signal, suggesting that the *in vitro* positivity of the assay may not have any clinical relevance.

The information provided by the 4-month safety update did not change the safety conclusions.

9. Advisory Committee Meeting

A meeting of the Endocrinologic and Metabolic Drugs Advisory Committee was held on May 27, 2010 to discuss the Egrifta application. The Division brought to the attention of the committee members several issues that were seen at the time to be central to establishing an accurate understanding of the benefits and potential risks of Egrifta and their impact on the approvability of the drug. From a safety standpoint the discussion focused on the adverse events related to glucose metabolism, the immunogenicity findings, and the excessive IGF-1 elevations (in the context of a theoretical risk of malignancy). The efficacy discussion focused on the significance and limitations of VAT as an endpoint particularly in the context of missing cardiovascular outcome data. In the end, when asked whether the overall risk-benefit assessment of a 2mg daily Egrifta regimen supports its approval for the treatment of excess abdominal fat in HIV-infected patients with lipodystrophy, **the committee voted in favor of approval 16-0 with no abstention**. The committee viewed the risks posed by glucose metabolism changes and IGF-1 elevations as manageable via proper patient selection (avoiding treating patients at risk) and monitoring of glucose status and IGF-1 levels. Several committee members recommended that Egrifta should be discontinued if IGF-1 levels are excessive; with respect to glucose elevations, some favored treatment discontinuation while others recommended selective use of antihyperglycemic medications. The general sense was that the Egrifta clinical program has provided enough information that practitioners can use to make individualized therapeutic decisions. With respect to the lack of a link between VAT reduction and cardiovascular outcome, the committee members agreed that this should be further pursued postapproval, but there was no clear consensus as to which is the best way to accomplish it (for instance, whether to conduct an outcome or a no harm cardiovascular trial, or even if such trials are feasible given the size of the target population). Some members also recommended long-term study of the potential risk of carcinogenicity (via a registry, for instance) although the consensus was that such a risk is low.

10. Pediatrics

Theratechnologies was given a pediatric waiver for studying children <18 years of age because such children have open epiphyses and treatment with Egrifta is likely to accelerate linear growth and result in excessive height.

11. Other Relevant Regulatory Issues

11.1 Study conduct

The potential effect of financial compensation on the conduct of the study was analyzed by Dr. Mohamadi. His review indicates that two investigators acted as consultants and members of the Theratechnologies Scientific Advisory Board and enrolled patients in the Phase 3 trial. However, these investigators did not have access to the Phase 3 study results until after the data had been locked and unblinded. Importantly, the number of patients enrolled at their sites was relatively small and the efficacy results for the main endpoint (VAT reduction) were reviewed and found to be consistent with those of the overall study. According to Dr. Mohamadi's review the data quality and completeness were adequate to permit review and the studies were conducted in accordance with the principles of good clinical practice; they included an ethical review board and informed consent.

11.2 DSI

A clinical inspection was conducted at two clinical investigator sites and two Contract Research Organizations (CROs). There was no evidence of underreporting of adverse events at the clinical sites. With respect to CROs, the monitoring was found to be acceptable. The reviewer concludes that "although some regulatory violations were noted [...], these are considered isolated occurrences and are unlikely to importantly impact data integrity. The data are considered reliable in support of the NDA" (review archived in DARRTS, 1/12/2010).

11.3 Maternal Health Team Consult

A consultation was provided by the Maternal Health Team (MHT) regarding the "Pregnancy" and "Nursing Mothers" sections of the Egrifta label (archived in DARRTS, 9/20/2010). After reviewing the findings of the pharmacology/toxicology review and the proposed label, the MHT recommended a Pregnancy Category X and revisions to these sections of the label, which have all been incorporated.

12. Labeling

A consult from the Division of Medication Error Prevention and Analysis (DMEPA) has evaluated the packaging, container labels, carton and insert labeling submitted by the applicant (archived in DARRTS 3/5/2010). The consult echoes concerns raised by several other disciplines regarding the fact that the daily Egrifta dose is provided in two separate Egrifta vials, which increases the complexity of the resuspension and raises the risk of medication errors (see also the postmarketing recommendations made by the microbiology team). The consult also identifies a series of vulnerabilities of the proposed labeling that could contribute to medication errors and it makes specific corrective recommendations such as, for instance, improvement in the display of information on the container label and carton labeling for the Medication Box and the Injection Kit Box. These specific recommendations have been sent to

the sponsor and incorporated in the current version of the label. In a Proprietary Name Review consult archived in DARRTS on 5/6/2010 DMEPA indicates that the proposed name, Egrifta, is acceptable.

