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*APPLICATION NUMBER:*

**22-393**

**MEDICAL REVIEW(S)**

## CLINICAL REVIEW

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Reviewer Name Qin Ryan, MD, PhD  
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Established Name Romidepsin  
(Proposed) Trade Name Istodax  
Therapeutic Class Histone deacetylase inhibitor  
Applicant Gloucester

Priority Designation S

Formulation IV  
Dosing Regimen 14 mg/m<sup>2</sup> weekly x3/4 weeks  
Indication Second line treatment for CTCL  
Intended Population Received prior treatment

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## 1 Recommendations/Risk Benefit Assessment

### 1.1 Recommendation on Regulatory Action

This reviewer recommends Istodax (romidepsin) administered at 14 mg/m<sup>2</sup> intravenously (IV) over a 4-hour period on days 1, 8 and 15 of a 28-day cycle for treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy.

### 1.2 Risk Benefit Analysis

The risk benefit analysis to support this recommendation was based on the efficacy and safety results of two multicenter, single arm clinical trials, GPI-04-0001, (GPI Study) and NCI1312, (NCI Study) in patients with CTCL. Overall, 167 patients with CTCL were treated in the US, Europe, and Australia. The GPI Study included 96 patients with confirmed CTCL after failure of at least 1 prior systemic therapy. The NCI Study included 71 patients with a primary diagnosis of CTCL who received at least 2 prior skin directed therapies or one or more systemic therapies. Patients were treated with Romidepsin at a 14 mg/m<sup>2</sup> infused over 4 hours on days 1, 8, and 15 every 28 days. In both studies, patients could be treated until disease progression at the discretion of the investigator and local regulators. Objective disease response was evaluated according to a composite endpoint that included assessments of skin involvement, lymph node and visceral involvement, and abnormal circulating T-cells (“Sézary cells.”).

The primary efficacy endpoint for both studies was overall objective disease response rate (ORR) based on the investigator assessments, and defined as the proportion of patients with confirmed complete response (CR) or partial response (PR). CR was defined as no evidence of disease and PR as  $\geq 50\%$  improvement in disease. Secondary endpoints in both studies included duration of response and time to response. The ORR was 34% in the GPI Study and 35% in the NCI Study. The response rates in these two studies are similar and CR rates were the same (6%), despite the use of different response criteria. The median duration of response was 15 months in the GPI Study and 11 months in the NCI Study. Median time to first response was 2 months (range 1 to 6) in both studies. Median time to CR was 6 months in Study 1 and 4 months in Study 2 (range 2 to 9).

The safety of romidepsin was evaluated in the 185 patients on the two CTCL single arm clinical trials included in the safety update. The mean duration of treatment in these studies was 5.6 months (range: <1 to 83.4 months). Due to methodological differences between the studies, the most common adverse reactions in the GPI Study were nausea, fatigue, infections, vomiting, and anorexia, and in the NCI Study were nausea, fatigue, anemia, thrombocytopenia, ECG T-wave changes, neutropenia, and lymphopenia. Serious adverse reactions reported in > 2% of patients in the GPI Study were infection, sepsis, and pyrexia. In the NCI Study, serious adverse reactions in > 2% of patients were infection, supraventricular arrhythmia, neutropenia, fatigue, edema, central line infection, ventricular arrhythmia, nausea, pyrexia, leukopenia, and

thrombocytopenia. Most deaths were due to disease progression. In the GPI Study, there were two deaths due to cardiopulmonary failure and one due to acute renal failure. In the NCI Study, there were six deaths due to infection (4), myocardial ischemia (1), and acute respiratory distress syndrome (1). Discontinuation due to an adverse event occurred in 21% of patients in the GPI Study and 11% in the NCI Study. Causes of discontinuation occurring in at least 2% of patients in either study included infection, fatigue, QT prolongation, and dyspnea.

The romidepsin specific safety issues which should be monitored and managed appropriately during treatment are as follows.

- a. *Monitoring Laboratory Tests:* Due to the risk of QT prolongation, potassium and magnesium should be within the normal range before administration of romidepsin.
- b. *Hematologic parameters:* Treatment with romidepsin can cause thrombocytopenia, leukopenia (neutropenia and lymphopenia), and anemia; therefore, these hematological parameters should be monitored during treatment with romidepsin, and a single dose modification to 10 mg/m<sup>2</sup> may be necessary.
- c. *Electrocardiographic Changes:* Several treatment-emergent morphological changes in ECGs (including T wave and ST-segment changes) have been reported in clinical studies. The clinical significance of these changes is unknown. In patients with congenital long QT syndrome, patients with a history of significant cardiovascular disease, and patients taking medicines that lead to significant QT prolongation, appropriate cardiovascular monitoring, such as the monitoring of electrolytes and ECGs at baseline and periodically during treatment, should be considered.
- d. *Use in Pregnancy:* There are no adequate and well-controlled studies of romidepsin in pregnant women. However, based on its mechanism of action, romidepsin may cause fetal harm when administered to a pregnant woman. A study in rats did not expose pregnant animals to enough romidepsin to fully evaluate adverse outcomes. If this drug is used during pregnancy, or if the patient becomes pregnant while taking romidepsin, the patient should be apprised of the potential hazard to the fetus.
- e. *Use in Women of Childbearing Potential:* Advise women of childbearing potential that romidepsin may reduce the effectiveness of estrogen-containing contraceptives. An in vitro binding assay determined that romidepsin competes with  $\beta$ -estradiol for binding to estrogen receptors.

Additional safety data from other studies in patients with other malignancies were reviewed in support of the safety data from the two single arm studies.

The romidepsin efficacy and safety results were presented to the Oncology Drug Advisory Committee (ODAC) on September 2, 2009. The ODAC concluded that the results of the two romidepsin single arm studies represented a favorable risk-benefit profile for patients with previously treated CTCL.

Therefore, this reviewer believes that the clinical efficacy and safety data provided in NDA 22-393 provides a favorable risk/benefit ratio and justifies the approval of romidepsin for treatment of cutaneous T-cell lymphoma in patients who have received at least one prior systemic therapy.

### 1.3 Recommendations for Risk Evaluation and Mitigation Strategies

None

### 1.4 Recommendations on Post Marketing Activities/Phase 4 Commitments

The FDA requested the applicant to complete the following post marketing pharmacotoxicology studies and clinical pharmacology trials because an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a known serious risk of increased toxicity from hepatic impairment, to identify an unexpected risk of toxicity from a \_\_\_\_\_, and to assess a signal for a serious risk of embryo-fetal toxicity, estrogenic/anti-estrogenic effects, Q-T prolongation and drug-drug interaction with romidepsin.

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i. Conduct a GLP embryo-fetal developmental reproductive toxicology study in rats to assess the embryo-fetal toxicity of romidepsin.

ii. Conduct an animal study(ies) to determine the estrogenic/ anti-estrogenic effects of romidepsin.

iii. Conduct a GLP toxicology study in an appropriate animal species to characterize the toxicity profile of \_\_\_\_\_

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iv. Conduct an in vitro induction study using cryopreserved human hepatocytes to evaluate the effects of romidepsin on the 3 inducible forms of cytochrome P450 (CYP1A2, CYP3B6 and CYP3A4).

v. Conduct a drug interaction clinical trial with the a CYP3A4 inhibitor, ketoconazole, in patients with advanced cancer.

vi. Conduct a drug interaction clinical trial with a CYP3A4 inducer, rifampin, in patients with advanced cancer.

vii. Conduct a clinical trial to determine the pharmacokinetics of romidepsin in advanced cancer patients with moderate and severe hepatic impairment.

vii. Gloucester will determine the potential of ISTODAX to prolong QT through using an expanded dataset of ECG matched PK data from Study the trial GPI-06-0005. Exposure-response, central tendency and outlier analyses will be included in the evaluation.

## 2 Introduction and Regulatory Background

### 2.1 Product Information

**Drug Established Name:** Romidepsin

**Proposed Trade Name:** Istodax

**Drug Class:** Histone deacetylase inhibitor

**Applicant:**

Gloucester Pharmaceuticals Inc.  
One Broadway, 14th floor  
Cambridge, MA  
02142

**Proposed Indication:**

Romidepsin is indicated for treatment of cutaneous T-cell lymphoma (CTCL), including relief of pruritus, in patients who have received at least one prior systemic therapy.

**Proposed Dose and Schedule:**

Romidepsin is administered at 14 mg/m<sup>2</sup> intravenously (IV) over a 4-hour period on days 1, 8 and 15 of a 28-day cycle. Cycles should be repeated every 28 days provided that the patient continues to benefit from and tolerate the drug. If a patient is intolerant to therapy, dose reduction to 10 mg/m<sup>2</sup> and further to 8 mg/m<sup>2</sup> can be considered.

### 2.2 Tables of Currently Available Treatments for Proposed Indications

The CTCL is an indolent malignancy. The table below summarized the prognosis of patients with CTCL.

**Table 1: CTCL prognosis**

<b>Survival Rate (%) of:</b>	<b>IA</b>	<b>IB</b>	<b>IIA</b>	<b>IIB</b>	<b>III</b>	<b>IVA</b>	<b>IVB</b>
5-year disease-specific survival	100	96	68	80	-	40	0
10-year disease-specific survival	97-98	83	68	42	-	20	0
5-year survival	96-100	73 - 86	49 - 73	40 - 65	40 - 57	15 - 40	0 - 15
10-year survival	84 - 100	58-67	45-49	20-39	20-40	5-20	0-5

Presently, there is no curative treatment for CTCL. Early stage disease with limited skin involvement is generally treated with skin-directed therapies and/or photopheresis. Treatment of advanced stage disease may also include skin directed therapy as well as some form of systemic therapy. The systemic therapies include immunomodulators, single- or combination-agent

chemotherapy, or combined modality therapies. Several systemic medications have been approved for use in cutaneous T cell lymphoma, as summarized in the table below.

**Table 2: Recently approved systemic therapy agents for CTCL**

Agent	Class	Indication	Evidence Supported Approval
Zolinza (vorinostat)	HDAC inhibitor	For treatment of cutaneous manifestations in patients with CTCL who have progressive, persistent or recurrent disease on or following 2 systemic therapies. Approved October 6, 2006.	Two single arm studies, one had 30% ORR (N=74), with 1 CR; the other had 24% ORR (N=33)
Ontak (denileukin diftitox)	Fusion protein	For treatment of patients with persistent or recurrent CTCL whose malignant cells express the CD25 component of the IL-2 receptors. Approved February 1999.	Two small randomized studies: The pivotal study had ORRs of 46% (p=0.002) vs. 37% (p=0.03) vs. 15% (N = 144, 55 received 18 mg/kg/day ontak, 45 received 9 mg/kg/day Ontak and 44 received placebo). The dose defining study had ORRs of 23% vs. 36%, with 9% and 11% CRs, respectively (N=71, 35 received 9 mg/kg/day and 36 received 18 mg/kg/day)
Targretin (bexarotene)	Retinoid X-receptor activator	Treatment of cutaneous manifestations of CTCL in patients who are refractory to at least 1 prior systemic therapy. Approved December 29, 1999.	Two single arm studies enrolled total of 152 patients. At 300 mg/m <sup>2</sup> /day dose, the ORR was 30% and CR was 1.6% (N= 62)

The most recent approval is Vorinostat. Vorinostat, like romidepsin, is a histone deacetylase inhibitor. It was approved in 2006 on the basis of 2 single arm studies. The response rates and durations of response are shown above. Denileukin diftitox or Ontak was given accelerated approval in 1999 based on a dose dependent response rate. Recently, it received regular approval based on a dose dependent improvement in PFS. Bexarotene received regular approval in 1999 based on 2 single arm studies. Not shown in the table, both Methotrexate and Methoxsalen were also approved for the treatment of CTCL. In addition to these medications, a large number of chemotherapeutic agents, including alpha interferon have been used singly and in combination to treat CTCL.

### 2.3 Availability of Proposed Active Ingredient in the United States

The proposed drug, presently, is not marketed in US.

### 2.4 Important Safety Issues with Consideration to Related Drugs

The cardiac toxicity has been a concern in the class of drugs that inhibit histone deacetylases.

### 2.5 Summary of Presubmission Regulatory Activity Related to Submission

Major regulatory interactions between the applicant and the FDA began in 1996 and have resulted in 2 INDs. By the end of 2005, three end of phase 2 meetings had been held with the applicant to discuss the GPI study, which was submitted for a Special Protocol Assessment in

August 2004. Three pre-NDA meetings took place from 2007 to 2008 and the NDA was submitted to the FDA this past January, as shown in the table below.

**Table 3: NDA submission related regulatory activities.**

Date	Activity	Description
1996	IND 51,810	The clinical development of romidepsin was initiated by the Cancer Therapy Evaluation Program (CTEP) of the U.S. NCI under the auspices of a Cooperative Research and Development Agreement (CRADA) with Fujisawa Pharmaceutical Co, Ltd. (now Astellas Pharma Inc). The supportive study, NCI 1312, was conducted under the IND 51,810.
4/30/2002	IND 63,573	Astellas Pharma furthered development of romidepsin in the US under a new IND 63,573, which was subsequently transferred to Gloucester Pharmaceuticals. The pivotal study, GPI-04-0001, was conducted under this IND.
02/24/2004	EOP1 meeting	Astellas and FDA held a discussion about the cardiac monitoring plan.
04/15/2004	Licensure	Gloucester Pharmaceuticals, Inc. acquired the license to develop romidepsin from Astellas Pharma and IND 63573 sponsorship transferred to Gloucester Pharmaceuticals, Inc.
8/5/2004	EOP2 meeting	FDA and the applicant discussed the sample size necessary to demonstrate clinical benefit and safety. FDA expressed concern about the difference in population between the proposed single arm study and the on going NCI study and invited the applicant to submit their proposed study for a special protocol review (SPA).
9/29/2004	Fast track designation	Fast track designation of romidepsin for CTCL treatment was granted to Gloucester's September 7, 2004 application.
10/25/2004	SPA	FDA completed SPA review of study GPI-04-0001 in CTCL. Considering that limited number of patients with refractory CTCL, FDA agreed with the single arm study design, but pointed out that the primary endpoint, clinical benefit rate (CR+PR+SD), was not acceptable. FDA recommended that the rate of objective response should be used as the primary analysis with support from a meaningful response duration. The Agency also stated that the study patient population should focus on advanced CTCL patients and in order to demonstrate clinical benefit and safety, the sample size should be no less than 100 patients. The applicant amended the study's primary endpoint to overall response (ORR=CR+PR).
7/13/2005	EOP2 meeting	To discuss development for CTCL . <del>_____</del>
12/1/2005	EOP2 meeting	To further discuss concerns about the heterogeneity of the CTCL patient population and endpoints of studies GPI-04-0001 and NCI 1312.
5/30/2007	pre-NDA meeting	CMC issues were addressed.
9/10/2007	pre-NDA meeting	To discuss the efficacy and safety data that might constitute an NDA application for the CTCL indication. It was agreed that the efficacy sample size for the NDA would be at least 100 evaluable patients in the GPI-04-0001 and NCI 1312 studies combined, provided that NCI Study 1312 is found acceptable as a supportive study. The primary efficacy analyses in both studies were to be investigator-assessed response and the IRC assessments were to be used as a secondary analysis. A clinical plan for QTc evaluation was to be submitted for interdisciplinary review.
5/7/2008	pre-NDA meeting	FDA concurred that safety and efficacy results from Study GPI-04-0001 and NCI Study 1312 were likely adequate for review and recommended that the applicant capture more mature response data for analysis of response duration.
1/12/09	NDA submission	The NDA was submitted to support the indication; treatment of CTCL patients who had received at least one prior systemic therapy.

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## 2.6 Pediatric Waiver

Orphan status was granted to romidepsin development under CFR316, subpart C. Therefore, no pediatric waiver request will be required according to CFR316 (d) Exemption for orphan drugs.

## 3 Ethics and Good Clinical Practices

### 3.1 Submission Quality and Integrity

NDA 22-393 was an electronic submission filed in the FDA electronic Document Room at \\CDSESUB1\EVSPROD\NDA022393. The entire NDA and relevant regulatory history were reviewed. Since the efficacy data included two single arm studies, an ODAC meeting was held to discuss the impact of single arm studies in the CTCL field.

As the NDA 22393 review progressed, the applicant submitted NDA amendments, some of them in response to FDA information requests (IR), as listed in the table below.

**Table 4: NDA 22334 submission and amendments, pre-specified and requested**

Submission Dates	Submitted Items
1-12-09	Original NDA submission
2-4-09	Resubmitting the Request for Proprietary Name Review per FDA regulatory IR
2-11-09	Applicant information update per FDA regulatory IR
2-18-09	Labeling update
3-4-09	Clinical site and patient information for studies GPI-04-0001 and NCI-1312
4-9-09	PK data update per NDA filling and IR from clinical pharmacology
5-7-09	SAS programs per FDA statistical reviewer request
5-15-09	4 month safety update
6-5-09	Clarification of patients enrolled and treated in study NCI 1312
7-29-09	Clarification of algorithm for duration of response per investigator assessment
7-30-09	Per clinical reviewer request, case report forms of patients who died or discontinued from study NCI 1312 were submitted.
7-31-09	Information concerning the statistical analyses information
8-3-09	Justification of acceptance criterion for _____ levels in drug product and the amount of _____ administered to patients in clinical trials.
8-20-09	Safety update datasets
8-26-09	CMC: characterization data for romidepsin isoforms
8-31-09	Clinical Pharmacology information on clinical adverse events for PI
9-17-09	Label revision
10-2-09	List of batch ID used in GPI and NCI studies. List of batches that each NCI study patient received.
10-14-09	Explanation of cardiac and hepatic assessment data
10-15-09	Response on _____ safety issue

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Source: NDA22393 submissions

Two single arm studies, GPI-04-0001 and NCI 1312, were submitted to support the approval of Romidepsin for second line treatment in patients with advanced CTCL. The following sites were identified as essential to evaluate the study quality and integrity (Table below). The basis of the selection was the number of enrollments, responses, severe AEs, deaths and protocol violations. As discussed with the Division of Scientific Investigation (DSI), Dr. John Lee, the Australian site for study NCI 1312 had been inspected for a different CTCL study 6 months before this request and was generally in order. Therefore, inspection was conducted for sites 02, 48, NCI intramural and CA043. In addition, DSI also inspected the applicant's central operation for this study at One Broadway, Cambridge, MA. The DSI inspection results are also included in the following table.

The DSI consultants conducted 5 inspections (4 clinical sites and applicant) between April 27, 2009 and June 19, 2009 in support of NDA 22-393. No major deficiencies were observed at the five inspections. The minor deficiencies were apparently isolated, did not suggest bias in study conduct, and were not expected to have important effects on data integrity. The data generated from the four clinical sites as reported by the sponsor under NDA 22-393 are considered acceptable in support of the proposed indication.

Clinical Review  
 Qin Ryan, MD, PhD  
 NDA 22393  
 Istodax (romidepsin, depsipeptide, FK-228)

**Table 5: Summary of clinical scientific inspection**

Study ID	Site number	Investigator and affiliation	Number of patients enrolled	Number of CR or PR	Number of deaths	Number of SAEs	Number of major protocol violations	DSI Inspection Date	Classification	
GPI-04-0001	02	Dr. Sean Whittaker St John's Institute of Dermatology, St. Thomas' Hospital Lambeth Palace Road, London SE1 7EH, UK	12	3	1	3	3	6/15-6/18/09	VAI	
GPI-04-0001	48	Dr. Adam Lerner Boston Medical Center, Center for Cancer and Blood Disorders 732 Harrison Avenue, Boston, MA 02118, USA	6	4	0	1	1	5/5-5/13/09	NAI	
NCI1312	NCI intramural study center	Bates, Susan, MD (Principal and Coordinating Investigator) Piekarz, Richard, MD, PhD (Protocol Chairman) National Cancer Institute 9000 Rockville Pike, Bethesda, MD 20892	39	11	2	23	5	4/27-5/18/09	NAI	
NCI1312	NCI extramural study center	Peter MacCullum Cancer Centre Centre for Blood Cell Therapies, St. Andrew's Place, East Melbourne, Victoria, Australia	15	7	1	8	0	n/a	Passed	
NCI1312	CA043	Dr Mark Kirschbaum / City of Hope National Cancer Center, Duarte, CA	5	4	2	3	1	6/16-6/19/09	VAI	
Gloucester Pharmaceuticals	Central operation	One Broadway, Cambridge, MA	the Sponsor/Monitor/Contract Research Organization compliance program							NAI

**Key to Classifications**

NAI = No deviation from regulations;  
 VAI = Deviation(s) from regulations;  
 OAI = Significant deviations from regulations. Data are unreliable;  
 Pending = Preliminary classification based on information in site inspection or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending;  
 Passed = recently inspected and classified as NAI or VAI.  
 Abbreviations: CR=complete response; PR=partial response; ORR=overall response rate (%); SAE=serious adverse event  
 Source: Studies GPI-04-001 and NCI 1312 Clinical Database

### 3.2 Compliance with Good Clinical Practices

The applicant stated that the studies were conducted in compliance with Good Clinical Practice, including the archiving of essential documents.