A consult from the Division of Risk Management (DRISK) has been archived in DARRTS (5/6/2010 and 9/15/2010). The consult makes significant recommendations for changes to both the Patient Product Information (PPI) and Instructions for Use (IFO) proposed by the applicant. These recommendations have been incorporated in the current PPI and IFO versions that are being negotiated with Theratechnologies.

DRISK has also provided comments with respect to applicant's proposed Risk Evaluation and Mitigation Strategy (REMS) for Egrifta which includes a Medication Guide, a communication plan (Dear Healthcare Provider Letter and Dear Pharmacist Letter), and a timetable for assessment. The DRISK consult points out, appropriately, there were no unique safety concerns associated with Egrifta and that most adverse events in the Egrifta Phase III clinical trials were mild to moderate in severity and were either injection site reactions or adverse events that are commonly reported with approved rhGH products. It concludes that a risk mitigation strategy is not warranted at this time. The consult recommends that the text submitted for the Medication Guide be used as a basis for a Patient Prescriber Information. DRISK finds acceptable the restricted distribution plan proposed by the applicant (the plan is not part of the REMS) aimed at curtailing the inappropriate use of Egrifta for unapproved indications. The consult is archived in DARRTS (9/16/2010).

This memorandum also acknowledges the Division of Drug Marketing, Advertising, and Communications (DDMAC) consult (in DARRTS 10/25/2010). The DDMAC suggestions were incorporated, where appropriate, in the label.

Labeling negotiations with Theratechnologies are in the final stages for the Prescriber Information, Patient Product Information and Instruction for Use labels. The label will recommend discontinuation of Egrifta treatment in patients who develop glucose intolerance and persistent excessive IGF-1 levels, particularly in patients who lack a robust efficacy response. The warnings and precautions section of the label will include information about the specific safety findings from the Egrifta program (injection site reactions, allergic reactions, glucose intolerance, IGF-1 elevations, immunogenicity) and an effort has been made to harmonize this section with that of rhGH labels, where appropriate.

13. Recommendations/Risk Benefit Assessment

13.1 Discussion and risk benefit assessment

The Egrifta Phase III program was successful in demonstrating that an Egrifta dose of 2 mg given daily to patients with HIV lipodystrophy and excess abdominal visceral fat reduces VAT by 12-20% relative to placebo. This dose regimen did not normalize VAT, but rather reduced it half-way between the markedly elevated baseline VAT values and a "threshold" VAT value that has been linked to increased cardiometabolic risk in non-HIV individuals. The evidence

submitted so far indicates that in order to maintain this effect Egrifta has to be given chronically since discontinuation of Egrifta treatment results in VAT returning to baseline levels.

The clear effect of Egrifta on VAT reduction was accompanied by smaller and less consistent effects in other endpoints of interest, such as triglycerides, non-HDL cholesterol, and patient-reported outcomes. The relatively small effect on triglycerides and non-HDL cholesterol should not be entirely surprising given the fact that Egrifta's mechanism of action involves stimulation of GH secretion and that the effect of rhGH on lipid metabolism in multiple clinical trials and across many patient population has not been dramatic and, oftentimes, not even consistent between different clinical trials. Similarly, the modest PRO results, when seen in the context of the degree of reduction in waist circumference should not be unexpected. With the exception of Belly Appearance Distress, all other PROs that were assessed as secondary endpoints measured primarily the patient's perception of his/her abdominal size, and the mean change in waist circumference of 1.5 cm cannot be expected to be associated with a major change in the visual perception of abdominal size. Belly Appearance Distress, on the other hand, does not measure abdominal dysmorphia *per se* but rather patient's emotional reaction to it and to the Egrifta-induced changes in abdominal size. In this respect, it is the most relevant PRO and a direct measure of clinical benefit for Egrifta.

The Egrifta Phase III clinical trials included a wide range of body composition endpoints. It should be noted that, although relegated as 'exploratory' in the hierarchy of endpoints evaluated in Phase III clinical trials, many of these endpoints are very relevant measurements of the pharmacodynamic effect of GHRH (or rhGH for that matter), and some of them are standard primary endpoints in rhGH registration trials. And although the trials were not specifically powered for demonstrating statistical differences relative to placebo, Egrifta treatment resulted in favorable changes in lean body mass, total fat mass, trunk fat mass which were not only statistically significant but also was consistent with many previous observations made with rhGH in registration trials of adult GH deficiency.

As an endpoint, VAT deserves additional comments for the reasons already referred to in this memorandum, but particularly because of the weight that it has in the assessment of efficacy of Egrifta. Although not a fully validated endpoint with respect to cardiovascular risk reduction (i.e. the direct evidentiary link of VAT reduction to a decline in cardiovascular morbidity and mortality is still missing), VAT is by no means an exploratory endpoint. VAT has been previously evaluated in other applications as a component of trunk fat (trunk fat itself being the sum of visceral and subcutaneous fat), and it is generally agreed that VAT elevations are associated with an increase in insulin resistance, a cardiovascular risk factor. In addition, as discussed in the introductory section of this memorandum, specific VAT 'thresholds' have been correlated with anthropometric indices (waist circumference and waist-to-hip ratio) and cardiovascular risk in non-HIV patients. In other related indications (e.g. adult GH deficiency) the excess of atherogenic abdominal visceral fat is recognized as an undesirable outcome and its reversal with rhGH supplementation a favorable intervention. Of interest, some HIV – infected patients with lipodystrophy also have a relative GHD. As already stated, as an endpoint, VAT has been previously evaluated by the Division in NDA 20-604 in which it was a primary efficacy endpoint for the Serostim HIV lipodystrophy program. VAT is also labeled

as a secondary endpoint for one of the rhGH products (Nutropin AQ) as (b) (4)

The argument can be raised that the potential cardiovascular benefit of VAT reduction may be negated by the increased risk of insulin resistance, in itself a cardiovascular risk factor. However, this should not be the case if glucose values are monitored and Egrifita discontinued in the face of developing insulin resistance (as instructed in fact by the current version of the Egrifita label). In this context it is worth mentioning that glucose values tend to normalize in a large number of patients upon discontinuation of Egrifita, and insulin sensitizers are available for those patients with persistent findings.

There were no safety issues that should preclude approval of Egrifita. Most of the safety observations that raised concerns by various reviewers (particularly the clinical review) and discussed at the Advisory Committee can be addressed through labeling. Particularly important is the inclusion of the recommendations that glucose and IGF-1 levels should be monitored in the course of Egrifita treatment. With knowledge of this information, practitioners will be able to make informed decisions regarding whether to continue or discontinue Egrifita treatment in individual cases. Additional side effects are, in general similar to those known for approved growth hormone products and to those documented in patients with acromegaly.

13.2 Recommendation

Given that Egrifita has resulted in consistent and statistically significant reductions in visceral adipose fat, along with other favorable changes in body composition comparable overall to those observed with other approved products, while demonstrating at the same time a direct clinical benefit via improvements in patient reported outcomes (particularly Belly Appearance Distress), Egrifita should be approved for the new indication of reduction of excess abdominal fat in patients with HIV-infected patients with lipodystrophy. This recommendation, which is in agreement with that made by the May 27, 2010, Endocrinologic and Metabolic Drugs Advisory Committee, takes into consideration the fact that there are no approved therapies for this indication in the intended patient population and that a cardiovascular outcome study is not feasible due to the limited prevalence of HIV lipodystrophy with associated excess abdominal fat. However, this recommendation should not be seen as an endorsement of VAT in patient populations with high prevalence (e.g. obese patients) wherein a direct link to reduction of cardiovascular risk can be evaluated.

13.3 Recommend for Postmarketing Risk Evaluation and Management Strategies Postmarketing

I agree with the DRISK consult that a REMS is not indicated at this time.

Since Egrifita has the potential for abuse for its anabolic activities just like rhGH and rhIGF-1, the restricted distribution plan proposed by Theratechnologies is a welcome step in an attempt to prevent inappropriate use.

Applicant's proposal for a post marketing "safety observation study" whose purpose is to monitor targeted adverse events (e.g. cancer, hypersensitivity, diabetic retinopathy), glucose status (i.e. fasting blood glucose, hemoglobin A1c), serum IGF-1 levels, adherence to antiretroviral therapy, major acute cardiac events (MACE), among others, is also acknowledged.

13.4 Recommend for Postmarketing Requirements and Commitments

I fully agree with the recommendation made by the microbiology reviewer for a postmarketing requirement from Theratechnologies to develop a single vial formulation for the daily 2 mg dose of Egrifta. This issue has been raised by multiple disciplines at different stages of the review process. Although there is no evidence from the data presented in the Phase III studies that the current formulation raised the risk of medication errors in the controlled setting of a clinical trial, this small theoretical risk of medication errors can be entirely avoided with the reformulation of the 2 mg daily Egrifta dose in a single-dose vial. The timeline suggested by the microbiology reviewer for a proposed plan is also acceptable. This recommendation should be included in the Action Letter, should the drug be approved.

I also agree with applicant's plan to formally evaluate in the postmarketing setting the aforementioned targeted adverse events (cancer, hypersensitivity, and diabetic retinopathy) along with glucose status, MACE, and IGF-1 levels. Multidisciplinary discussions are ongoing regarding what would be the most appropriate study design that could achieve this objective given the prevalence of HIV- associated lipodystrophy.

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/s/

DRAGOS G ROMAN
11/01/2010

MARY H PARKS
11/02/2010