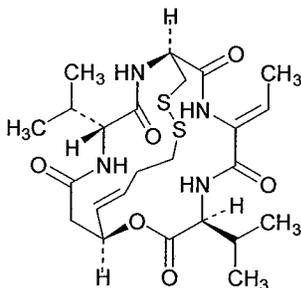
### 3.3 Financial Disclosures

The applicant provided spreadsheets detailing all the clinical investigators participating in studies GPI-04-0001 and NCI 1312 (at US and non-US sites). The disclosure information was tabulated by center, principal investigator, study facility and address. There were no investigators participating in either study who disclosed a conflict of interest.

## 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

### 4.1 Chemistry Manufacturing and Controls

For details please see CMC review. Briefly, romidepsin, a histone deacetylase (HDAC) inhibitor, is a bicyclic depsipeptide. At room temperature, romidepsin is a white powder and is described chemically as (1S,4S,7Z,10S,16E,21R)-7-ethylidene-4,21-bis(1-methylethyl)-2-oxa-12,13-dithia-5,8,20,23-tetraazabicyclo[8.7.6]tricos-16-ene-3,6,9,19,22-pentone. The empirical formula is C<sub>24</sub>H<sub>36</sub>N<sub>4</sub>O<sub>6</sub>S<sub>2</sub>. The molecular weight is 540.71 and the structural formula is:



Romidepsin for injection is intended for intravenous infusion only after reconstitution with the supplied diluent and after further dilution with 0.9% Sodium Chloride, USP.

### 4.2 Clinical Microbiology

For details please see CMC and clinical microbiology review. Briefly, romidepsin for injection is a sterile lyophilized white powder and is supplied in a single-use vial containing

10 mg romidepsin and 20 mg povidone, USP. Diluent for romidepsin is a sterile clear solution and is supplied in a single-use vial containing a 2-mL deliverable volume. Diluent for romidepsin contains 80% (v/v) propylene glycol, USP and 20% (v/v) dehydrated alcohol, USP.

### 4.3 Preclinical Pharmacology/Toxicology

#### 4.3.1 Carcinogenesis and Mutagenesis

For details please see Pharmacology/Toxicology review. Briefly, carcinogenicity studies have not been performed with romidepsin. Romidepsin was not mutagenic in vitro in the bacterial reverse mutation assay (Ames test) or the mouse lymphoma assay. Romidepsin was not clastogenic in an in vivo rat bone marrow micronucleus assay when tested to the maximum tolerated dose (MTD) of 1 mg/kg in males and 3 mg/kg in females (6 and 18 mg/m<sup>2</sup> in males and females, respectively). These doses were up to 1.3-fold the recommended human dose, based on body surface area.

#### 4.3.2 Impairment of Fertility

Based on non-clinical findings, male and female fertility may be compromised by treatment with romidepsin. In a 26-week toxicology study, romidepsin administration resulted in testicular degeneration in rats at 0.33 mg/kg/dose (2 mg/m<sup>2</sup>/dose) following the clinical dosing schedule. This dose resulted in AUC<sub>0-inf.</sub> values that were approximately 2% the exposure level in patients receiving the recommended dose of 14 mg/m<sup>2</sup>/dose. A similar effect was seen in mice after 4 weeks of drug administration at higher doses. Seminal vesicle and prostate organ weights were decreased in a separate study in rats after 4 weeks of daily drug administration at 0.1 mg/kg/day (0.6 mg/m<sup>2</sup>/day), approximately 30% the estimated human daily dose based on body surface area. Romidepsin showed high affinity for binding to estrogen receptors in pharmacology studies. In a 26-week toxicology study in rats, atrophy was seen in the ovary, uterus, vagina and mammary gland of females administered doses as low as 0.1 mg/kg/dose (0.6 mg/m<sup>2</sup>/dose) following the clinical dosing schedule. This dose resulted in AUC<sub>0-inf.</sub> values that were 0.3% of those in patients receiving the recommended dose of 14 mg/m<sup>2</sup>/dose. Maturation arrest of ovarian follicles and decreased weight of ovaries were observed in a separate study in rats after four weeks of daily drug administration at 0.1 mg/kg/day (0.6 mg/m<sup>2</sup>/day). This dose is approximately 30% the estimated human daily dose based on body surface area.

### 4.4 Clinical Pharmacology

For details please see Clinical Pharmacology review.

#### 4.4.1 Mechanism of Action

Romidepsin is a histone deacetylase (HDAC) inhibitor. HDACs catalyze the removal of acetyl groups from acetylated lysine residues in histones, resulting in the modulation of gene expression. HDACs also deacetylate non-histone proteins, such as transcription factors. In vitro, romidepsin causes the accumulation of acetylated histones, and induces cell cycle arrest and apoptosis of some cancer cell lines with IC50 values in the nanomolar range. The mechanism of the antineoplastic effect of romidepsin observed in nonclinical and clinical studies has not been fully characterized.

#### 4.4.2 Pharmacodynamics

##### *Effect of Age, Gender or Race*

The population pharmacokinetic analysis of romidepsin showed that age, gender, or race (white vs. black) did not appear to influence the pharmacokinetics of romidepsin.

##### *Effect of Hepatic Impairment*

No dedicated hepatic impairment study has been conducted for romidepsin. The population pharmacokinetic analysis indicates that mild hepatic impairment [total bilirubin (TB)  $\leq$  upper limit of normal (ULN) and aspartate aminotransferase (AST)  $>$  ULN; or TB  $>$  1.0x - 1.5x ULN and any AST] and moderate hepatic impairment (TB  $>$  1.5x - 3x ULN and any AST) had no significant influence on romidepsin pharmacokinetics. As the effect of severe (TB  $>$  3x ULN and any AST) hepatic impairment on the pharmacokinetics of romidepsin is unknown, patients with severe hepatic impairment should be treated with caution.

##### *Effect of Renal Impairment*

No dedicated renal impairment study has been conducted for romidepsin. The population pharmacokinetic analysis showed that romidepsin pharmacokinetics were not affected by mild (estimated creatinine clearance 50 - 80 mL/min), moderate (estimated creatinine clearance 30 - 50 mL/min), or severe (estimated creatinine clearance  $<$  30 mL/min) renal impairment. Nonetheless, the effect of end-stage renal disease on romidepsin pharmacokinetics has not been studied. Thus, patients with end-stage renal disease should be treated with caution.

#### 4.4.3 Pharmacokinetics

##### *Absorption*

Romidepsin exhibited linear pharmacokinetics across doses ranging from 1.0 to 24.9 mg/m<sup>2</sup> when administered intravenously over 4 hours in patients with advanced cancers. In patients with T cell lymphomas who received 14 mg/m<sup>2</sup> of romidepsin intravenously over a 4-hour period on days 1, 8 and 15 of a 28-day cycle, geometric mean values of the maximum plasma concentration (C<sub>max</sub>) and the area under the plasma concentration versus time curve (AUC<sub>0-inf</sub>) were 377 ng/mL and 1549 ng\*hr/mL, respectively.

##### *Distribution*

Romidepsin is highly protein bound in plasma (92% to 94%) over the concentration range of 50 ng/mL to 1000 ng/mL with  $\alpha$ 1-acid-glycoprotein (AAG) being the principal binding protein.

#### *Metabolism*

Romidepsin undergoes extensive metabolism in vitro primarily by CYP3A4 with minor contribution from CYP3A5, CYP1A1, CYP2B6, and CYP2C19. At therapeutic concentrations, romidepsin did not competitively inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4 in vitro.

#### *Excretion*

Following 4-hour intravenous administration of romidepsin at 14 mg/m<sup>2</sup> on days 1, 8 and 15 of a 28-day cycle in patients with T cell lymphomas, the terminal half-life (t<sub>1/2</sub>) was approximately 3 hours. No accumulation of plasma concentration of romidepsin was observed after repeated dosing.

## 4.5 Tables of Clinical Studies

The studies supporting efficacy, PK and major safety for the proposed indication are summarized in the table below.

**Table 6: Primary studies supporting the efficacy, PK, and major safety**

Study ID	Title	enrollments	Support
GPI-04-0001	A Single Agent Phase II Study of Depsipeptide (FK228) in the Treatment of Cutaneous T Cell Lymphoma (CTCL)	96	Efficacy and Safety
NCI1312	Phase II Trial of Depsipeptide in Patients with Cutaneous T-cell Lymphoma and Relapsed Peripheral T-cell Lymphoma	71	Efficacy, Safety and PK

Source: NDA 22393.

Beside these two CTCL studies, the results of 32 additional studies reported in this NDA, as summarized in the following table, support the safety of romidepsin.

Clinical Review  
 Qin Ryan, MD, PhD  
 NDA 22393  
 Istodax (romidepsin, depsipeptide, FK-228)

**Table 7: Studies supporting safety**

Disease/Study ID	Applicant Studies / patient no.		NCI Studies / patient no.		All
	Phase 2	Phase 1	Phase 2	Phase 1	Total
<b>CTCL</b>					
GPI-04-0001	96	-	-	-	96
NCI 1312	-	-	71	-	71
Total	-	-	-	-	<b>167</b>
<b>PTCL</b>					
GPI-06-002	12	-	-	-	12
NCI-1312	-	-	39	-	39
Total	-	-	-	-	<b>51</b>
<b>Hematologic Malignancies</b>					
NCI 1751	-	-	-	13	13
NCI 27	-	-	-	21	21
NCI 5563	-	-	-	2	2
NCI 5961	-	-	-	2	2
NCI 5965	-	-	-	21	21
NCI 5996	-	-	-	13	13
NCI 6051	-	-	-	2	2
NCI 7869	-	-	-	6	6
Total	-	-	-	-	<b>80</b>
<b>Solid Tumors</b>					
GPI-06-0003	-	29	-	-	29
GPI-06-0005	-	6	-	-	6
FJ-228-001	29	-	-	-	29
FJ-228-0002	35	-	-	-	35
FJ-228-0007	2	-	-	-	2
T95-0022	-	-	-	33	33
T-95-0077	-	-	-	48	48
NCI 1053	-	-	19	-	19
NCI 5270	-	-	-	33	33
NCI 5483	-	-	-	26	26
NCI 5987	-	-	-	5	5
NCI 6319	-	-	40	-	40
NCI 6321	-	-	3	-	3
NCI 6325	-	-	15	-	15
NCI 6335	-	-	12	-	12
NCI 6338	-	-	20	-	20
NCI 6351	-	-	2	-	2
NCI ADVL0212	-	-	-	26	26
NCI CALGB-30304	-	-	16	-	16
NCI E1603	-	-	4	-	4
NCI NABTC-03-03	-	-	50	-	50
NCI S0336	-	-	28	-	28
NCI S0400	-	-	6	-	6
Total	-	-	-	-	<b>487</b>
<b>Overall Total</b>	<b>174</b>	<b>35</b>	<b>369</b>	<b>207</b>	<b>785</b>

Source: NDA 22393

## **4.6 Review Strategy**

This clinical review primarily focused on the efficacy and safety of romidepsin in CTCL patients in the two single arm studies, GPI-04-0001 and NCI 1312. The other 32 studies included 579 patients with other malignancies and 39 PTCL patients from the NCI study 1312 for a total of 618 patients. These were also reviewed as support for the safety of romidepsin. The final safety analyses used data from the 120-day safety update, which included 185 CTCL patients and 685 patients with non-CTCL malignancies.

The key review materials and activities are outlined below:

- Electronic submission of the NDA;
- Relevant published literature;
- Relevant submissions in response to medical officer's questions;
- Sponsor presentation slides; and
- Major efficacy and safety analyses reproduced or audited using the SAS datasets.

## **4.7 Discussion of Individual Studies**

The protocols of study GPI-04-0001 and NCI 1312 were reviewed in parallel, since the efficacy and safety data of the two studies were presented together in the proposed label to support the claim.

**Table 8: Summary of studies GPI-04-0001 and NCI1312 protocol and status**

Protocol Contents		Study ID
		<b>GPI-04-0001</b>
Title	A Single Agent Phase II Study of Depsipeptide (FK228) in the Treatment of Cutaneous T Cell Lymphoma (CTCL)	
Reviewer Discussion:	GPI-04-0001 is the primary study and NCI 1312 is the supportive study.	
Design	International, multicenter, single arm	
Reviewer Discussion:	NCI study has mixed patient population, CTCL and PTCL. Only the CTCL patient data was the subject of this NDA review.	
Eligibility	<p>Inclusion</p> <ul style="list-style-type: none"> <li>-Males or non-pregnant females aged ≥ 18 years.</li> <li>-Histologically confirmed diagnosis of CTCL, including mycosis fungoides and Sézary syndrome.</li> <li>-Patients with CTCL stages IB, IIA, IIB, III and IVA only.</li> <li>-Patients who have failed standard skin-directed therapy and have had at least one course of systemic therapy, such as interferon, which they have also failed.</li> <li>-Anticipated life expectancy greater than six months.</li> <li>-Written informed consent to participate in the study.</li> </ul>	<p align="center"><b>NCI 1312</b></p> <p>Phase II Trial of Depsipeptide in Patients with Cutaneous T-cell Lymphoma and Relapsed Peripheral T-cell Lymphoma</p> <p>International, multicenter, non-randomized, 5 single arms</p> <ul style="list-style-type: none"> <li>- Patient with CTCL (mycosis fungoides or Sézary syndrome), stage IA-IIA refractory or intolerant to two prior non-steroidal therapies, including skin directed therapy, immunotherapy, or cytotoxic chemotherapy; stage IIB-IVB no more than two systemic cytotoxic chemotherapies or radiolabeled monoclonal antibody therapy, but no restriction on skin directed, biological, targeting or radiation therapies.</li> <li>- Measurable disease</li> <li>- &gt; 18 year old and ECOG 0-2</li> <li>- Negative pregnancy test for female of child bearing age</li> <li>- Laboratory values meet: ANC &gt; 1000/ul, platelets &gt; 100,00/ul, Cr &lt; 1.5 ULN or CrCl &gt; 60 ml/min, bilirubin (total and direct) &lt; 1.5 ULN, AST &lt; 3 x ULN, PT/PTT &lt; 1.1 ULN, and EF by MUGA &gt; 45%.</li> </ul>
Exclusion	<ul style="list-style-type: none"> <li>-ECOG Performance Status &gt;1 (see Appendix H).</li> <li>-No prior systemic chemotherapy regimen.</li> <li>-Visceral involvement i.e. Stage 4b disease (lymphadenopathy is allowed).</li> <li>-Patients with known cardiac abnormalities such as: Congenital long QT syndrome; QTc interval &gt; 500 milliseconds; Cardiomegaly or cardiomyopathy from prior treatment or other causes.</li> <li>- Concomitant use of any anti-cancer therapy.</li> <li>- Concomitant use of warfarin.</li> <li>- Use of any investigational agent within 4 weeks of study entry.</li> <li>- Concomitant use of drugs which may cause a prolongation of the QTc.</li> <li>- Patients with a potassium level of &lt;3.5 mmol/L and a magnesium level of &lt;0.8 mmol/L.</li> <li>- Clinically significant active infection.</li> <li>- Known infection with human immunodeficiency virus (HIV), hepatitis B, or hepatitis C.</li> <li>- Inadequate bone marrow or other organ function, as evidenced by: unsupported hemoglobin &lt;9.0 g/dL (transfusions and/or erythropoietin</li> </ul>	<ul style="list-style-type: none"> <li>- Unconfirmed diagnosis of B-cell lymphoma</li> <li>- Prior or concurrent malignancies that have not been curatively treated</li> <li>- CNS lymphoma</li> <li>- prior histone deacetylase inhibitor treatment</li> <li>- chemotherapy &lt; 4 weeks, nitrosourea or mitomycin C &lt; 6 weeks</li> <li>- HIV</li> <li>- Pregnant or breast feeding</li> <li>- Major surgery &lt; 21 days</li> <li>- Uncontrolled infection</li> <li>- MI, 6 months, EF &lt;45%, unstable angina, heart block without pacemaker.</li> </ul>

Protocol Contents		Study ID	
		GPI-04-0001	NCI 1312
	<p>are permitted); absolute neutrophil count (ANC) <math>\leq 1.5 \times 10^9/L</math>; platelet count <math>&lt; 100 \times 10^9/L</math>; total bilirubin <math>&gt; 1.25 \times</math> upper limit of normal (ULN) for institution; aspartate transaminase/serum glutamic oxaloacetic transaminase (AST/SGOT) and alanine transaminase/serum glutamic pyruvic transaminase (ALT/SGPT) <math>&gt; 2.0 \times</math> ULN, serum creatinine <math>&gt; 2 \times</math> ULN for age and sex.</p> <ul style="list-style-type: none"> <li>- Coexistent second malignancy or history of prior malignancy within previous 5 years (excluding basal or squamous cell carcinoma of the skin or cervical epithelial neoplasm [CIN I, carcinoma in situ] that has been treated curatively).</li> <li>- Any significant medical or psychiatric condition that might prevent the patient from complying with all study procedures.</li> <li>- Patients who are pregnant or breast-feeding or taking inadequate contraceptive during treatment period and for at least 1 month thereafter.</li> <li>- Male patients must use a barrier method of contraception during the treatment period and for at least 1 month thereafter.</li> <li>- Use of topical steroids in the previous 2 weeks or systemic steroids in the previous 4 weeks.</li> <li>- Having previously given consent to participate in this study.</li> </ul>		
Reviewer Discussion:	<p>Unlike study GPI-04-0001, NCI 1312 patients with CTCL were enrolled in 3 arms: in two of the 3 arms (1 and 5), patients were to have refractory disease with a <math>\geq 6</math>-month disease response plateau after receiving <math>\leq 2</math> prior lines of systemic therapy or were to be intolerant to such therapy. Patients enrolled in arm 3 were to have experienced disease progression after receiving <math>\geq 2</math> prior lines of systemic therapy.</p>		
Treatment Regimen	<p>14 mg/m<sup>2</sup> (4-hour infusions on Days 1, 8, and 15 of 28-day cycles)</p>		<p>14 mg/m<sup>2</sup> (4-hour infusions on Days 1, 8, and 15 of 28-day cycles), allowed to escalate to 17.5 mg/m<sup>2</sup>.</p>
Reviewer Discussion:	<p>It study NCI 1312, the initial 3 CTCL patients received romidepsin at a starting dose of 18 mg/m<sup>2</sup> on the same schedule before change to 14 mg/m<sup>2</sup>. In addition, a later amendment allowed NCI study patients who tolerated romidepsin to receive a dose escalation to 17.5 mg/m<sup>2</sup>. The number of patients receiving a dose escalation is not clear.</p>		
Concomitant Treatment	<p>No other systemic anti-cancer treatment or radiotherapy may be used during the trial. If individual plaque radiation becomes necessary in an otherwise responding patient, the irradiated lesion was no longer assessable for response. These patients were NOT eligible for assessment as CCR or CR and were assessed as PR, assuming other criteria for this designation were met.</p>		<p>Radiation therapy- Localized external beam radiotherapy for palliative treatment of metastatic cancer was permitted in patients with evidence of response to depsipeptide and could be administered concurrently with protocol treatment. Lesions that were treated with radiation were not to be used for evaluation of response.          Surgery for palliative treatment of metastatic cancer was permitted in patients with evidence of response to depsipeptide and could be performed concurrently with protocol treatment. Lesions that were treated with surgery were not to be used for evaluation of response.</p>
Reviewer Discussion:	<p>According to applicant provided data, no patient in either study received radiation or surgery for local disease control during the study.</p>		
Dose Modification	<p>For grade 3-4 adverse events, dose delay, if recurs, dose reduction  <i>Nonhematologic toxicities except alopecia</i></p>		<p>For grade 3-4 adverse events, dose delay, if recur, 3 dose reductions, Dose reduction should be used if grade 3 neutropenia or</p>

Protocol Contents		Study ID	
		<b>GPI-04-0001</b>	<b>NCI 1312</b>
	<ul style="list-style-type: none"> <li>Grade 2 or 3 toxicity: Treatment with romidepsin should be delayed until toxicity returns to <math>\leq</math> Grade 1 or baseline, then therapy may be restarted at 14 mg/m<sup>2</sup>. If Grade 3 toxicity recurs, treatment with romidepsin should be delayed until toxicity returns to <math>\leq</math> Grade 1 or baseline and the dose should be permanently reduced to 10 mg/m<sup>2</sup>.</li> <li>Grade 4 toxicity: Treatment with romidepsin should be delayed until toxicity returns to <math>\leq</math> Grade 1 or baseline, then the dose should be permanently reduced to 10 mg/m<sup>2</sup>.</li> <li>Romidepsin should be discontinued if Grade 3 or 4 toxicities recur after dose reduction.</li> </ul> <p><i>Hematologic toxicities</i></p> <ul style="list-style-type: none"> <li>Grade 3 or 4 neutropenia or thrombocytopenia: Treatment with romidepsin should be delayed until the specific cytopenia returns to ANC <math>\geq 1.5 \times 10^9/L</math> and/or platelet count <math>\geq 75 \times 10^9/L</math> or baseline, then therapy may be restarted at 14 mg/m<sup>2</sup>.</li> <li>Grade 4 febrile (<math>\geq 38.5^\circ C</math>) neutropenia or thrombocytopenia that requires platelet transfusion: Treatment with romidepsin should be delayed until the specific cytopenia returns to <math>\leq</math> Grade 1 or baseline, and then the dose should be permanently reduced to 10 mg/m<sup>2</sup>.</li> </ul>	<p>thrombocytopenia is found before the next dose. The dose reduction schema consisted of 4 dose levels depending on the previous dose, 14 to 10.5, 10.5 to 8, 8 to 6 and 6 to 4.5 mg/m<sup>2</sup>.</p> <p>Treatment should be held if grade 3-4 non-hematological toxicity (except for fatigue, taste changes, anorexia, hypophosphatemia or hypocalcemia) or grade 4 neutropenia or thrombocytopenia occurs. Held until toxicities resolve to <math>\leq</math> grade 2.</p> <p>If there was bone marrow involvement, investigator may retreat without reduction.</p> <p>Discontinuation would occur if the same AE recurred after the 4th dose reduction.</p>	
Reviewer Discussion:	<p>Dose delay was permitted in both studies, but criteria for resumption of therapy differed between studies. The NCI study allowed patients to resume dosing with grade 2-3 toxicities while the GPI study required grade 0-1 toxicity. Further, the GPI study allowed only one dose reduction to 10 mg/m<sup>2</sup>. Patients who experienced the same toxicity after this reduction discontinued romidepsin. The NCI study allowed 4 dose reductions. If there was bone marrow involvement, investigators could retreat without dose reduction. In the GPI study, patients who experienced the same toxicity discontinued romidepsin. The impact of these differences in the safety results will be discussed in the safety review section.</p>		
Safety Monitoring	Physical examination, EKG, laboratory tests were done before each dose		Physical examination, EKG, laboratory tests were done before and 24 hours after each dose
Reviewer Discussion:	While both studies allowed additional safety assessments, if clinically indicated, the physical examination, EKG, and laboratory tests were planned before and 24 hours after each dose in the NCI study, but only before each dose in the GPI study. In addition, troponin, holter monitoring, and echocardiograms were only performed on the NCI study. The impact of these differences in the safety results will be discussed in the safety review section.		
Primary Endpoint:	Proportion of patients with confirmed objective disease responses of CR, CCR, or PR, as determined by the Investigator using the protocol-defined Objective Primary Disease Response Evaluation Criteria (OPDREC), which is a composite of changes in skin involvement, lymph node involvement, and abnormal circulating T-cells.		Proportion of patients with confirmed objective disease response of CR or PR, as determined by the investigator based on a composite of changes in skin involvement, lymph node and visceral involvement, where applicable, and abnormal circulating T-cells, where applicable
Overall Response (ORR)			
Reviewer Discussion:	The initial primary endpoint of study GPI-04-0001 was best clinical response (CR+PR+SD). FDA recommended using CR rate with support from a clinically meaningful CR duration as the primary endpoint. However, the GPI study endpoint was changed to ORR (CR+PR) and FDA agreed. Patient's skin was assessed at each cycle and scans were done every other cycle. The weighted body surface area was derived from an assessment of the percentage of the body surface area affected with patches, plaques, or tumors and summed for a total score. Erythroderma was		

Protocol Contents		Study ID	
		NCI 1312	
		determined separately using a 0-3 scale and lymph nodes were measured using the RECIST criteria. Note that patients with a partial response in the skin and stable disease in the nodes were considered a PR. In the NCI study, skin assessments and scans varied with the number of cycles and the patient's disease status. A Physician's Global Assessment of the skin response was retrospectively applied to the NCI study in 2007. Again, patients could have a partial response based on improvement in the skin alone.	
Secondary Endpoints:	<i>Duration of ORR</i>	The time from the first date of objective disease response (later confirmed) to the first date of diagnosis of PD. For patients without PD, duration of response is censored at the last visit date with non-missing response data.	The time from the first date of objective disease response (later confirmed) to the first date of diagnosis of PD. For patients without PD, duration of response is censored at the last visit date with non-missing response data.
	<i>Time to confirmed ORR</i>	For patients with confirmed objective disease response, the number of days from the first date of study drug to the first date of objective disease response (later confirmed).	For patients with confirmed objective disease response, the number of days from the first date of study drug to the first date of objective disease response (later confirmed).
	<i>Time to Progression</i>	The time from the first date of study drug to the first date of diagnosis of PD. For patients without PD, duration of response is censored at the last visit with any OPDREC data.	The time from the first date of study drug to the first date of diagnosis of PD. For patients without PD, duration of response is censored at the last visit with any response data.
	<i>Pruritus</i>	Quality of life measure by patient reported outcome	None
<b>Reviewer Discussion:</b>		The time to event endpoints in a single armed study can only be considered as exploratory. A PRO endpoint can only be reliably measured in a randomized, double blind study with a validated measuring tool.	
Analyses Populations:	<i>Primary - Evaluable Patients (EP)</i>	All patients who received 2 consecutive cycles of study treatment (with at least 2 of the 3 doses received in each cycle) and had disease assessments performed at Baseline and after the last of 2 consecutive cycles; and who did not receive concomitant steroid therapy or other therapy for CTCL (whether systemic or topical) that may have biased the assessment of disease response.	All patients who received at least 2 consecutive cycles of study treatment (with at least 2 of the 3 planned doses received in each of these cycles), and had at least one non-missing response assessment on or after Cycle 2. Per protocol, patients were not to receive concurrent therapy active in CTCL.
	<i>Secondary - Treated Patients (TP)</i>	All enrolled patients who received at least one dose of study treatment	All enrolled patients who received at least one dose of study treatment
<b>Reviewer Discussion:</b>		The primary and secondary endpoints are similar between the two studies, except that the response assessment criteria are somewhat different. Study GPI-04-0001 use the protocol-defined Objective Primary Disease Response Evaluation Criteria (OPDREC), whereas study NCI1312 use a RECIST composite with skin and circulating cell assessment as described below.	
Efficacy Evaluation	<i>Skin</i>	-Weighted body surface area (BSA)/SWAT score at Baseline and on Day 1 of each cycle, and at the End of Treatment to determine evolution of skin involvement. <sup>2</sup> -Erythroderma score determined at Baseline; on Day 1 of each cycle; and at the end of treatment. <sup>2</sup> -Skin photography at Baseline; on Day 1 each cycle; and at the end of	-Skin assessments at Baseline, serially over time on treatment, and at the End of Treatment to determine the evolution of skin involvement. -Presence of erythroderma assessed at Baseline; serially over time on treatment; and at the end of treatment. <sup>1</sup> - Skin photography at Baseline; serially over time during the inter-cycle rest periods, and at End of Treatment. <sup>1</sup>

Clinical Review  
 Qin Ryan, MD, PhD  
 NDA 22393

Istodax (romidepsin, depsipeptide, FK-228)

Protocol Contents		Study ID	
		GPI-04-0001	NCI 1312
	treatment. - Skin biopsy at Baseline with repeat biopsy performed and reviewed centrally to confirm CR.		- Skin biopsy for confirmation of CTCL.
<i>Lymph nodes / nodal masses / visceral disease</i>	-Assessed via physical examination at Baseline; Days 1 and 15 of each cycle; and at End of Treatment. -Assessed via CT or MRI at Baseline; at every other treatment cycle, starting with Cycle 2, and at end of treatment.		-Assessed via CT or MRI at Baseline, serially over time on treatment, and at End of Treatment. -If negative at Baseline, repeat assessments not required.
<i>Abnormal circulating T cells</i>	-Assessed in peripheral blood by flow cytometry at Baseline; Day 1 of every cycle, starting in Cycle 2, and at end of treatment. -If negative at Baseline, repeat assessments not required.		-Assessed in peripheral blood by flow cytometry at Baseline; serially over time on treatment, and at End of Treatment. -If negative at Baseline, repeat assessments not required.
<i>Disease Response</i>	-Assessed every cycle, starting with Cycle 2 based on available data with complete assessments every other cycle, and at end of treatment.		-Assessed serially over time on treatment and at End of Treatment.
<i>Pruritus</i>	Assessed using a Visual Analog Scale (VAS) at Baseline; on Day 1 of each cycle; and at End of Treatment.		Not prospectively specified.
<b>Reviewer Discussion:</b>	<p>1. The difference in response assessment between the two studies is described in the next section.            2. The duration of response between the two studies may vary due to the change in the frequency of assessment with response status (Study NCI 1312 assessed response every 3 cycles for patients who achieved confirmed CR).            3. Only study GPI-04-0001 assessed pruritus whereas study NCI 1312 did not. In a single arm study, any patient reported outcome (PRO) would be considered as exploratory and questionable for any labeling claim.</p>		
<b>Safety Evaluation</b>	Adverse events were evaluated by NCT CTCAEV3.		
<b>Statistical Analysis</b>	Descriptive statistics only		
<b>Planned Sample Size</b>	90		
<b>Reviewer Discussion:</b>	FDA recommends that study GPI-04-0001 enroll at least 100 patients. NCI study 1312 was brought in later to include more subjects and to support the efficacy and safety claims of romidepsin.		
<b>Independent Review</b>	For both efficacy and safety		
<b>Sponsor</b>	Gloucester		
<b>PI / Study Sites</b>	Prentice / US and Europe		
<b>No. of Sites</b>	33		
<b>Study Status</b>	01/2005-Ongoing Data cut-off: Efficacy - 05/2008; Safety - 10/2007		

Source: NDA 22393, study GPI-04-0001 and study NCI 1312 reports

1. For patients who achieved CCR, response assessment was to be conducted every 3 cycles thereafter.

2. Study GPI-04-0001 Weighted BSA Skin Assessment Tool, see description in the table below.

As elucidated in the table above, although both studies used ORR as the primary endpoint; differences may exist between the ORR of each study because the disease assessment methods differed between the two studies.

**Table 9: Comparison of disease assessment methods of studies GPI-04-0001 and NCI 1312**

Protocol Contents	Study ID	NCI 1312
<p>Skin Assessment for Patients without Erythroderma</p>	<p><b>GPI-04-0001</b></p> <p>Weighted BSA Skin Assessment Tool (SWAT or WBSA) was used for determining the percentage of the BSA affected by patches, plaques, and tumors in each of 12 specified body regions. Each region was given a total possible percentage BSA: head (7%); neck (2%); anterior trunk, without neck or genitalia (13%); posterior trunk, without neck or buttocks (13%); buttocks (5%); genitalia (1%); upper arms (8%); forearms (6%); hands (5%); thighs (19%); lower leg (14%); feet (7%). The fraction of that body region involved with patch, plaque, and tumor was multiplied by the total possible percent BSA for that region to determine the overall percent BSA affected by each lesion type within that region. The data were then subtotaled across lesion type. A weighted score was then applied to each subtotal, with patch = 1, plaque = 2, and tumor = 3. The 3 “weighted” subtotals were then added to determine the total score.</p>	<p>The skin assessments were based on the PGA tool for CTCL patients and were used in the efficacy assessments of bexarotene. Skin assessments were quantitative with the Investigator recording an overall assessment based on changes from baseline as follows:</p> <ul style="list-style-type: none"> <li>• Complete resolution of skin patches/plaques, tumors, and/or erythroderma</li> <li>• At least 50% improvement in skin patches/plaques, tumors, or erythroderma</li> <li>• No significant (less than 50% improvement or less than 25% worsening) change</li> <li>• At least 25% worsening in skin patches/plaques, tumors, or erythroderma</li> </ul>
<p>Reviewer Discussion:            Skin Assessment for Patients with Erythroderma</p>	<p>The skin assessment criteria of studies GPI-04-0001 were more precise in the body area calculation and skin lesion scoring.</p> <p>For patients with erythroderma, 5 areas of skin involvement were selected and followed during the study. Each area was assessed using a scale from 0 (no erythroderma) to 5 (severe, diffuse erythroderma with all of the following: edema, confluent scaling [generalized exfoliation], fissuring, and exudation). A total erythroderma score was determined by summing the score for each of the 5 selected areas; thus the maximum total score was 20.</p> <p>Study GPI-04-0001 Erythroderma Scale            Scale Severity Definition Skin Appearance</p> <ol style="list-style-type: none"> <li>0 None No erythroderma</li> <li>1 Mild diffuse erythroderma without edema, scaling, fissuring or exudation</li> <li>2 Mild to moderate diffuse erythroderma with one of the following: edema, non-confluent scaling, fissuring, exudation</li> <li>3 Moderate to severe diffuse erythroderma with 2-3 of the following: edema, non-confluent scaling, fissuring, exudation</li> <li>4 Severe diffuse erythroderma with all of the following: edema, confluent scaling (generalized exfoliation), fissuring, exudation</li> </ol> <p>Changes from study entry in the total WBSA/SWAT score or the erythroderma score (as applicable) were included as part of the response criteria.</p>	<p>The presence or absence of erythroderma or skin tumors also was recorded. Assessments of erythroderma were included in the overall assessment described above.</p>

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Protocol Contents		Study ID	
		NCI 1312	
Response Criteria	To be classified as CR, CCR, or PR, the response had to be confirmed. A confirmed assessment was one that was repeated at least 1 month after the initial assessment.	Criteria not defined for Study NCI-1312, limited skin biopsy data were available.	
Complete Response (CR)	Findings same as CCR plus findings confirmed by skin biopsy		
Complete Clinical Response (CCR)	<ul style="list-style-type: none"> <li>- Complete resolution of skin patches, skin plaques, and skin tumors, or erythroderma (as applicable).</li> <li>- No evidence of new tumors (cutaneous or noncutaneous).</li> <li>- No evidence of abnormal lymph nodes.</li> <li>- Absence of circulating Sézary cells.</li> </ul>	<ul style="list-style-type: none"> <li>- Complete resolution of skin patches / plaques, tumors and/or erythroderma and no evidence of new tumors;</li> <li>- No evidence of abnormal nodal or extranodal (visceral) masses or lesions or negative at Baseline and not repeated at this time point;</li> <li>- Negative for abnormal circulating T-cells or negative at Baseline;</li> </ul>	
Partial Response (PR)	<ul style="list-style-type: none"> <li>≥ 50% improvement in the summation of (Δ Skin + Δ Lymph Node + Δ Peripheral Blood) with:</li> <li>- At least &gt;30% improvement in Skin;</li> <li>- No worsening in Lymph Node or Sézary cells; and</li> <li>- No evidence of new tumors (cutaneous or noncutaneous).</li> </ul>	<ul style="list-style-type: none"> <li>• ≥50% improvement in skin patches / plaques, tumors, or erythroderma and no evidence of new tumors;</li> <li>• No worsening in abnormal lymph nodes or nodal masses (i.e., &lt;25% increase in the sum of the longest axis of abnormal nodal masses or lesions and &lt;25% increase in the sum of the longest axis of extranodal [visceral] masses or lesions) or negative at Baseline and not repeated at this time point.</li> <li>• The status of abnormal circulating T-cells in peripheral blood is not used as a criterion for PR.</li> </ul>	
Stable Disease (SD)	<ul style="list-style-type: none"> <li>- Patients who do not have enough improvement or worsening in the summation of (Δ Skin + Δ Lymph Node + Δ Peripheral Blood) to qualify as PR or PD, respectively.</li> <li>- No evidence of new tumors (cutaneous or noncutaneous).</li> </ul>	<ul style="list-style-type: none"> <li>• Patients who do not have enough improvement or worsening in skin and lymph nodes to qualify for PR or PD, with:</li> <li>• No significant (&lt;50% improvement or &lt;25% worsening) change in skin patches / plaques, tumors, or erythroderma and no evidence of new tumors; and</li> <li>• No worsening in abnormal lymph nodes or nodal masses (i.e., &lt;25% increase in the sum of the longest axis of abnormal nodal masses or lesions and &lt;25% increase in the sum of the longest axis of extranodal [visceral] masses or lesions) or negative at Baseline and not repeated at this time point.</li> <li>• The status of abnormal circulating T-cells in peripheral blood is not used as a criterion for SD.</li> </ul>	
Progressive Disease (PD)	<ul style="list-style-type: none"> <li>• &gt;25% worsening in the summation of (Δ Skin + Δ Lymph Node + Δ Peripheral Blood) with &gt;15% worsening in Δ Skin;</li> <li>• Evidence of new tumor (cutaneous or noncutaneous);</li> <li>• ≥25% worsening in skin patches / plaques, tumors, or erythroderma or evidence of new tumors; or</li> <li>• Worsening in nodal or extranodal (visceral) masses or lesions. For patient with CR or PR, PD was to be confirmed.</li> </ul>	<ul style="list-style-type: none"> <li>• ≥25% increase in the sum of the longest axis of abnormal lymph nodes, nodal masses, or extranodal [visceral] masses or lesions or presence of at least 2 new abnormal lymph nodes with a longest axis ≥1.5 cm or a new extranodal [visceral] lesion).</li> <li>• The status of abnormal circulating T-cells in peripheral blood is not used as a criterion for PD.</li> </ul>	
Reviewer Discussion:	GPI-04-0001 implemented confirmation for PD only, in patient had achieved a CR or PR, which potentially would be a confounding factor in the		

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Protocol Contents	Study ID
GPI-04-0001 analysis of response duration.	NCI 1312

Source: NDA 22393, study GPI-04-0001 and study NCI 1312 reports.

**Reviewer Discussion:** Although the primary endpoint of both studies was ORR. Based on the discussions in the Tables above, which described the differences between the two studies in response evaluation criteria and the study patient population, the results of both studies should not be pooled.

Major amendments to both studies are summarized as below.

**Table 10: Study GPI-04-0001 amendments**

Amendment	Date	No. of patient treated	Major changes
Original protocol	08/17/04	0	-
1	11/23/04	0	Change primary endpoint to ORR. Objective disease control became a secondary endpoint. Change eligibility criteria from no prior systemic chemotherapy to "Patients who have to failed at least one course of systemic therapy including interferon, chemotherapy, Ontak, or Targretin" Change sample size from 76 to 90.
Start open	01/2005	1	-
2	09/13/05	n/a	Change secondary endpoint, rate of objective disease control from 6 months to 3 months. Clarified that response (CR or PR) should be confirmed. Add cardiac disease exclusion and changed QTc exclusion from > 500 msec to > 480 msec, based on 6 deaths observed in 400 patients receiving depsipeptide. Add interim analysis for data safety monitoring. Add confirmation for PD in patient who had a CR or PR in view of CTCL's fluctuating nature
3	04/20/06	n/a	Allow patient to be treated beyond 6 cycles. Addition of central pathology review on locally confirmed CTCL cases.

Source: NDA 22393, study GPI-04-0001 and study NCI 1312 reports.

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**Table 11: Study NCI 1312 amendments**

Amendment #	Date	No. of patient enrolled	Major changes
Original Protocol	12/08/2000	-	-
Study Open	03/2001	1	-
2	11/9/2001	5	After first 5 patients (3 CTCL and 2 PTCL) treated, regimen dose changed from 18 mg/m <sup>2</sup> to 14 mg/m <sup>2</sup>
3	12/07/2001	n/a	Add arm of patients who received > 2 prior systemic therapies. Add eligibility criteria for EF > 50% on ECHO or 45% on MUGA and QTc < 500 msec
4	06/28/2002	n/a	No longer exclude patient who failed prior histone deacetylase inhibitor. Allowed depsipeptide to be infused peripherally.
5	07/19/2002	n/a	Clarify that potassium and magnesium should be administered prior to depsipeptide infusion.
7	05/02/2003	n/a	Allowed to escalate to 17.5 mg/m <sup>2</sup> in patients who may benefit and who tolerated treatment.
8	07/18/2003	n/a	Reducing laboratory and cardiac monitoring
10	01/02/2004	n/a	Add one more arm to allow additional CTCL patients (same as arm one) to be enrolled.
10	02/27/2004	n/a	Reduced cardiac monitoring requirement. Allowed outpatient treatment. Additional extramural study center
13	04/08/2005	n/a	Normal potassium and magnesium levels need to be obtained within 8 hours before dosing. INR monitoring implemented. A list of drugs which prolong QT intervals was added. Arm 3 closed.
14	03/17/2006	n/a	Revised consent and eligibility for sudden cardiac death.
16	04/21/2006	n/a	A 6 <sup>th</sup> arm was added to enroll PTCL patients. Sample size increase to 173 patients.
17	12/15/2006	n/a	CTCL staging criteria were modified.

Source: NDA 22393, study GPI-04-0001 and study NCI 1312 reports.

## **5 Review of Efficacy**

### **5.1 Indication**

The proposed indication: “Romidepsin is indicated for treatment of cutaneous T-cell lymphoma (CTCL), including relief of pruritus, in patients who have received at least one prior systemic therapy”

#### **5.1.1 Methods**

As described in Sections 5.1 and 5.2, based on the efficacy claim in the proposed label, the efficacy review is focused on studies GPI-04-0001 and NCI 1312.

#### **5.1.2 Patient Disposition**

The patient disposition of both studies is summarized below. The patient disposition for both studies shows that every patient enrolled in either study was treated with at least one dose of romidepsin. While most patients discontinued treatment prior to Cycle 6 due to disease progression, 17 patients on the GPI study and 6 on the NCI study discontinued due to an adverse event. We also examined the categories Informed Consent Withdrawn and Other. From our assessments, it does not appear that these patients discontinued due to an adverse event. However, some of these patients did have progressive disease and should have been included under that category.

**Table 12: Studies GPI-04-0001 (05-2008 cut-off) and NCI 1312 (03-2007 cut-off) patient disposition**

Parameter / Study ID (cut-off date)	GP-04-0001 (5/2008)	NCI 1312 (3/2007)
<b>Enrolled*</b>	<b>96</b>	<b>71</b>
Early Discontinuation of Treatment During Cycles 1 to 6	61 (64)	44 (62)
Completed 6 Cycles of Treatment	35 (37)	27 (38)
<b>Reasons for Discontinuation Before Cycle 6</b>		
Disease Progression:	21 (22)	27 (38)
Adverse Event	17 (18)	6 (9)
Informed Consent Withdrawn	16 (17)	4 (6)
On Study Death	0	2 (3)
Investigator's Decision	2 (2)	0
Switch to Other Therapy	0	1 (1)
Other	5 (5)	4 (6)
<b>Off Study as of Study Data Cut-off</b>	<b>87 (91)</b>	<b>65 (92)</b>
<b>Ongoing on Treatment</b>	<b>4 (4)</b>	<b>6 (8)</b>
<b>Off Treatment Being Followed</b>	<b>5 (5)</b>	<b>0</b>
As Treated Patients (TP) Analysis Set	96 (100)	71 (100)
Evaluable Patients (EP) Analysis Set	72 (75)	63 (89)

\* All patients (100%) enrolled in either study GPI-04-0001 or study NCI 1312 had received at least one dose of study drug. The applicant defined evaluable patients as those who received at least 2 cycles of treatments with at least two doses per each cycle.

Source: Source: NDA22393 study GPI-04-0001 and NCI 1312 reports

For study NCI 1312, CTCL patients were enrolled into 3 arms. Both arms 1 and 5 enrolled patients with stage IIB-IVB disease who had received no more than two systemic cytotoxic chemotherapies or cytotoxic therapy and a radiolabeled monoclonal antibody. There was no restriction on skin directed, biological, targeted or radiation therapies. Arm 3 enrolled patients with stage IA-IIA disease who were refractory or intolerant to two prior therapies (other than steroids), including skin directed therapy, immunotherapy, or cytotoxic chemotherapy. The number of patients enrolled in each arm is summarized below.

**Table 13: Study NCI 1312 arms 1, 3, and 5 enrollments.**

Parameter / Study ID	NCI 1312 (3/2007)			
	All	Arm 1	Arm 3	Arm 5
Patient Disposition				
Enrolled*	71	27	15	29
Analysis Sets				
As Treated Patients (TP) Analysis Set	71 (100)	27	15	29
Evaluable Patients (EP) Analysis Set	63 (89)	23	15	25

\* All patients (100%) enrolled in either study GPI-04-0001 or study NCI 1312 had received at least one dose of study drug.

Source: NDA 22393 study NCI 1312 reports.

Reviewer Discussion: Applicant defined the treated population (TP) as patients (100%) in either study GPI-04-0001 or NCI 1312 who had received at least one dose of study drug. This population is identical to the population containing all enrolled patients. The applicant also defined the evaluable population (EP) as patients who received at least 2 cycles of treatment with at least two doses per cycle. Interestingly, the EP for study GPI-04-0001 was 75% of its TP (72/96), whereas the EP for study NCI-1312 was 89% of its TP (63/71).

### 5.1.3 Demographics

The patient demographics of studies GPI-04-0001 and NCI 1312 are summarized below. From the patient information acquired in these trials, the age, and male predominance are consistent with CTCL patient demographics found in the literature. The majority of patients on both studies were Caucasians.

**Table 14: Studies GPI-04-0001 and NCI 1312 patient demographics**

Study	GPI-04-0001		NCI 1312	
	TP (N=96)	EP (N=72)	TP (N=71)	EP (N=63)
Sex, n (%)				
Male, n (%)	59 (62)	48 (67)	46 (68)	43 (68)
Female	37 (39)	24 (33)	23 (32)	20 (32)
Age (Years)				
Mean (±Std Dev)	56.9 (12.0)	57.0 (11.0)	56.0 (12.9)	56.0 (13.4)
Median	57.0	57.5	57.0	56.0
Range	21.0, 89.0	21.0, 80.0	28.0, 84.0	28.0, 84.0
Race, n (%)				
Caucasian	90 (94)	68 (94.)	55 (76)	50 (79)
Black	5 (5)	3 (4)	15 (21)	12 (19)
Asian	0	0	0	0
Other	1 (1)	1 (1)	1 (1)	1 (1)
BSA (m <sup>2</sup> )				
Mean (±Std Dev)	1.90 (0.24)	1.90 (0.24)	2.0 (0.24)	1.9 (0.22)
Median	1.92	1.93	2.0	2.0
Range	1.42, 2.64	1.42, 2.37	1.4, 2.5	1.4, 2.3
ECOG, n (%)				
0	49 (51)	40 (56)	16 (23)	16 (25)
1	47 (49)	32 (44)	41 (58)	36 (57)
≥2	0	0	10 (14)	7 (11)
Missing	0	0	4 (6)	4 (6)
Geographic Region				
America	18 (19)	12 (17)	56 (79)	49 (79)
Australia	0	0	15 (21)	14 (22)
Europe	78 (81)	60 (83)	0	0

Source: Source: NDA22393 study GPI-04-0001 and NCI 1312 reports

#### 5.1.4 Baseline Disease Characteristics

The patient baseline disease characteristics of studies GPI-04-0001 and NCI 1312 are summarized below. The median duration of disease in both studies was 3 years. Although patients were distributed among all eligible stages of disease, the majority of patients were Stage IIB or higher. This is consistent with a population that requires systemic therapy.

**Table 15: Studies GPI-04-0001 and NCI 1312 patient baseline disease characteristics**

Parameter	GPI-04-0001		NCI 1312	
	TP (N=96)	EP (N=72)	TP (N=71)	EP (N=63)
<b>Time since diagnosis (months)</b>				
Mean ( $\pm$ Std Dev)	4.12 (4.104)	4.31 (4.461)	4.4 (4.55)	4.3 (4.05)
Median	3.03	3.11	3.0	3.0
Range	0.061, 25.54	0.061, 25.54	1, 23.7	0, 14.8
<b>Disease Stage at Study Entry</b>				
IA	0	0	1 (1)	1 (1)
IB	15 (16)	13 (18)	6 (9)	5 (8)
IIA	13 (14)	11 (15)	2 (3)	2 (3)
IIB	21 (22)	16 (22)	14 (20)	12 (19)
IIIA or B	23 (24)	18 (25)	8 (11)	8 (12)
IVA	24 (25)	14 (19)	27 (38)	22 (35)
IVB	0	0	12 (17)	12 (19)
<b>Pruritus at Study Entry</b>				
Moderate	31 (32)	23 (32)	n/a	n/a
Severe	40 (42)	29 (40)	n/a	n/a
<b>Disease parameters</b>				
Erythroderma	n/a	n/a	23 (32)	22 (35)
Abnormal Nodes by CT	n/a	n/a	46 (65)	40 (64)
External Disease by CT	n/a	n/a	8 (11)	7 (11)
Abnormal Circulating T Cells	n/a	n/a	21 (30)	19 (30)

Source: Source: NDA22393 study GPI-04-0001 and NCI 1312 reports

#### 5.1.5 Prior Therapy

The prior therapies of patient who entered studies GPI-04-0001 and NCI 1312 are summarized below. At least one prior therapy was documented for all GPI and 96% of NCI patients. The median number of prior skin-directed therapies was 2 for both studies. In the GPI study, more than 30% received prior skin-directed radiotherapy and topical steroid treatments; whereas only 13% of NCI study patients received topical steroids and none received prior radiotherapy.

Table 16: Studies GPI-04-0001 and NCI 1312 patient baseline disease characteristics

Parameter	GPI-04-0001		NCI 1312	
	TP (N=96)	EP (N=72)	TP (N=71)	EP (N=63)
Number of Patients with Prior CTCL Therapy	96 (100.0)	72 (100.0)	68 (96)	n/a
<b>Number of Prior CTCL Therapies</b>				
N	96	72	68	60
Mean (±Std Dev)	4.6 (2.40)	4.5 (2.41)	3.4 (1.47)	3.4 (2.29)
Median	4.0	4.0	3	3
Range	1.0, 11.0	1.0, 11.0	1, 10	1, 10
<b>Number of Prior Systemic CTCL Therapies</b>				
N	96	72	63	56
Mean (±Std Dev)	2.7 (1.70)	2.5 (1.71)	2.4 (1.47)	2.5 (1.50)
Median	2.0	2.0	2	2
Range	1.0, 8.0	1.0, 8.0	1, 7	1, 7
<b>Type of Prior Systemic Therapy</b>				
Chemotherapy	74 (77.1)	55 (76.4)	48 (68)	43 (68)
Immunotherapy	36 (37.5)	24 (33.3)	24 (34)	23 (37)
Bexarotene	32 (33.3)	24 (33.3)	31 (44)	28 (44)
Denileukin Diftitox	14 (14.6)	9 (12.5)	13 (18)	11 (17)
Steroids	12 (12.5)	8 (11.1)	17 (24)	16 (25)
Monoclonal Antibodies	4 (4.2)	3 (4.2)	9 (13)	7 (11)
Vorinostat	2 (2.1)	0	n/a	n/a
Other Retinoids	9 (9.4)	8 (11.1)	6 (9)	5 (8)
Other Systemic Therapy	2 (2.1)	2 (2.8)	5 (7)	5 (8)
<b>Number of Prior Skin-Directed Therapies/Photopheresis</b>				
N	90 (93.8)	69 (95.8)	43	37
Mean (±Std Dev)	2.1 (1.22)	2.0 (1.19)	1.8 (0.80)	1.8 (0.83)
Median	2.0	2.0	2	2
Range	1.0, 6.0	1.0, 6.0	1, 3	1, 3
<b>Type of Skin-Directed Therapy/Photopheresis</b>				
Phototherapy	51 (53.1)	39 (54.2)	38 (54)	33 (52)
Skin-Directed Radiotherapy	36 (37.5)	28 (38.9)	0	0
Steroids	35 (36.5)	25 (34.7)	8 (13)	8 (13)
Other Skin-Directed Therapy	18 (18.8)	12 (16.7)	18 (25)	15 (24)
Photopheresis	18 (18.8)	12 (16.7)	12 (17)	9 (14)

Source: Source: NDA22393 study GPI-04-0001 and NCI 1312 reports

At least one prior therapy was documented for all GPI and for 96% of NCI patients. The median number of prior skin-directed therapies was 2 for both studies. In the GPI study, more than 30% of patients received prior skin-directed radiotherapy and topical steroid treatments; whereas only 13% of NCI study patients received topical steroids and none received prior radiotherapy. Similarly, the median number of prior systemic therapies was 2, with the majority of patients receiving prior chemotherapy. Immunotherapy was primarily alpha interferon. Other retinoids and other systemic therapies included agents not available in the United States.

Reviewer Discussion: All (100%) patients on study GPI-04-0001 received prior systemic therapy. Ninety-six percent patients on study NCI 1312 received prior systemic chemotherapy.

### 5.1.6 Protocol Deviations

The protocol deviations occurring in studies GPI-04-0001 and NCI 1312 are summarized below.

**Table 17: Protocol deviation in studies GPI-04-0001 and NCI 1312**

Deviation	GPI-04-0001		NCI 1312	
	TP (N=96)	ORR (N=33)	TP (N=71)	ORR (N=25)
No documentation of any prior therapies	-	-	2	-
Less than the number of required prior therapies	-	-	2	2 PRs
Steroid: topical within 2 week or systemic within 4 weeks	4	-	-	-
Potassium < 3.5 mmol/L or Magnesium <0.8 mmol/L	2	-	-	-
Concomitant use of anticancer therapy	1	-	-	-
2 <sup>nd</sup> malignancy: coexist or prior history < 5 years	1	-	-	-

Note: one subject had two deviations.

Source: NDA22393 study GPI-04-0001 and NCI 1312 reports.

Most protocol deviations were minor. Four patients on the pivotal GPI study received concomitant topical or oral steroids and four patients on NCI 1312 did not meet the study eligibility criteria concerning the number of prior therapies. The four patients were enrolled in arm 3, which required >2 prior therapies. The two patients with PRs had two prior chemotherapies (900-00-3880 and 900-00-4757) and the other two (900-00-4865 and 900-00-4947) has no documentation of any prior systemic chemotherapy.

### 5.1.7 Analysis of Primary Endpoint: Response Rate

Although FDA suggested durable ORR in all treated patients would be the best primary efficacy measure, as highlighted in the table below, the applicant chose to assess the objective response rate, per the investigator, in the evaluable population as the primary analysis. The ORR by independent review assessment and ORR of the TP were used as supportive analyses (highted).

**Table 18: ORR, CR and PR of both studies assessed by INV or IRC in TP or EP**

Response Rates in TP	Assessment	GPI-04-0001 (N=96)	NCI 1312 (N=71)
Confirmed ORR n (%) [95%CI]	INV	33 (34.4) [25.0, 44.8]	25 (35.2) [25.4, 49.3]
	IRC	28 (29.2) [20.3, 39.3]	18 (25.4) [16.5, 38.6]
Complete Response n (%) [95%CI]	INV	6 (6.3) [2.3, 13.1]	4 (5.6) [1.6, 14.4]
	IRC	7 (7.3) [3.0, 14.4]	4 (5.6) [1.6, 14.4]
Partial Response n (%) [95%CI]	INV	27 (28.1) [19.4, 38.2]	21 (29.6) [20.2, 43.3]
	IRC	21 (21.9) [14.1, 31.5]	14 (19.7) [11.7, 32.1]
Response Rates in EP	Assessment	GPI-04-0001 (N=72)	NCI 1312 (N=63)
Confirmed ORR n (%) [95%CI]	INV	30 (41.7) [30.2, 53.9]	25 (39.7) [27.6, 52.8]
	IRC	26 (36.1) [25.1, 48.3]	18 (28.6) [17.9, 41.3]
Complete Response n (%) [95%CI]	INV	6 (8.3) [3.1, 17.3]	4 (6.3) [1.8, 15.5]
	IRC	7 (9.7) [4., 19.0]	4 (6.3) [1.8, 15.5]
Partial Response n (%) [95%CI]	INV	24 (33.3) [24, 45.4]	21 (33.3) [22.0, 46.3]
	IRC	19 (26.4) [16.7, 38.1]	14 (22.2) [12.7, 34.5]

TP = all enrolled patients EP = patients received at least 2 cycles of treatment and at least 2 dose per cycle INV = investigator, IRC = independent review committee

Data cut-off: GPI-04-0001 May 2008, NCI1312 March 2007

Source: Source: NDA22393 study GPI-04-0001 and NCI 1312 reports.

**Reviewer Discussion:** As described before, all patients enrolled on both studies received at least one dose of romidepsin and this constitutes the total patient population (TP) of each study.

The applicant's primary analysis used the efficacy evaluable subgroup of patients and was based on the Investigator-assessed response. The evaluable population (EP) was defined as the patients who received 2 cycles of romidepsin with at least 2 doses in each cycle. The evaluable population excluded 25% of patients in the GPI study and 11% in the NCI study. Response rates in the EP were 42 and 40%, respectively.

The FDA's primary analysis included all enrolled patients, since all enrolled patients received romidepsin. The Investigator assessed response was considered to be primary, since skin disease was difficult to assess from photographs and all locally confirmed CR and PR were evaluated by central pathology. Furthermore, we noted that the Independent Response Review Committee was added retrospectively to these studies. From the FDA's primary analysis, the response rates were 34% in the GPI study and 35% in the NCI study.

**Table 19: The difference in TP and EP ORR**

ORR (EP-TP, %)	Assessment	GPI-04-0001 (N=96)	NCI 1312 (N=71)
EP/ TP (%)		72/96 (75)	63/71(89)
EP ORR > TP ORR	INV	8%	5%
	IRC	7%	4%
EP CR > TP CR	INV	2%	<1%
	IRC	3%	<1%
Change in Partial Response (%)	INV	5%	3%
	IRC	6%	2%

TP = all enrolled patients EP = patients received at least 2 cycles of treatment and at least 2 dose per cycle INV = investigator, IRC = independent review committee

Data cut-off: GPI-04-0001 May 2008, NCI1312 March 2007

Source: Source: NDA22393 study GPI-04-0001 and NCI 1312 reports

#### 5.1.8 Sensitivity Analyses for the Primary Analysis

The following sensitivity analyses were conducted by the applicant and/or FDA reviewers to examine the reliability of ORR in both studies.

##### 5.1.8.1 Analysis of Response in Various Disease Stages

Response rates were further evaluated in relation to disease stage. Both studies showed responses in all stages of disease, as shown below.

**Table 20: ORR of each disease stage by INV and IRC assessment in TP and EP populations.**

Study ID	GPI-04-0001						NCI 1312					
	Population, N Disease Stage at Study Entry	TP N = 96 (%)		CR (%)		PR (%)		TP N=71 (%)	CR (%)		PR (%)	
		INV	IRC	INV	IRC	INV	IRC		INV	IRC	INV	IRC
IA		0	0	0	0	0	0	1 (1)	0	0	1 (5)	0
IB		15 (16)	0	0	4 (15)	4 (18)	6 (9)	2 (3)	0	0	3 (14)	2 (14)
IIA		13 (14)	1 (17)	2 (33)	2 (7)	2 (9)	2 (3)	1 (25)	0	0	1 (5)	1 (7)
IIB		21 (22)	2 (33)	1 (17)	7 (26)	7 (32)	14 (20)	0	0	0	5 (24)	4 (29)
IIIA or B		23 (24)	1 (17)	1 (17)	8 (30)	4 (18)	8 (11)	0	0	0	4 (19)	3 (21)
IVA		24 (25)	2 (33)	2 (33)	6 (22)	5 (23)	27 (38)	2 (50)	2 (50)	2 (9)	2 (9)	2 (14)
IVB		0	0	0	0	0	12 (17)	1 (25)	1 (25)	5 (24)	2 (14)	2 (14)
Total		96	6	6	27	22	71	4	4	21	21	14

Study ID	GPI-04-0001						NCI 1312					
	Population, N Disease Stage at Study Entry	EP N = 72 (%)		CR (%)		PR (%)		EP N=63 (%)	CR (%)		PR (%)	
		INV	IRC	INV	IRC	INV	IRC		INV	IRC	INV	IRC
IA		0	0	0	0	0	1 (1)	0	0	1 (5)	0	0
IB		13 (18)	0	0	4 (15)	4 (18)	5 (8)	0	0	3 (14)	2 (14)	2 (14)
IIA		11 (15)	1 (17)	1 (17)	2 (7)	2 (9)	2 (3)	0	0	1 (5)	1 (7)	1 (7)
IIB		16 (22)	2 (33)	2 (33)	7 (26)	7 (32)	12 (19)	1 (25)	1 (25)	5 (24)	4 (29)	4 (29)
IIIA or B		18 (25)	1 (17)	1 (17)	8 (30)	4 (18)	8 (12)	0	0	4 (19)	3 (22)	3 (22)
IVA		14 (19)	2 (33)	2 (33)	6 (22)	5 (23)	22 (35)	2 (50)	2 (50)	2 (9)	2 (14)	2 (14)
IVB		0	0	0	0	0	12 (19)	1 (25)	1 (25)	5 (24)	2 (14)	2 (14)
Total		72	6	6	27	22	63	4	4	21	21	14

Source: NDA 22393, study GPI-04-0001 and study NCI 1312 reports

Reviewer comments: The responses were not confined to patients with early stage disease, but also occurred among patients with late stage disease.

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### 5.1.8.2 Analyses of Prior Therapies among Responders

In studying the response rate by prior therapy, the results were examined in terms of the number and types of prior therapies. The response rates were analyzed in subgroups of patients who received 1, 2, or 3 or more prior therapies. Our assessment shows that response rate was not clearly related to the number of prior therapies. Analyses of the number of prior therapies that each responder received are tabulated below.

**Table 21: Number of prior therapies in responders by disease stage by INV assessment in GPI-04-0001 TP**

Prior systemic treatments	1	2	3	4	5	6	7	Total
IA	0	0	0	0	0	0	0	0
IB	2	2	0	0	0	0	0	4
IIA	1	1	1	0	0	0	0	3
IIIB	1	1	3	2	1	1	0	9
III A or B	3	4	0	0	2	0	0	9
IVA	4	1	1	1	0	0	1	8
IVB	0	0	0	0	0	0	0	0
Total	11	9	5	3	3	1	1	33

Source: NDA 22393, study GPI-04-0001 and study NCI 1312 reports

**Table 22: Number of prior therapies in responders by disease stage by INV assessment in NCI 1312 TP**

Prior systemic treatments	1	2	3	4	5	6	7	Total
IA	0	0	0	0	0	0	0	0
IB	2	1	0	0	0	0	0	3
IIA	0	0	0	1	0	0	0	1
IIIB	2	2	0	0	0	0	0	4
III A or B	0	1	0	1	0	2	0	4
IVA	1	2	1	0	0	0	0	4
IVB	2	3	0	1	0	0	0	6
Total	7	9	1	3	0	2	0	22

Source: NDA 22393, study GPI-04-0001 and study NCI 1312 reports

Reviewer Comments: There was a decrease in response rate with prior therapy, but responses did occur in patients with 3 or more prior therapies.

The response analysis by the type of therapy, including individual medications, is summarized below.

**Table 23: Analyses of INV assessed response and prior therapies (TP)**

Prior Treatment /INV Assessment	GPI-04-0001			NCI 1312		
	ORR/N	CR	PR	ORR/N	CR	PR
<b>No. of prior therapies</b>						
1	0/2	0	0	7/19	1	6
2	8/19	3	5	6/10	1	5
3	7/17	1	6	2/9	1	1
4	2/14	0	2	4/11	0	4
5	3/14	0	3	0/6	0	0
6	4/8	1	3	1/7	0	1
7	4/9	0	4	3/3	0	3
8	3/5	1	2	0/1	0	0
9	1/4	0	1	1/1	0	1
10	0/2	0	0	0/1	0	0
11	1/2	0	0	0/0	0	0
<b>No. of skin directed therapies</b>						
1	12/36	4	8	8/19	1	7
2	9/28	0	9	4/14	0	4
3	4/14	1	3	3/10	0	3
4	6/9	1	5	0/0	0	0
6	1/3	0	1	0/0	0	0
<b>No. of systemic therapies</b>						
1	11/30	3	8	7/20	1	6
2	9/22	1	8	9/20	2	7
3	5/20	1	4	1/9	0	1
4	3/8	1	2	3/8	0	3
5	3/8	0	3	0/3	0	0
6	1/5	0	1	2/2	0	2
7	1/2	0	1	0/1	0	0
8	0/1	0	0	0/0	0	0
<b>No. of chemotherapies</b>						
1	15/47	3	12	17/48	1	16
2	7/14	3	4	0/0	0	0
3	1/5	0	1	0/0	0	0
4	1/4	0	1	0/0	0	0
5	1/3	0	1	0/0	0	0
6	0/1	0	0	0/0	0	0
<b>Type of therapies</b>						
Chemotherapy	25/74	6	19	17/48	1	16
Other systemic therapy	0/2	0	0	2/5	1	1
Immunotherapy	13/36	1	9	9/24	0	9
Retinoid	5/9	1	4	2/6	0	2
Ontak	5/14	0	5	4/13	2	2
Bexarotene	12/32	1	11	8/31	0	8
Monoclonal Ab	1/4	0	1	2/9	1	1
Vorinostat	0/2	0	0	0/0	0	0
Steroid	2/12	0	2	8/17	0	8
Phototherapy	19/51	3	16	13/38	1	12
Photopheresis	8/18	1	7	5/12	0	5

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Prior Treatment /INV Assessment	GPI-04-0001			NCI 1312		
	ORR/N	CR	PR	ORR/N	CR	PR
Radiotherapy	12/35	4	8	0/0	0	0
Skin directed steroid	13/35	1	12	2/9	0	2
Other skin directed	8/18	0	8	5/18	0	5

Source: NDA 22393, study GPI-04-0001 and study NCI 1312 reports

**Table 24: Analyses of IRC assessed response and prior therapies (TP)**

Prior Treatment /IRC Assessment	GPI-04-0001			NCI 1312		
	ORR/N	CR	PR	ORR/N	CR	PR
<b>No. of prior therapies</b>						
1	0/2	0	0	3/19	1	2
2	7/19	3	4	4/10	1	3
3	6/17	1	5	2/9	1	1
4	1/14	0	1	4/11	0	4
5	2/14	0	2	0/6	0	0
6	3/8	1	2	0/7	0	0
7	4/9	1	3	3/3	0	3
8	3/5	1	2	0/1	0	0
9	1/4	0	1	1/1	0	1
10	0/2	0	0	0/1	0	0
11	1/2	0	1	0/0	0	0
<b>No. of skin directed therapies</b>						
1	10/36	4	6	7/19	1	6
2	7/28	0	7	3/14	0	3
3	3/14	1	2	3/10	0	3
4	6/9	2	4	0/0	0	0
6	1/3	0	1	0/0	0	0
<b>No. of systemic therapies</b>						
1	9/30	3	6	4/20	1	3
2	7/22	1	6	7/20	2	5
3	5/20	2	3	1/9	0	1
4	3/8	1	2	2/8	0	2
5	2/8	0	2	0/3	0	0
6	1/5	0	1	2/2	0	2
7	1/2	0	1	0/1	0	0
8	0/1	0	0	0/0	0	0
<b>No. of chemotherapies</b>						
1	12/47	3	9	11/48	1	10
2	6/14	3	3	0/0	0	0
3	1/5	0	1	0/0	0	0
4	1/4	0	1	0/0	0	0
5	0/3	0	0	0/0	0	0
6	0/1	0	0	0/0	0	0
<b>Type of therapies</b>						
Chemotherapy	27/74			11/48		
Other systemic therapy	0/2	0	0	2/5	1	1
Immunotherapy	13/36	2	11	8/24	0	8
Retinoid	5/9	2	3	1/6	0	1
Ontak	5/14	0	5	4/13	2	2

Prior Treatment /IRC Assessment	GPI-04-0001			NCI 1312		
	ORR/N	CR	PR	ORR/N	CR	PR
Bexarotene	12/32	1	11	7/31	0	7
Monoclonal Ab	1/4	0	1	2/9	1	1
Vorinostat	0/2	0	0	0/0	0	0
Steroid	1/12	0	1	6/17	0	6
Phototherapy	15/51	4	12	11/38	1	10
Photopheresis	8/18	2	6	5/12	0	5
Radiotherapy	11/36	4	7	0/0	0	0
Skin directed steroid	10/34	2	8	1/9	0	1
Other skin directed	8/18	1	7	5/18	0	5

Source: NDA 22393, study GPI-04-0001 and study NCI 1312 reports

Reviewer comments: When looking at response based on the type of prior therapy, either investigator assessed or IRC assessed, the response rate in patients who received prior chemotherapy is similar to the overall response rate. With individual medications, the number of patients is too small to draw any firm conclusions. However, the response rate in patients who received prior chemotherapy, deneleukin difitox and bexarotene was similar to the overall response rate.

### 5.1.8.3 Analysis of Response With or Without Concomitant Anti-Infective Therapies

Concomitant antibiotic therapy, topical and/or systemic, was allowed. We were concerned that it may be difficult to distinguish response from a clearing of infection in the patient's skin lesions so we examined the role of concomitant antibacterial therapy in responders and non-responders, as shown below. Half of the GPI and 2/3 of the NCI patients did not receive concomitant topical and/or systemic antibiotics. Patient response rates in those that did NOT receive antibiotics were substantially lower than the response rates in patient who DID receive concomitant antibiotics.

**Table 25: Analyses of concomitant anti-infective therapies and INV response rates (TP)**

Concomitant Anti-infective Therapy	GPI-04-0001 N=96		NCI 1312 N=71	
	ORR		ORR	
	Use	No Use	Use	No Use
Systemic (%) [95%CI]	20/48 (42%) [27.6,56.8]	13/48 (27%) [15.3,41.9]	7/16 (44%) [19.8,70.1]	18/55 (33%) [20.7,46.7]
Antibacterial (%) [95%CI]	21/48 (44%) [29.5,58.8]	12/48 (25%) [13.6,39.6]	8/20 (40%) [19.1,64.0]	17/51 (33%) [20.8,47.9]
Topical (%) [95%CI]	6/20 (30%) [11.9,54.3]	27/76 (36%) [24.9,47.3]	8/16 (50%) [24.7,75.4]	17/55 (31%) [19.1,44.8]
Antiviral (%) [95%CI]	1/9 (11%) [0.3,48.3]	32/87 (37%) [26.7,47.8]	3/7 (43%) [9.9,81.6]	22/64 (34%) [23.0,47.3]
Antifungal (%) [95%CI]	6/22 (27%) [10.7,50.2]	27/74 (37%) [25.6,48.5]	2/5 (40%) [5.3,85.3]	23/66 (35%) [23.5,47.6]

Source: NDA 22393, study GPI-04-0001 and study NCI 1312 reports

The lower limit of the 95% confidence interval for the response rate in patients who did not receive concomitant systemic anti-infectives and did not receive concomitant antibacterial therapy in GPI-04-0001 was 15.3% and 13.6%, respectively. Whereas the lower limit of the 95% confidence interval for the response rate in patients who received concomitant systemic anti-infectives or antibacterial therapy in GPI-04-0001 was 27.6% and 29.5%, respectively.

The difference in CR rate is also observed in study NCI 1312.

**Table 26: Analyses of concomitant anti-infective therapies and INV CR rates (TP)**

Concomitant Anti-infective Therapy	GPI-04-0001		NCI-1312	
	Use	No Use	Use	No Use
Systemic	3/48 (6%)	3/48 (6%)	2/16 (13%)	2/55 (4%)
Antibacterial	3/48 (6%)	3/48 (6%)	1/20 (5%)	3/51 (6%)
Topical	1/20 (5%)	5/76 (7%)	2/16 (13%)	2/55 (4%)
Antiviral	0/9	6/87 (7%)	2/7 (29%)	2/64 (3%)
Antifungal	0/22	6/74 (8%)	1/5 (20%)	3/66 (5%)

Source: NDA 22393, study GPI-04-0001 and study NCI 1312 reports

Reviewer comments: The difference in response rate suggests that concomitant antibacterial therapy may be a confounding factor for estimating romidepsin efficacy.

#### 5.1.8.4 Discrepancy between INV and IRC Assessments

The differences between INV and IRC assessments are summarized below. We examined discrepancies between the Investigator and Independent Review Committee assessed CTCL patient response from both studies. The number of CRs by the investigator and independent review were identical while the independent review committee assessed some patients in both studies as stable disease rather than a partial response. In addition to agreement between the 10 CRs assessed by INV and IRC, the IRC identified one more CR which was assessed as PR by INV review. However, the IRC considered 11 INV assessed PRs to be SD.

**Table 27: INV and IRC assessed response discrepancy in TP of both studies**

INV	IRC				
	CR	PR	SD	PD	Total
CR	10	0	0	0	10
PR	1	35	11	1	48
SD	0	0	66	6	72
PD	0	0	9	28	37
<b>Total</b>	11	35	86	35	167

IRC = independent assessment, INV = investigator's assessment, CR = complete response, PR = partial response, SD = stable disease, and PD = disease progression

Source: Source: NDA22393 study GPI-04-0001 and NCI 1312 reports

The analyses of case by case discrepancies are summarized as below.

**Table 28: Case by case INV and IRC response assessment discrepancies**

USUBJID	INV	IRC
GPI-04-0001-02003	PD	SD
GPI-04-0001-22006	PD	SD
GPI-04-0001-45058	PD	SD
GPI-04-0001-02064	PD	SD90
GPI-04-0001-47063	PD	SD90
NCI1312-39-72-17-3	PD	SD90
GPI-04-0001-45095	PR	CCR
NCI1312-900-00-5027	PR	PD
NCI1312-900-00-5023	PR	SD
NCI1312-900-00-5103	PR	SD
GPI-04-0001-32043	PR	SD90
GPI-04-0001-34014	PR	SD90
GPI-04-0001-35032	PR	SD90
GPI-04-0001-55069	PR	SD90
NCI1312-36-21-45-5	PR	SD90
NCI1312-900-00-4986	PR	SD90
NCI1312-900-00-5124	PR	SD90
NCI1312-900-00-5344	PR	SD90
GPI-04-0001-02030	SD	PD
GPI-04-0001-95087	SD	PD
NCI1312-37-55-25-3	SD90	PD
NCI1312-900-00-4865	SD90	PD
NCI1312-900-00-4947	SD90	PD
GPI-04-0001-01001	SD90	SD
GPI-04-0001-34054	SD90	SD

IRC = independent assessment, INV = investigator's assessment, CR = complete response, PR = partial response, SD = stable disease, and PD = disease progression

Source: Source: NDA22393 study GPI-04-0001 and NCI 1312 reports

Reviewer comments: The Investigator and Independent Review assessment of complete responses was similar, but the independent review assessed some patients on both studies as having stable disease rather than a partial response. Since skin disease is difficult to assess with photographs, we consider the Investigator assessed response to be primary. Further, we note that the Independent Response Review Committee was added, post-hoc, to these studies.

### 5.1.8.5 Analysis of Response in Special Populations: Gender, Race and Age

Tables below present the ORR in the subgroup analysis for study GPI-04-0001 and NCI 1312, respectively. For some subgroups with a small sample size, the lower 95% CI bound is less than 15%.

**Table 29: Subgroup Analysis on ORR in Study GPI-04-0001**

Subgroup	Category	GPI-04-0001 (N=96)			
		INV		IRC	
		n (%)	95% CI	n (%)	95% CI
Age	<65	26 (35.1)	(24, 47)	23 (31.1)	(21, 43)
	≥65 <sup>†</sup>	7 (31.8)	(14, 55)	5 (22.7)	(8, 45)
Race	White	33 (36.7)	(27, 47)	28 (31.1)	(22, 42)
	Other <sup>†</sup>	0 (0)	NE	0 (0)	NE
Gender	Female <sup>†</sup>	8 (21.6)	(10, 38)	7 (18.9)	(8, 35)
	Male	25 (42.4)	(30, 56)	21 (35.6)	(24, 49)

Note: 95% CI constructed using exact methods based on the binomial distribution  
<sup>†</sup> Lower 95% CI bound is lower than 15%

IRC = independent assessment, INV = investigator's assessment  
 Source: Source: NDA22393 study GPI-04-0001 and NCI 1312 reports

**Table 30: Subgroup analysis on ORR in Study NCI 1312**

Subgroup	Category	NCI 1312 (N=71)			
		Inv		IRRC	
		n (%)	95% CI	n (%)	95% CI
Age	<65 <sup>†</sup>	18 (36.0)	(23, 51)	12 (24.0)	(13, 38)
	≥65 <sup>†</sup>	7 (33.3)	(15, 57)	6 (28.6)	(11, 52)
Race	White	23 (41.8)	(29, 56)	16 (29.1)	(18, 43)
	Other <sup>†</sup>	2 (12.5)	(2, 38)	2 (12.5)	(2, 38)
Gender	Female <sup>†</sup>	9 (39.1)	(20, 61)	6 (26.1)	(10, 48)
	Male	16 (33.3)	(20, 48)	12 (25.0)	(14, 40)

Note: 95% CI constructed using exact methods based on the binomial distribution  
<sup>†</sup> Lower 95% CI bound is lower than 15%

IRC = independent assessment, INV = investigator's assessment  
 Source: Source: NDA22393 study GPI-04-0001 and NCI 1312 reports

### 5.1.9 Analysis of Secondary Endpoints(s): Response duration

Although FDA advised the application to estimate the duration of complete response, the applicant conducted an analysis (ORRD) of the duration of response (CR + PR) due to limited numbers of patients with CR.

**Table 31: Response duration**

Median Response Duration in TP	Assessment	GPI-04-0001 (N=96)	NCI 1312 (N=71)
Confirmed ORRD (Days , 95% CI)	INV CR+PR	33	25
	INV	454 [454, NE]	336 [148, NE]
	IRC CR+PR	28	18
	IRC	NE [NE, NE]	392 [170, NE]
Response Duration in EP	Assessment	GPI-04-0001 (N=72)	NCI 1312 (N=63)
Confirmed ORRD (Days , 95% CI)	INV CR+PR	30	25
	INV	NE [454, NE]	336 [148, NE]
	IRC CR+PR	26	18
	IRC	NE [NE, NE]	392 [170, NE]

TP = all enrolled patients EP = patients received at least 2 cycles of treatment and at least 2 dose per cycle INV = investigator, IRC = independent review committee  
 Data cut-off: GPI-04-0001 May 2008, NCI1312 March 2007  
 Source: Source: NDA22393 study GPI-04-0001 and NCI 1312 reports.

Reviewer Discussion: The median response duration by investigator assessment was 15 months for study GPI-04-0001 and 11 months for study NCI 1312.

## 5.1.10 Other Endpoints

### 5.1.10.1 Time to Confirmed Response (TTR)

The Time to Response (Days) by the investigators' assessment for both studies is summarized below.

**Table 32: Time to response by investigator's assessment (GPI-04-0001 and NCI 1312)**

Time to Response (days)	GPI-04-0001 (N=96)	NCI 1312 (N=71)
Objective Disease Response <sup>1</sup> (n)	30	25
Mean (SD)	66.3 (32.12)	67.6 (40.68)
Median (range)	57.0 (27, 145)	56.0 (20, 188)
Complete Clinical Response <sup>2</sup> (n)	6	4
Mean (SD)	131.2 (49.15)	195.5 (59.88)
Median (range)	133.5 (57, 209)	182.5 (139, 278)

<sup>1</sup>Time (days) from date of first dose to date of first recorded OR (PR or CCR) (later confirmed)

<sup>2</sup>Time (days) from date of first dose to date of first recorded CCR (later confirmed)

TP = all enrolled patients EP = patients received at least 2 cycles of treatment and at least 2 doses per cycle INV = investigator, IRC = independent review committee  
 Data cut-off: GPI-04-0001 May 2008, NCI1312 March 2007  
 Source: Source: NDA22393 study GPI-04-0001 and NCI 1312 reports

Reviewer Discussion: Median time to an objective response was 2 months. It appears that the EP criterion of at least 2 cycles of treatment was based on the mean time to objective response.

Median time to CR was 6 months in Study 1 and 4 months in Study 2 (range 2 to 9).

#### 5.1.10.2 Time to Disease Progression (TTP)

TTP was defined in both studies as the duration from the date of the first study drug dose to the first date of progression; patients who did not progress were censored at their last evaluation with a response assessment. However, a time to event endpoint in a nonrandomized study would only be considered exploratory and would not be able to support any efficacy claim. Both study GPI-04-0001 and NCI 1312 were nonrandomized studies.

#### 5.1.10.3 Pruritus

The pruritus endpoint was used in study GPI-04-0001 only. Pruritus was assessed with a PRO tool. Per FDA CDER SEALD consultant, the data collected on GPI-04-0001 does not justify a "relief of pruritus" labeling claim. Their reasons are outlined below.

- PRO-derived data from open-label studies are rarely credible because responses to PRO measures are subjective. Therefore, every effort should be made to assure that patients are masked to treatment assignment. The study is also nonrandomized and, therefore, there is no concurrent control group from which a treatment effect on pruritus can be ascertained.
- The characteristics of the PRO instrument used should also be considered. Questions that ask how patients' current status compares to baseline seem likely to be more influenced by unblinding (optimism can readily be expressed as a favorable comparison) than questions that ask about current status. Questions that ask for current status, or PRO instruments that ask many questions, are harder to answer in a biased way when previous answers are not available. Therefore, it is useful to consider whether patients had access to their previous responses at subsequent assessments.
- The PRO instrument used to quantify itch in this study is a pure VAS scale comprising a line of fixed length with words that anchor the scale at the extreme ends and no words describing intermediate positions. These scales often produce a false sense of precision. This is because the response is measured in terms of change (in mm) on a 100 mm scale.
- Patient instructions were as follows: "indicate the amount of itching you are experiencing by marking a vertical line through the line below." The case report forms should be reviewed in order to ascertain whether patients understood the term "vertical" and responded accordingly with an unambiguous vertical line.
- What was measured was not "relief of pruritus" (as stated in current proposed labeling), but rather pruritus severity (using VAS) at certain points in time. Neither the proposed labeling nor the clinical study protocol defines what constitutes "pruritus relief." A "relief of pruritus" claim is not justified in the absence of empirically-derived response criteria demonstrating that pruritus was, in fact, relieved.

- In general, PROs should be measured at clinic visits before other clinical assessments. This is to avoid influencing the patient's responses. It should be clarified whether this was done in this study.
- The measurement of itch is important in this patient population and is encouraged in future studies, especially randomized, well-controlled clinical studies

In addition, 8 patients (8%, ID #02029, #0203, #32038, #33009, #34012, #46096, #47062, and #47063) received medications that may interfere with the evaluation of Pruritus VAS scores.

Reviewer comments: In summary, the applicant prospectively collected information concerning pruritus in the GPI study. Since this was an open label, single arm trial, this data is not interpretable. Also note that pruritus has been reported as an adverse event in patients with solid tumors who have received romidepsin.

We understand that pruritus is of great concern to patients with CTCL and encourage applicants to examine pruritus, but believe that this is best assessed in a randomized, blinded trial with a validated tool.

## 6 Review of Safety

### 6.1 Methods

The safety evaluation of romidepsin 14 mg/m<sup>2</sup> on days 1, 8 and 15 every 28 days, administered as monotherapy, was based on data from 185 CTCL patients that received romidepsin in two single arm studies, shown in the table below. This safety review focused on data, in patients with CTCL, from both study's safety update. Beyond the two studies, the focus is primarily on patients who received the 14 mg/m<sup>2</sup> weekly x3 every 28 days in other monotherapy studies for malignancies other than CTCL.

**Table 33: Studies reviewed for the safety of romidepsin**

Indication/Study Number	GPI-Sponsored		NCI-Sponsored		Overall		
	ISS n (%) <sup>1</sup>	Update n (%) <sup>2</sup>	ISS n (%) <sup>1</sup>	Update n (%) <sup>2</sup>	ISS n (%) <sup>1</sup>	Update n (%) <sup>2</sup>	Update 14 mg/m <sup>2</sup> n (%) <sup>3</sup>
CTCL							
Study GPI-04-0001	96 (12)	102 (12)	-	-	96 (12)	102 (12)	102 (17)
Study NCI 1312	-	-	71 (9)	83 (10)	71 (9)	83 (10)	80 (13)
Total	96 (12)	102 (12)	71 (9)	83 (10)	167 (21)	185 (21)	182 (30)
PTCL and other T-cell Lymphomas							
Study GPI-06-0002	12 (2)	43 (5)	-	-	12 (2)	43 (5)	43 (7)
Study NCI 1312	-	-	39 (5)	48 (6)	39 (5)	48 (6)	46 (8)
Total	12 (2)	43 (5)	39 (5)	48 (6)	51 (6)	91 (10)	89 (15)
Hematologic Malignancies							
Study NCI 1715	-	-	13 (2)	13 (1)	13 (2)	13 (1)	0
Study NCI 27	-	-	21 (3)	21 (2)	21 (3)	21 (2)	21 (3)
Study NCI 5563 <sup>4</sup>	-	-	2 (<1)	2 (<1)	2 (<1)	2 (<1)	0
Study NCI 5961	-	-	2 (<1)	2 (<1)	2 (<1)	2 (<1)	2 (<1)
Study NCI 5965	-	-	21 (3)	21 (2)	21 (3)	21 (2)	21 (3)
Study NCI 5996	-	-	13 (2)	13 (1)	13 (2)	13 (1)	13 (2)
Study NCI 6015	-	-	2 (<1)	2 (<1)	2 (<1)	2 (<1)	2 (<1)
Study NCI 7869	-	-	6 (<1)	8 (<1)	6 (<1)	8 (<1)	8 (1)
Total	-	-	80 (10)	82 (9)	80 (10)	82 (9)	67 (11)
Solid Tumors							
Study GPI-06-0003 <sup>4</sup>	29 (4)	36 (4)	-	-	29 (4)	36 (4)	0
Study GPI-06-0005 <sup>5</sup>	6 (<1)	11 (1)	-	-	6 (<1)	11 (1)	11 (2)
Study FJ-228-0001	29 (4)	29 (3)	-	-	29 (4)	29 (3)	29 (5)
Study FJ-228-0002	35 (4)	35 (4)	-	-	35 (4)	35 (4)	35 (6)
Study FJ-228-0007 <sup>6</sup>	26	26	-	-	26	26	26
Study T95-0022	-	-	33 (4)	33 (4)	33 (4)	33 (4)	0
Study T95-0077	-	-	48 (6)	48 (6)	48 (6)	48 (6)	0
Study NCI 1053	-	-	19 (2)	19 (2)	19 (2)	19 (2)	0
Study NCI 52704	-	-	33 (4)	34 (4)	33 (4)	34 (4)	0
Study NCI 5483	-	-	26 (3)	28 (3)	26 (3)	28 (3)	0
Study NCI 5987 <sup>4</sup>	-	-	5 (<1)	16 (2)	5 (<1)	16 (2)	0
Study NCI 6319	-	-	40 (5)	40 (5)	40 (5)	40 (5)	40 (7)
Study NCI 6321	-	-	3 (<1)	3 (<1)	3 (<1)	3 (<1)	3 (<1)

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Study NCI 6325	-	-	15 (2)	15 (2)	15 (2)	15 (2)	15 (2)
Study NCI 6335	-	-	12 (2)	13 (1)	12 (2)	13 (1)	13 (2)
Study NCI 6338	-	-	20 (3)	20 (2)	20 (3)	20 (2)	20 (3)
Study NCI 6351	-	-	2 (<1)	2 (<1)	2 (<1)	2 (<1)	2 (<1)
Study NCI ADVL0212	-	-	26 (3)	26 (3)	26 (3)	26 (3)	0
Study NCI CALGB-30304	-	-	16 (2)	16 (2)	16 (2)	16 (2)	16 (3)
Study NCI E1603	-	-	4 (<1)	4 (<1)	4 (<1)	4 (<1)	4 (<1)
Study NCI NABTC-03-03	-	-	50 (6)	50 (6)	50 (6)	50 (6)	50 (8)
Study NCI S0336	-	-	28 (4)	28 (3)	28 (4)	28 (3)	28 (5)
Study NCI S0400	-	-	6 (<1)	6 (<1)	6 (<1)	6 (<1)	6 (<1)
Total <sup>6</sup>	99 (13)	111 (13)	386 (49)	401 (46)	485 (62)	512 (59)	272 (45)
<b>Overall Total<sup>6</sup></b>	<b>207</b>	<b>256</b>	<b>576</b>	<b>614</b>	<b>783</b>	<b>870</b>	<b>610</b>

Source: NDA 22393, ISS, Appendix 14.1, Table 1.1.1; 4-month Update, Section 9.2, Table 1.1.1.

Note: numbers in italics represent increased patient enrollment since the ISS data cut-off dates.

<sup>1</sup>Percents are based on the overall total patients for the ISS (N=783).

<sup>2</sup>Percents are based on the overall total patients for the safety update (N=870).

<sup>3</sup>Percents are based on the overall total patients for the 14 mg/m<sup>2</sup> group (N=610).

<sup>4</sup>Romidepsin is administered in combination with other agents in these trials.

<sup>5</sup>One patient with non-Hodgkin's lymphoma was enrolled in Study GPI-06-0005.

<sup>6</sup>Two patients in Study FJ-228-0007 were treated previously with romidepsin in Study FJ-228-0002; these patients are not included in the total count for solid tumors or the overall total count. Note that they were included in the total counts in the ISS tabulation.

**Table 34: Data Cut-off Dates in the ISS and the 4-Month Safety Update**

Study	ISS Data Cut-off Date	4-Month Safety Update Cut-off Date
GPI-04-0001	October 2007	Study Complete; last patient/last visit October 2008 (final data included in this update)
NCI 1312 CTCL	December 2007 for patients who received at least 1 study drug dose before March 2007	Enrollment complete; patients ongoing on treatment April 2009
GPI-06-0002	December 2007	February 2009
GPI-06-0003	December 2007	Study Complete; last patient/last visit September 2008 (final data included in this update)
GPI-06-0005	December 2007	March 2009
NCI Studies in other indications	October 2007 as contained in the December 2007 quarterly transfer of the NCI CDUS and AdEERS databases	December 2008 for CDUS and November 2008 for AdEERS

Source: NDA 22393

## 6.2 Adequacy of Safety Assessments

### 6.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The overall exposure of romidepsin in the two CTCL studies is shown below.

**Table 35: Romidepsin exposure in studies GPI-04-0001 and NCI 1312**

	GPI-04-0001 n (%)		NCI 1312 n (%)	
Enrolled	96	102	71	83
Treated	96	102	71	83
Mean (±Std Dev)	4.7 (3.68)	n/a	7.5 (10.03)	n/a
Median	4.0	n/a	4.0	n/a
Range	1, 23	n/a	1, 72	n/a
Treated in:				
Cycle 1	96 (100)	n/a	71 (100)	n/a
Cycle 2	84 (88)	n/a	65 (92)	n/a
Cycle 3	72 (75)	n/a	58 (82)	n/a
Cycle 4	55 (57)	n/a	44 (62)	n/a
Cycle 5	45 (47)	n/a	33 (47)	n/a
Cycle 6	36 (38)	37 (36)	27 (38)	34 (41)
Cycle ≥7	10 (10)	10 (10)	23 (32)	27 (33)
Cycle ≥12	5 (5)	5 (5)	13 (18)	13 (16)
Duration of Treatment (Days)				
Mean (±Std Dev)	120.4 (108.66)	n/a	211.7 (322.33)	n/a
Median	110.0	n/a	106.0	n/a
Range	1, 666	n/a	5, 2284	n/a
Total Romidepsin Dose (mg)				
Mean (±Std Dev)	331.8 (284.45)	n/a	557.3 (772.15)	n/a
Median	278.8	n/a	306.0	n/a
Range	24.0, 1764	n/a	42.8, 5681	n/a

Data cut-off: GPI-04-0001 May 2008, NCI1312 March 2007  
 Source: NDA 22393

Reviewer comments: The median number of cycles and the median dose of romidepsin were similar in both studies. However, more patients had dose delay in the GPI study whereas more patients had dose reductions in the NCI study. This is due to differences in the dose modification criteria. We will revisit these differences in the discussion of adverse events.

### 6.3 Major Safety Results

#### 6.3.1 Deaths

The table below includes all deaths which occurred at the safety cut-off and 120-day safety update. There is no predominant cause of death. On initial examination, it appears that a number of patients on study NCI 1312 died due to infection. However, three of these patients were off study and had received non-study therapy prior to the event. Also seven causes of death are listed

for study GPI-04-0001. In one patient, the cause of death was listed as both dyspnea and disease progression.

**Table 36: Deaths on studies GPI-04-0001 and NCI 1312 (initial safety and 120-day safety up data cut-off)**

Death	Study GPI-04-0001		NCI Study 1312	
	N=96 (%)	N=102* (%)	N=71 (%)	N=83* (%)
Total number of patients at cut-off				
On study death	6	6	6	7
<30 days	1	1	0	0
30-60 days	3	3	3	3
60-90 days	1	1	0	0
> 90 days	1	1	3	4
<b>Cause of death<sup>1</sup></b>				
Cardiopulmonary failure	1	1	0	0
Myocardial ischemia	0	0	1	1
Acute renal failure	1	1	0	0
Dyspnea/ARDS	1	1	1	1
Infection/neutropenic infection/sepsis/septic shock	0	0	4	4
Disease progression	4	4	0	1

<sup>1</sup>Subject 91084 of study GPI-04-0001 had both dyspnea and disease progression as the cause of death.

\* 120-day safety update; Only one additional death observed on NCI study 1312, a 73 year old man who received 3 cycles of romidepsin 14 mg/m<sup>2</sup>, died 26 days post-treatment; the cause of death was reported as disease progression. No other adverse reactions were reported in this patient. No additional patient on-study deaths were reported in Study GPI-06-0001 for this safety update.

Source: NDA 22393

In addition to the deaths reported in both GPI-04-0001 and NCI 1312 studies, 6 unexpected deaths have occurred in other romidepsin clinical trials (N = 513) in patients with non-CTCL malignancies. Four cases were clearly cardiogenic, regardless of the relationship to the study drug. In the other two patients, one cause of death was unknown (per autopsy) and one was disease progression.

Reviewer comments: The deaths were associated with AEs are of concern, but the number of deaths appeared to be acceptable.

### 6.3.2 Nonfatal Serious Adverse Events

The table below lists the non-fatal serious adverse events in  $\geq 2\%$  of patients in either study from the safety cut off and 120-day safety update cut-off. Progressive disease has been removed from the serious adverse events.

**Table 37: Serious adverse events of studies GPI-04-0001 and NCI 1312 (initial safety and 120-day safety update cut-off)**

Adverse Reactions	GPI-04-0001		NCI Study 1312	
	N=96 (%)	N=102* (%)	N=71 (%)	N=83* (%)
Total number of patients at cut-off				
At least one serious treatment emergent adverse reaction	21 (22)	23 (23)	40 (56)	49 (59)
<b>Cardiac Disorders</b>	<b>5 (5)</b>	<b>5 (5)</b>	<b>8 (11)</b>	<b>9 (11)</b>

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Adverse Reactions	GPI-04-0001		NCI Study 1312	
	N=96 (%)	N=102* (%)	N=71 (%)	N=83* (%)
Total number of patients at cut-off				
Supraventricular arrhythmia	0	0	4 (6)	5 (6)
Ventricular arrhythmia	0	0	3 (4)	3 (4)
<b>Gastrointestinal Disorders</b>	<b>2 (2)</b>	<b>2 (2)</b>	<b>6 (8)</b>	<b>6 (7)</b>
Dyspepsia	0	0	2 (3)	2 (2)
Nausea	0	0	3 (4)	3 (4)
<b>General Disorders and Administration Site Conditions</b>	<b>6 (6)</b>	<b>6 (6)</b>	<b>13 (18)</b>	<b>15 (18)</b>
Fatigue	1 (1)	1 (<1)	5 (7)	6 (7)
Pyrexia	3 (3)	3 (3)	2 (3)	3 (4)
Edema	0	0	4 (6)	4 (5)
Disease progression	2 (2)	2 (2)	0	6 (7)
Rigors	1 (1)	1 (<1)	1 (1)	1 (1)
Injection site reaction	0	0	2 (3)	2 (2)
Immune system disorders	0	0	1 (1)	2 (2)
Hypersensitivity	0	0	1 (1)	2 (2)
<b>Infections and Infestations</b>	<b>7 (7)</b>	<b>8 (8)</b>	<b>20 (28)</b>	<b>26 (31)</b>
Infection	0	0	15 (21)	8 (10)
Sepsis	2 (2)	3 (3)	3 (4)	3 (4)
Catheter /central line related infection	0	0	5 (7)	8 (10)
Pneumonia	0	0	2 (2)	2 (2)
Skin infection	0	0	2 (2)	2 (2)
Urinary tract infection	1 (1)	1 (<1)	1 (1)	1 (1)
<b>Investigations</b>	<b>2 (2)</b>	<b>2 (2)</b>	<b>10 (14)</b>	<b>13 (16)</b>
Neutrophil count	0	0	3 (4)	5 (6)
White blood cell count decreased	0	0	3 (4)	3 (4)
Platelet count decreased	0	0	3 (4)	3 (4)
Aspartate aminotransferase increased	0	0	2 (3)	3 (4)
Blood bilirubin increased	0	0	2 (3)	2 (2)
Blood creatinine increased	0	0	2 (3)	2 (2)
Hemoglobin decreased	0	0	2 (2)	2(2)
<b>Metabolism and Nutrition Disorders</b>	<b>3 (3)</b>	<b>3 (3)</b>	<b>8 (11)</b>	<b>10 (12)</b>
Hyperuricemia	0	0	4 (6)	4 (5)
Dehydration	0	0	3 (4)	3 (4)
Anorexia	1 (1)	1 (<1)	2 (3)	2 (2)
Hypophosphatemia	1 (1)	0	1 (1)	3 (4)
Hypoalbuminemia	0	1 (<1)	1 (1)	1 (1)
<b>Neoplasms Benign, Malignant and Unspecified</b>	<b>5 (5)</b>	<b>5 (5)</b>	<b>1 (1)</b>	<b>1 (1)</b>
Neoplasm progression	4 (4)	4 (4)	0	0
Tumour lysis syndrome	2 (2)	2 (2)	0	0
<b>Nervous System Disorders</b>	<b>1 (1)</b>	<b>1 (&lt;1)</b>	<b>4 (6)</b>	<b>5 (6)</b>
Syncope	1 (1)	1 (<1)	1 (1)	2 (2)
<b>Respiratory, Thoracic and Mediastinal Disorders</b>	<b>2 (2)</b>	<b>2 (2)</b>	<b>3 (4)</b>	<b>5 (6)</b>
Dyspnea	0	0	3 (4)	3 (4)
<b>Skin and Subcutaneous Tissue Disorders</b>	<b>1 (1)</b>	<b>1 (&lt;1)</b>	<b>3 (4)</b>	<b>3 (4)</b>
Dermatitis exfoliative	0	0	2 (3)	2 (2)
<b>Surgical and Medical Procedures</b>	<b>0</b>	<b>0</b>	<b>3 (4)</b>	<b>3 (4)</b>
Packed red blood cell transfusion	0	0	2 (3)	2 (2)
<b>Vascular Disorders</b>	<b>3 (3)</b>	<b>4 (4)</b>	<b>5 (7)</b>	<b>5 (6)</b>
Hypotension	2 (2)	2 (2)	4 (6)	4 (5)
Thrombosis	1 (1)	1 (<1)	1 (1)	1 (1)

\* 120-day safety update

Source: NDA 22393

Reviewer comments: A two fold increase in serious AEs was reported in the NCI study when compared to the GPI study and may be due to, in part, to differences in the criteria for dose delay.

The increase in SAEs may also in part be due to increased use of hospitalization at the NCI Clinical Center. The difference in SAEs was primarily due to infections, and includes neutropenic infection, sepsis, septic shock, endocarditis, and catheter or IV site infection, etc.

### 6.3.3 Discontinuation

The table below summarizes the applicant's analyses of adverse events associated with discontinuation in at least 2% of patients. Three patients with discontinuation due to allergic dermatitis are not included in the table; one patient each with dermatitis medicamentosa, allergic dermatitis, and toxic skin eruption. Patient 52061 developed a pustular rash (ultimately grade 4) associated with fever on C1, D4. Patient 54049 developed grade 2 allergic dermatitis on C1, D4 and patient 94083 developed a grade 2 toxic skin eruption on C1, D2 which was treated with intravenous steroids. In all cases the investigator attributed this to study drug.

**Table 38: Adverse events associated with treatment discontinuation**

System/Term	GPI-04-0001		NCI 1312	
	N = 96	N = 102*	N = 71	N = 83*
<b>Discontinuation due to AE**</b>	<b>20 (21)</b>	<b>24 (24)</b>	<b>8 (11)</b>	<b>10 (12)</b>
General Disorders	5 (5)	5 (5)	1 (1)	2 (2)
Fatigue	4 (4)	4 (4)	1 (1)	1 (1)
Pyrexia	2 (2)	2 (2)	0	0
Infection and Infestation	3(3)	4 (4)	4 (6)	4 (5)
Investigations	5 (5)	5 (5)	0	0
QT Prolongation	3 (3)	3 (3)	0	0
Neoplasms Benign, Malignant and Unspecified	4 (4)	4 (4)	0	0
Neoplasms Progression	2 (2)	3 (3)	0	0
Respiratory, Thoracic and Medial Disorders	2 (2)	2 (2)	2 (3)	2 (2)
Dyspnea	0	0	2 (3)	2 (2)

\* 120-day safety update

\*\* Three patient in GPI study and 1 patients in NCI study discontinued treatment because of disease progression.

Source: NDA 22393

Per applicant information, complete information on dose modifications due to adverse events was only available from Study 1 (GPI-04-0001, N=102). Fourteen of the 102 patients (14%) had dose reductions due to adverse events: vomiting in 3% (3/102) of patients; nausea, weight decreased, and ECG QT/QTc prolongation, each in 2% (2/102) of patients; and the remainder in 1 patient each. Thirty-five of the 102 patients (34%) had at least 1 dose delay reported due to adverse events: neutropenia and hypomagnesemia, each in 5% (5/102) of patients, asthenia in 4% (4/102) of patients; nausea, sepsis, pharyngitis, upper respiratory tract infection,

hypokalemia, and thrombocytopenia, each in 2% (2/102) of patients; and the remainder in 1 patient each.

Reviewer comments: In contrast to SAEs, AEs causing treatment discontinuation in the GPI study were 2 fold higher in the GPI study than the NCI study. This could be due to differences in the dose modification plans. In addition, 5 discontinuations caused by AEs in the GPI study and not shown on this table, include four patients with allergic rash and one with an infusion reaction. The treatment discontinuation because AEs, excluding disease progression, was 21% for GPI study and 11% for NCI study.

### 6.3.4 Significant Adverse Events

#### 6.3.4.1 Cardiology/EKG

Due to concern over observation of fatal cardiac events, prolonged QT interval, SVT/VT events, and a high percentage of ST-T changes, we conducted a detailed cardiac safety analysis focusing on serious and potentially serious events, as shown in the tables below. A large number of ST-T wave segment changes were reported on the NCI study, primarily T wave flattening with non-specific ST changes. Troponins were not routinely collected in patients with an abnormal EKG. However, 7 patients with ST-T changes had troponin elevation and 5 were grade 3 based on the safety update data. In addition, a prolonged QT interval was reported in 59 patients at the time of safety update. Among patients with QT prolongations, one had a ventricular arrhythmia, 1 a nodal rhythm, 2 a supraventricular arrhythmia, and one patient had a QT interval of 526 msec, a grade 3 abnormality.

Given these reports, we examined all patients who had received romidepsin, including the 616 patients with other tumor types. We found three patients with grade 3-4 ventricular arrhythmias and one patient with a grade 2 wide complex tachycardia.

**Table 39: Cardiac toxicities in CTCL patients received romidepsin by category**

Patients with at least 1 of the following	Study GPI-04-0001 (N=96) n (%)	NCI Study 1312 (N=71) n (%)
Cardiac disorder	16 (17)	12 (17)
Study-drug related cardiac disorder	12 (13)	9 (13)
≥Grade 3 cardiac disorder	5 (5)	4 (6)
≥Grade 3, study-drug related cardiac disorder	4 (4)	3 (4)
Grade 4 cardiac disorder	3 (3)	0
Grade 4, study-drug related cardiac disorder	2 (2)	0
Grade 5 cardiac disorder	1 (1)	1 (1)
Serious cardiac disorder	5 (5)	8 (11)
Cardiac disorder leading to study drug discontinuation	3 (3)	0

\* 120-day safety update

Source: NDA 22393

**Table 40: Cardiac toxicities in CTCL patients received romidepsin by term**

Cardiac Adverse Events	GPI All	GPI 3-4	GPI G5	NCI All	NCI G3-4	NCI Death
Acute Cardio - Pulmonary Insufficiency	1	0	1	0	0	0
Acute Myocardial Infarction	1	0	1	0	0	0
Bradyarrhythmia	2	1	0	2	0	0
Bradycardia	1	0	0	2	0	0
CHF	2	2	0	0	0	0
Cardiac Ischemia	1	0	0	1	0	1
Cardiac Tamponade	1	1	0	0	0	0
Cardiovascular/Arrhythmia-Other	1	0	0	1	0	0
Chest Pain (Cardiac)	3	0	0	0	0	0
Conduction Abnormality/Atrioventricular Heart Block	3	2	0	1	0	0
Metabolic Cardiomyopathy	1	0	0	0	0	0
Mitral Insufficiency	1	0	0	0	0	0
Palpitation	3	0	0	2	0	0
Sinus Tachycardia	3	0	0	1	0	0
Supraventricular Arrhythmias (SVT/Atrial Fibrillation/Flutter)	2	1	0	10	3	0
Tricuspidal Insufficiency	1	0	0	0	0	0
Ventricular Arrhythmia (PVCs/Bigeminy/Trigeminy/Ventricular Tachycardia)	2	1	0	6	0	0
Cardiac Troponin I (Ctni)	3	3	0	4	2	0
Prolonged QTc Interval (QTc >0.48 Seconds)	4	2	0	55	0	0
ST-T Segment Change	1	0	0	38	0	0
CPK (Creatine Phosphokinase)	0	0	0	13	1	0
New U-Wave In ECG	1	0	0	0	0	0
ST - Depression	2	1	0	0	0	0
Hypotension	6	2	0	22	3	0
Hypertension	2	0	0	2	0	0

Source: NDA 22393

Reviewer comments: Several treatment-emergent morphological changes in ECGs (including T wave and ST-segment changes) have been reported in clinical studies. The clinical significance of these changes is unknown.

In addition, a few fatal functional cardiac events, such as myocardial ischemia and cardiopulmonary failure, and severe AEs, such as SVT and VT have been observed in patients receiving romidepsin. Therefore, in patients with congenital long QT syndrome, patients with a history of significant cardiovascular disease, and patients taking medicine that lead to significant QT prolongation, appropriate cardiovascular monitoring precautions should be considered, such as the monitoring of electrolytes and ECGs at baseline and periodically during treatment.

### 6.3.4.2 Infection

Patients with CTCL are immunocompromised and do not have an intact skin barrier. Therefore, one critical concern is infection. Assessment showed 47 patients on the GPI study and 45 on the NCI study developed an infection. We assessed patients with grade 3-4 infections and found substantial differences between the GPI and NCI studies. Infections in the GPI study were due to skin infections, sepsis, and oral candidiasis whereas in the NCI study, infection NOS, febrile neutropenia, and sepsis, were the most frequently reported terms. The largest number of grade 3-4 events was infection NOS in the NCI study. Additional information concerning the type of infection was only available for a subset of these patients and these have been discussed under serious adverse events.

**Table 41: Infections in CTCL patients receiving romidepsin**

Infection AEs	GPI ALL	GPI G3-4	NCI All	NCI G3-4	NCI G5
Number of Patients has at least one infection	47	11	45	27	1
Skin Infection	27	6	6	0	0
Acute Bronchitis	1	0	0	0	0
Acute Periostitis Abscess Of Teeth 3, 4 Right Upper	1	0	1	0	0
Upper Respiratory Infection	6	0	0	0	0
Sepsis	6	5	6	6	0
Candida Oral	9	4	0	0	0
Endocarditis	0	0	1	1	0
Catheter-Related Infection	0	0	4	3	0
Cold	8	0	0	0	0
Ear Infection	5	0	0	0	0
Erysipelas	1	0	0	0	0
Eye Infection	1	0	0	0	0
Infection Of The Urinary Tract	3	0	36	24	0
Infection With Unknown NOS	3	0	16	8	1
Bacteremia	0	0	2	0	0
Infection/Febrile Neutropenia	0	0	7	7	0
Influenza	2	0	0	0	0
Cellulitis	4	0	0	0	0
Perineal Abscess	1	1	0	0	0
Pharyngitis/ Tonsillitis	6	2	0	0	0
Pneumonia	2	2	0	0	0
Skin Abscesses	1	0	0	0	0
Sinus Infection	1	0	0	0	0
Viral Infection	1	0	0	0	0
Wound Infection	2	0	0	0	0

Source: NDA 22393

Reviewer comments: Given the nature of the disease and the myelosuppressive effects of romidepsin, a large number of infectious AEs were observed in both studies. Skin infection was the predominate infection in the GPI-04-0001 study. For the NCI 1312 study, UTI and systemic infections were predominate. This difference, observed between the two studies, may due to differences in the dose modification criteria used for each study.

### 6.3.4.3 Skin

In patients with CTCL, the skin lesions are the primary source of symptoms and comorbidity. Therefore, an increase in skin system AEs would be expected when systemic treatment is administered to a CTCL patient. The skin system AEs observed in both single arm romidepsin studies are summarized below.

**Table 42: Skin toxicities in CTCL patients receiving romidepsin**

Skin AEs	GPI All	GPI G3-4	NCI All	NCI G3-4
Allergic Dermatitis	4	0	4	1
Alopecia/ Hair Loss	3	0	2	0
Atopic Eczema	1	0	0	0
Burning of Skin/Tumor	3	1	0	0
Dermatology/Skin-Other (Blemish On Forehead)	0	0	1	0
Ecchymosis	0	0	3	0
Erythemata of Skin	2	0	2	0
Pruritus	7	0	39	8
Rash/Desquamation	4	0	2	2
Dry Skin	2	0	2	0
Edema	1	0	1	0
Edema of Face	1	0	0	0
Erythema Multiforme	0	0	1	1
Nail Changes	0	0	2	0
Pain (Superficial Skin Pain)	1	0	0	0
Skin Lesion With Exudation / Nonhealing Ulcers	3	0	0	0
Perspiration/Sweating	1	0	2	0
Pigmentation Changes (e.g., Vitiligo)	0	0	1	0
Pyoderma	1	0	0	0
Right Forearm Fissure	1	0	0	0
Skin Cysts Of Abdomen	1	1	0	0
Skin Soreness	1	0	0	0
Toxicoderma/ Pustular Toxicodermatosis	2	1	0	0
Weeping Skin Tumors	1	0	0	0

Source: NDA 22393

Reviewer comments: The predominate skin AEs were manifestations of either their underlying disease or romidepsin treatment. In a single arm study, these cannot be differentiated.

### 6.3.5 Submission Specific Primary Safety Concerns

The pharmacology/toxicology reviewers brought a potential safety issue to the clinical reviewers' attention. The final romidepsin drug product contains a [redacted] [redacted] not currently listed in ICH Q3C. The proposed specification limit for [redacted] [redacted] /vial with a maximum allowed dose of four vials (40 mg romidepsin). This would result in a maximum dose of [redacted] [redacted] per patient. Since the safety of I.V. administered [redacted] [redacted] has not been adequately established, the total level of [redacted] [redacted] per patient should not exceed levels previously given to patients in clinical trials, i.e., up to [redacted] [redacted]. Therefore, based on patient exposure of up to 33.8 mg romidepsin (approximately 3.4 vials with 10 mg romidepsin per vial) and the recommended dose of 14 mg/m<sup>2</sup>, the level of [redacted] [redacted] in the final drug product may not exceed [redacted] [redacted] 10 mg romidepsin vial.

b(4)

To investigate whether any [redacted] [redacted] safety signal may be present in the available data from the CTCL clinical trials, the clinical and statistical reviewers conducted the following analyses.

b(4)

#### 6.3.5.1 Safety Analyses by Body Surface Area (BSA)

The patients from both CTCL studies were sub-grouped by their BSA, <2 m<sup>2</sup> or ≥2 m<sup>2</sup>.

Table 43: Patients grouped by BSA

BSA	All	GPI	NCI
<2	104	58	46
≥2	75	44	30
No record*	6	0	7
No AE	3	3	0

\*NCI1312-900-00-5498, NCI1312-900-00-4865, NCI1312-900-00-4874, NCI1312-42-62-96-7, NCI1312-900-00-5679, NCI1312-900-00-5708, and NCI1312-900-00-5714 did not have BSA recorded in the dataset.

The body system AEs observed in each study were summarized by body surface area (<2, ≥2) in the table below. There was no obvious difference in the frequency of AEs between the two BSA groups of each study, except for a slight increase in AEs involving the nervous system for patients with a BSA ≥ 2 m<sup>2</sup> in study GPI-04-0001.

The [redacted] [redacted] level was discussed with the CMC review team and was found to vary by the batch that was used in the clinical trial. Therefore, we requested that the applicant provide information on the batch IDs used for each CTCL study and each patient in the two CTCL trials for further analyses.

b(4)

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**Table 44: Body system AEs by BSA in each CTCL clinical trial**

Body Systems	GPIBSA <2			GPIBSA ≥2			NCI BSA <2			NCI BSA ≥2		
	All	%	G3-4	All	%	G3-4	All	%	G3-4	All	%	G3-4
Blood And Lymphatic System Disorders	18	30	4	7	11	33	0	0	24	63	15	39
Cardiac Disorders	9	15	3	5	5	15	0	0	5	13	0	0
Congenital, Familial And Genetic Disorders	1	2	0	0	0	0	0	0	0	0	0	0
Ear and Labyrinth Disorders	2	3	0	0	0	0	0	0	2	5	0	0
Endocrine Disorders	1	2	0	0	0	0	0	0	0	0	0	0
Eye Disorders	3	5	0	0	1	3	0	0	4	11	0	0
Gastrointestinal Disorders	42	69	4	7	24	73	1	3	35	92	7	18
General Disorders and Administration Site	37	61	7	11	23	70	6	18	37	97	8	21
Conditions												
Hepatobiliary Disorders	2	3	0	0	1	3	1	3	0	0	0	0
Immune System Disorders	1	2	0	0	1	3	0	0	1	3	1	3
Infections and Infestations	28	46	5	8	17	52	6	18	19	50	13	34
Injury, Poisoning and Procedural Complications	6	10	0	0	4	12	0	0	2	5	0	0
Investigations	27	44	4	7	16	48	2	6	36	95	19	50
Metabolism and Nutrition Disorders	25	41	4	7	12	36	1	3	34	89	12	32
Musculoskeletal and Connective Tissue Disorders	9	15	2	3	7	21	1	3	11	29	1	3
Neoplasms Benign, Malignant and Unspecified (Incl Cysts And Polyps)	3	5	0	0	4	12	3	9	4	11	1	3
Nervous System Disorders	18	30	1	2	14	42	0	0	23	61	2	5
Psychiatric Disorders	5	8	0	0	6	18	0	0	10	26	2	5
Renal and Urinary Disorders	2	3	0	0	0	0	0	0	1	3	0	0
Reproductive System and Breast Disorders	0	0	0	0	0	0	0	0	1	3	0	0
Respiratory, Thoracic and Mediastinal Disorders	11	18	2	3	7	21	2	6	7	18	3	8
Skin and Subcutaneous Tissue Disorders	21	34	3	5	8	24	0	0	22	58	7	18
Surgical and Medical Procedures	1	2	0	0	0	0	0	0	3	8	2	5
Vascular Disorders	15	25	4	7	5	15	3	9	16	42	2	5

Source: NDA 22393

6.3.5.2 \_\_\_\_\_ exposure and AEs in study GPI-04-0001

b(4)

The \_\_\_\_\_ level per 10 mg romidepsin vial in batches used in study GPI-04-0001 is summarized in the table below.

b(4)

Batch ID	_____ (mg/10 mg romidepsin)	First and last shipment date
485665	_____	Dec 2004 – May 2007
909090	_____	April 2007 – April 2008
914734	_____	April 2008 – Oct 2008

b(4)

Source: NDA 22393 Oct 2, 2009 amendment

Since the \_\_\_\_\_ of all batches used for study GPI-04-0001 were \_\_\_\_\_, the amount of \_\_\_\_\_ given to each GPI patient was solely determined by their BSA. The maximal romidepsin exposure was 36.1 mg (14mg/m<sup>2</sup>) and the maximal \_\_\_\_\_ exposure was \_\_\_\_\_ in the same patient with BSA of 2.6 m<sup>2</sup> in study GPI-04-0001.

b(4)

Table 45: Estimated \_\_\_\_\_ exposure in study GPI-04-0001

BSA groups	_____ received (mg)	Number
1.4	_____	4
1.5	_____	5
1.6	_____	7
1.7	_____	9
1.8	_____	20
1.9	_____	13
2	_____	16
2.1	_____	14
2.2	_____	6
2.3	_____	5
2.4	_____	2
2.6	_____	1

b(4)

Source: NDA 22393, safety update and Oct 2, 2009 amendment

The AEs observed in study GPI-04-0001 were analyzed by BSA subgroups in 0.1 m<sup>2</sup> increments using the body system or specific terms, as shown in two tables below. Using the multiple variable analysis, only the metabolic system AEs that are ≥ grade 3 had a statistically significant increase in frequency with an increase in BSA (p = 0.262). This increase in frequency was only seen by multivariate analysis.

Table 46: Study GPI-04-0001 AEs in each body system by BSA groups

BSA groups (m <sup>2</sup> ) / Body System All AEs (n, %)	1.4 n=4	1.5 n=5	1.6 n=7	1.7 n=9	1.8 n=20	1.9 n=13	2.0 n=16	2.1 n=14	2.2 n=6	2.3 n=5	2.4 n=2	2.6 n=1
Blood And Lymphatic System Disorders	50	20	57	33	45	8	13	29	50	80	50	0
Cardiac Disorders	25	20	29	22	5	15	13	21	17	40	0	0

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<b>BSA groups (m<sup>2</sup>) / Body System All AEs (n, %)</b>	<b>1.4 n=4</b>	<b>1.5 n=5</b>	<b>1.6 n=7</b>	<b>1.7 n=9</b>	<b>1.8 n=20</b>	<b>1.9 n=13</b>	<b>2.0 n=16</b>	<b>2.1 n=14</b>	<b>2.2 n=6</b>	<b>2.3 n=5</b>	<b>2.4 n=2</b>	<b>2.6 n=1</b>
Congenital, Familial and Genetic Disorders	0	0	0	11	0	0	0	0	0	0	0	0
Ear and Labyrinth Disorders	0	20	14	0	0	0	0	0	0	0	0	0
Endocrine Disorders	0	0	0	0	5	0	0	0	0	0	0	0
Eye Disorders	0	0	14	0	15	0	0	0	0	0	50	0
Gastrointestinal Disorders	50	60	100	67	65	62	69	79	67	80	100	100
General Disorders and Administration Site Conditions	75	80	71	44	50	77	56	86	50	100	50	100
Hepatobiliary Disorders	0	0	0	0	5	0	6	0	0	20	0	0
Immune System Disorders	0	0	0	0	5	0	0	0	0	20	0	0
Infections and Infestations	25	60	71	78	35	31	38	50	67	60	50	100
Injury, Poisoning and Procedural Complications	0	0	14	0	15	8	13	7	0	20	50	0
Investigations	50	20	43	56	30	54	38	64	33	100	0	0
Metabolism and Nutrition Disorders	25	80	57	33	40	38	31	21	50	60	50	100
Musculoskeletal and Connective Tissue Disorders	0	0	57	22	15	15	6	14	50	20	50	0
Neoplasms Benign, Malignant and Unspecified	0	0	0	11	5	15	6	14	17	20	50	0
Nervous System Disorders	25	20	57	11	40	38	31	43	50	20	50	100
Psychiatric Disorders	0	40	14	11	5	15	0	21	17	20	50	0
Renal and Urinary Disorders	25	0	0	11	5	0	0	0	0	20	0	0
Respiratory, Thoracic and Mediastinal Disorders	0	20	43	22	5	31	13	21	17	40	0	100
Skin and Subcutaneous Tissue Disorders	25	40	43	33	40	23	19	21	33	40	50	0
Surgical and Medical Procedures	0	0	0	0	5	0	0	0	0	0	0	0
Vascular Disorders	0	60	29	44	20	0	19	21	0	40	0	0

\* Statistically significant with an increase in BSA (p = 0.262)

Source: NDA 22393, safety update and Oct 2, 2009 amendment

**Table 47: GPI >G3 AEs by BSA**

BSA groups (m <sup>2</sup> ) / Body System G3-4 AEs (n, %) /	1.4 n=4	1.5 n=5	1.6 n=7	1.7 n=9	1.8 n=20	1.9 n=13	2.0 n=16	2.1 n=14	2.2 n=6	2.3 n=5	2.4 n=2	2.6 n=1
Blood and Lymphatic System Disorders	50	20	14	0	10	0	0	0	0	0	0	0
Cardiac Disorders	0	0	14	0	5	8	6	7	0	20	0	0
Congenital, Familial and Genetic Disorders	0	0	0	0	0	0	0	0	0	0	0	0
Ear and Labyrinth Disorders	0	0	0	0	0	0	0	0	0	0	0	0
Endocrine Disorders	0	0	0	0	0	0	0	0	0	0	0	0
Eye Disorders	0	0	0	0	0	0	0	0	0	0	0	0
Gastrointestinal Disorders	25	20	0	0	0	8	6	0	0	40	0	0
General Disorders and Administration Site Conditions	25	40	0	11	15	15	6	29	17	20	0	0
Hepatobiliary Disorders	0	0	0	0	0	0	0	0	0	20	0	0
Immune System Disorders	0	0	0	0	0	0	0	0	0	0	0	0
Infections and Infestations	25	20	29	11	0	8	0	29	0	40	0	0
Injury, Poisoning and Procedural Complications	0	0	0	0	0	0	0	0	0	0	0	0
Investigations	0	0	0	22	0	15	0	14	0	0	0	0
Metabolism and Nutrition Disorders*	0	20	0	0	10	8	0	7	0	20	0	0
Musculoskeletal and Connective Tissue Disorders	0	0	0	0	5	0	6	7	0	0	0	0
Neoplasms Benign, Malignant and Unspecified	0	0	0	0	5	0	6	14	17	0	0	0
Nervous System Disorders	0	0	14	0	0	0	0	0	0	0	0	0
Psychiatric Disorders	0	0	14	0	0	0	0	0	0	0	0	0
Renal and Urinary Disorders	25	0	0	0	0	0	0	0	0	0	0	0
Respiratory, Thoracic and Mediastinal Disorders	0	0	0	11	0	8	0	7	0	20	0	0
Skin and Subcutaneous Tissue Disorders	0	20	0	0	10	0	0	0	0	0	0	0
Surgical and Medical Procedures	0	0	0	0	0	0	0	0	0	0	0	0
Vascular Disorders	0	40	14	0	5	0	6	7	0	40	0	0

\* Statistically significant with an increase in BSA (p = 0.262)

Source: NDA 22393, safety update and Oct 2, 2009 amendment

6.3.5.3 Exposure and AEs in study NCI 1312

b(4)

Batches with various strength levels per 10 mg romidepsin vial used in study NCI1312 are summarized in the table below. The amount of drug given to each patient at each dose could vary not only by the body surface area, but also by differences in the batches' strength level.

b(4)

Table 48: Batches used in study NCI 1312

Batch ID	Strength (mg/10 mg romidepsin)	First and last shipment date
96209		Mar 2001 - Mar 2002
01-202		April 2002 - Oct 2004
339331		Oct 2004 - Oct 2005
482083		June 2005 - June 2005
485665		Nov 2005 - March 2007
909090		April 2007 - Dec 2008
914734		Dec 2008 - Dec 2008
1286403		Jan 2009 - April 2009

b(4)

Source: NDA 22393 and Oct 2, 2009 amendment.

The estimated drug exposure for each patients of study NCI 1312 was calculated based on the strength in each romidepsin batch. The highest drug exposure was observed (NCI1312-34-34-48-5) with 41.9 mg (18 mg/m<sup>2</sup>) romidepsin. Another patient received the highest romidepsin dose, 44.3 mg (18 mg/m<sup>2</sup>) and was observed. Based on the information provided by the applicant and our estimate in the table below, 33 patients received batches with 4 different strength levels, 11 patients received batches with 3 different strength levels and 10 patients received batches with 2 different strength levels. Just 30 patients received batches with same strength level. The BSA value was missing for seven patients in the study NCI 1312 dataset, therefore, drug exposure was not estimated in these 7 patients.

b(4)

Table 49: Estimated drug exposure of each study NCI 1312 patient by batch

b(4)

Drug exposure	18 mg/m <sup>2</sup>	14 mg/m <sup>2</sup>	10 mg/m <sup>2</sup>	7 mg/m <sup>2</sup>	5 mg/m <sup>2</sup>	3 mg/m <sup>2</sup>
N (n=83)	32	11	3	2		
NCI 1312 Patient ID (safety update)	BSA	Romidepsin dose (mg/m <sup>2</sup> )	18 mg	14 mg	10 mg	7 mg
NCI1312-34-34-48-5	2.33	18				
NCI1312-35-06-77-0	2.46	18				
NCI1312-35-54-80-6	1.43	18				
NCI1312-29-63-79-6	1.89	14				
NCI1312-35-93-87-3	2.05	14				
NCI1312-35-98-77-9	1.61	14				
NCI1312-36-00-75-0	1.70	14				
NCI1312-36-21-45-5	2.16	14				
NCI1312-36-26-18-0	1.72	14				
NCI1312-36-29-63-6	2.26	14				

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exposure						
N (n=83)	32	11	3	2		
NCI 1312 Patient ID (safety update)	BSA	Romidepsin dose (mg/m <sup>2</sup> )	(mg)	(mg)	(mg)	(mg)
NCI1312-36-46-27-0	2.25	14				
NCI1312-36-74-61-7	1.93	14				
NCI1312-36-77-68-0	1.85	14				
NCI1312-37-01-34-7	1.88	14				
NCI1312-37-27-53-1	1.95	14				
NCI1312-37-41-53-9	2.27	14				
NCI1312-37-43-51-2	2.13	14				
NCI1312-37-55-25-3	1.84	14				
NCI1312-37-58-87-4	2.30	14				
NCI1312-37-72-13-5	2.36	14				
NCI1312-38-36-15-0	1.73	14				
NCI1312-38-55-93-4	2.10	14				
NCI1312-38-89-88-9	1.93	14				
NCI1312-39-11-21-4	2.02	14				
NCI1312-39-19-88-2	2.05	14				
NCI1312-39-72-17-3	1.97	14				
NCI1312-40-18-10-2	2.15	14				
NCI1312-40-38-57-5	1.98	14				
NCI1312-40-49-84-6	1.95	14				
NCI1312-40-54-33-7	1.92	14				
NCI1312-40-66-50-9	1.96	14				
NCI1312-40-73-32-0	1.82	14				
NCI1312-40-79-18-8	2.01	14				
NCI1312-40-91-88-7	1.75	14				
NCI1312-40-96-14-9	1.93	14				
NCI1312-41-05-79-5	2.31	14				
NCI1312-41-19-00-9	1.70	14				
NCI1312-41-47-15-7	2.19	14				
NCI1312-41-48-69-1	2.17	14				
NCI1312-42-62-96-7	.	14				
NCI1312-43-66-97-9	1.77	14				
NCI1312-44-14-02-0	1.56	14				
NCI1312-900-00-3570	2.03	14				
NCI1312-900-00-3880	2.00	14				
NCI1312-900-00-4262	1.85	14				
NCI1312-900-00-4757	2.32	14				
NCI1312-900-00-4853	2.10	14				
NCI1312-900-00-4865	.	14				
NCI1312-900-00-4874	.	14				
NCI1312-900-00-4892	1.68	14				
NCI1312-900-00-4919	1.46	14				

b(4)

b(4)

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exposure						
N (n=83)	32	11	3	2		
<i>NCI 1312 Patient ID (safety update)</i>	<i>BSA</i>	<i>Romidepsin dose (mg/m<sup>2</sup>)</i>	<i>(mg)</i>	<i>(mg)</i>	<i>(mg)</i>	<i>(mg)</i>
NCI1312-900-00-4932	2.16	14				
NCI1312-900-00-4947	1.72	14				
NCI1312-900-00-4965	1.98	14				
NCI1312-900-00-4986	1.76	14				
NCI1312-900-00-5023	1.82	14				
NCI1312-900-00-5027	1.41	14				
NCI1312-900-00-5048	1.76	14				
NCI1312-900-00-5091	2.10	14				
NCI1312-900-00-5103	1.56	14				
NCI1312-900-00-5124	2.11	14				
NCI1312-900-00-5125	2.19	14				
NCI1312-900-00-5141	2.14	14				
NCI1312-900-00-5228	1.83	14				
NCI1312-900-00-5318	1.99	14				
NCI1312-900-00-5344	2.05	14				
NCI1312-900-00-5435	1.87	14				
NCI1312-900-00-5450	2.08	14				
NCI1312-900-00-5471	1.63	14				
NCI1312-900-00-5494	2.05	14				
NCI1312-900-00-5498	.	14				
NCI1312-900-00-5514	1.96	14				
NCI1312-900-00-5520	1.60	14				
NCI1312-900-00-5536	1.63	14				
NCI1312-900-00-5572	1.85	14				
NCI1312-900-00-5590	1.97	14				
NCI1312-900-00-5591	1.94	14				
NCI1312-900-00-5621	1.72	14				
NCI1312-900-00-5629	1.53	14				
NCI1312-900-00-5679	.	14				
NCI1312-900-00-5708	.	14				
NCI1312-900-00-5714	.	14				
NCI1312-900-00-5716	1.77	14				

b(4)

b(4)

Source: NDA 22393, safety update and Oct 2, 2009 amendment

The body system AEs of study NCI 1312 were analyzed by the level of        received and sub-grouped by        as shown in table below. Besides patients whose        exposure cannot be estimated (n = 7), three patients who received 18 mg/m<sup>2</sup> romidepsin were excluded from this analysis in order to maintain the romidepsin exposure relatively constant. Of all the AEs, grade 3 or higher cardiac toxicity was statistically significantly higher in patients who received at least        (p = 0.0231).

b(4)

Table 50: Body system AEs in NCI 1312 study patients received 14mg/m<sup>2</sup> romidepsin

AEs by body systems	n=43				n=29			
	All	All%	>G3	>G3%	All	All%	>G3	>G3%
Blood and Lymphatic System Disorders	29	67	17	40	17	59	12	41
Cardiac Disorders	6	14	0	0	7	24	4	14*
Ear and Labyrinth Disorders	2	5	0	0	0	0	0	0
Endocrine Disorders	0	0	0	0	0	0	0	0
Eye Disorders	5	12	1	2	1	3	0	0
Gastrointestinal Disorders	39	91	6	14	28	97	7	24
General Disorders and Administration Site Conditions	41	95	8	19	26	90	6	21
Hepatobiliary Disorders	0	0	0	0	1	3	1	3
Immune System Disorders	2	5	1	2	2	7	0	0
Infections and Infestations	21	49	16	37	19	66	13	45
Injury, Poisoning and Procedural Complications	4	9	0	0	1	3	0	0
Investigations	42	98	21	49	27	93	13	45
Metabolism and Nutrition Disorders	40	93	14	33	23	79	9	31
Musculoskeletal and Connective Tissue Disorders	13	30	1	2	10	34	1	3
Neoplasms Benign, Malignant and Unspecified (Incl Cysts And Polyps)	5	12	1	2	4	14	0	0
Nervous System Disorders	24	56	2	5	15	52	1	3
Psychiatric Disorders	7	16	2	5	5	17	0	0
Renal and Urinary Disorders	2	5	1	2	3	10	0	0
Reproductive System and Breast Disorders	1	2	0	0	3	10	0	0
Respiratory, Thoracic and Mediastinal Disorders	9	21	4	9	8	28	3	10
Skin and Subcutaneous Tissue Disorders	24	56	9	21	15	52	3	10
Surgical and Medical Procedures	4	9	3	7	3	10	2	7
Vascular Disorders	18	42	2	5	8	28	3	10

b(4)

The grade 3 cardiac toxicity is statistically significantly higher (p = 0.0231) in patients who received         
Source: NDA 22393, safety update and Oct 2, 2009 amendment

b(4)

The significant AEs in 3 patients who received 18 mg/m<sup>2</sup> romidepsin are summarized in the table below.

Table 51: Maximal dose and significant AEs in study NCI 1312 patients receiving 18 mg/m<sup>2</sup> romidepsin

Subject ID (safety update)	BSA (m <sup>2</sup> )	Max Romidepsin dose (mg)	Max Dose (mg)	Significant AEs (mg)
NCI1312-34-34-48-5	2.33	41.9	—	Grade 4 neutropenia and leukopenia, grade 3 lymphopenia, thrombocytopenia and hypophosphatemia, frequent grade 2 anxiety/mood disturbances, and taste disturbance
NCI1312-35-06-77-0	2.46	44.3	—	Grade 3 confusion, hypomagnesemia, and thrombocytopenia
NCI1312-35-54-80-6	1.43	25.7	—	Grade 4 neutropenia and leukopenia, grade 3 lymphopenia, thrombocytopenia, AST, ALT, hyperkalemia, and hypermagnesemia

Source: NDA 22393, safety update and Oct 2, 2009 amendment

Reviewer comments: As described above, the FDA safety analyses regarding exposure in the CTCL clinical trial patients neither revealed a clear safety signal nor provided assurance of the safety of the clinical use of various levels of

In order to further explore the safety of the following information request was sent to (10/10/09) and discussed (10/13/09) with the applicant.

1) The highest dose (mg) of romidepsin and given to patients with CTCL in the GPI study.

2) Describe the AE profile for 20 patients who received the highest dose (mg) of. Please compare these AEs to the AEs of patients who received lower doses of. Please limit your analysis to patients who received at least 3 cycles of romidepsin.

3) Provide convincing data to indicate that doses higher than will not significantly add to toxicities associated with romidepsin. For example an intra-patient analysis which compares the AE profile following administration of study product with a small amount (such as a batch containing per vial) of and the AE profile following administration of study product with a larger amount (e.g., batch containing per vial) of

4) Please provide the datasets for all the above analyses.

FDA also informed the applicant that the above requests can be avoided if they can keep the /10 mg romidepsin vial. On Oct 15, 2009, the applicant submitted their revised CMC acceptance criteria to limit level equal or below vial.

## 6.4 Supportive Safety Results

### 6.4.1 Common and Grade 3/4 Adverse Events

The safety of romidepsin was evaluated in the 185 patients on the two CTCL single arm clinical trials included in the safety update. The mean duration of treatment in these studies was 5.6 months (range: <1 to 83.4 months). Due to methodological differences between the studies, the most common adverse reactions in the GPI Study were nausea, fatigue, infections, vomiting, and anorexia, and in the NCI Study were nausea, fatigue, anemia, thrombocytopenia, ECG T-wave changes, neutropenia, and lymphopenia. The common AEs and grade 3-4 AEs observed the time of initial safety cut-off are shown in the table below.

**Table 52: Common and grade 3/4 adverse events observed in either CTCL study**

Adverse Event	GPI-04-0001 (N=96)		NCI 1312 (N=71)	
	n (%)		n (%)	
	All	Grade 3-4	All	Grade 3-4
At least 1 treatment-emergent adverse event	93 (97)	33 (33)	71 (100)	71 (100)
Nausea	54 (56)	2 (20)	60 (85)	5 (7)
Asthenia/fatigue	50 (52)	8 (8)	57 (80)	12 (17)
Infection and infestation	45 (45)	19 (19)	37 (52)	26 (37)
Anemia	17 (18)	3 (3)	51 (72)	13 (18)
Vomiting	28 (29)	1 (1)	36 (51)	7 (10)
Anorexia	22 (23)	1 (1)	39 (55)	3 (4)
Thrombocytopenia/platelet count decreased	13 (14)	0	44 (62)	11 (16)
ST-T wave changes	3 (3)	0	63 (87)	0
Hypocalcemia	4 (4)	0	41 (58)	5 (7)
Neutropenia	8 (8)	2 (2)	37 (52)	18 (25)
Hypoalbuminemia	4 (4)	1 (1)	37 (52)	3 (4)
Lymphopenia/lymphocyte count decreased	3 (3)	0	39 (55)	27 (38)
Constipation	9 (9)	2 (2)	28 (39)	1 (1)
Diarrhea	17 (18)	1 (1)	21 (30)	0
Dysgeusia	11 (11)	0	27 (38)	0
Hypomagnesemia	20 (21)	1 (1)	18 (25)	0
Pyrexia	19 (20)	1 (1)	18 (25)	
Leukopenia	1 (1)	0	34 (48)	17 (24)
Hyperglycemia	1 (1)	1 (1)	33 (46)	1 (1)
Headache	14 (15)	0	16 (23)	0
Pruritus	5 (5)	0	25 (35)	0
Hyperuricemia	0	0	25 (35)	6 (9)
Aspartate aminotransferase increased	3 (3)	0	20 (28)	2 (3)
Hypotension	7 (7)	2 (2)	15 (21)	5 (3)
Alanine aminotransferase increased	3 (3)	0	15 (21)	2 (3)
Dermatitis exfoliative	2 (2)	2 (2)	18 (25)	0
Hypermagnesemia	0	0	18 (25)	6 (8)
Hypophosphatemia	0	0	18 (25)	7 (10)
ECG QT corrected interval prolonged	5 (5)	2 (2)	15 (21)	0
Hyponatremia	1 (1)	1 (1)	16 (23)	2(3)

Source: NDA 22393

The AEs summarized by body systems for each study are shown in tables below.

**Table 53: Adverse events occurred in GPI-04-0001 study by body system**

SOC	All Grade	%	Grade 3	%	Grade 4	%	Grade 5	%
Gastrointestinal Disorders	66	69	2	2	2	2	0	0
General Disorders and Administration Site Conditions	62	65	10	10	1	1	2	2
Infections and Infestations	45	47	6	6	2	2	0	0
Investigations	43	45	5	5	1	1	0	0
Metabolism and Nutrition Disorders	37	39	4	4	1	1	0	0
Nervous System Disorders	32	33	1	1	0	0	0	0
Blood and Lymphatic System Disorders	29	30	4	4	0	0	0	0
Skin and Subcutaneous Tissue Disorders	28	29	1	1	1	1	0	0
Vascular Disorders	20	21	5	5	1	1	0	0
Respiratory, Thoracic and Mediastinal Disorders	18	19	1	1	2	2	0	0
Cardiac Disorders	16	17	2	2	1	1	1	1
Musculoskeletal and Connective Tissue Disorders	16	17	2	2	0	0	0	0
Psychiatric Disorders	11	11	0	0	0	0	0	0
Injury, Poisoning and Procedural Complications	10	10	0	0	0	0	0	0
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	9	9	2	2	1	1	2	2
Eye Disorders	4	4	0	0	0	0	0	0
Hepatobiliary Disorders	3	3	0	0	0	0	0	0
Renal and Urinary Disorders	3	3	0	0	0	0	1	1
Ear and Labyrinth Disorders	2	2	0	0	0	0	0	0
Immune System Disorders	2	2	0	0	0	0	0	0
Congenital, Familial and Genetic Disorders	1	1	0	0	0	0	0	0
Endocrine Disorders	1	1	0	0	0	0	0	0
Surgical and Medical Procedures	1	1	0	0	0	0	0	0

Source: NDA 22393

**Table 54: Adverse events occurred in NCI-1312 study by body system**

CTCAECAT	All Grade	%	Grade 3	%	Grade 4	%	Grade 5	%
Gastrointestinal	65	92	12	17	1	1	0	0
Constitutional Symptoms	63	89	10	14	2	3	0	0
Blood/Bone Marrow	60	85	33	46	7	10	0	0
Cardiovascular (General)	57	80	7	10	2	3	1	1
Metabolic/Laboratory	55	77	17	24	6	8	0	0
Hepatic	45	63	5	7	2	3	0	0
Pain	42	59	5	7	0	0	0	0
Dermatology/Skin	38	54	11	15	1	1	0	0
Infection/Febrile Neutropenia	38	54	21	30	2	3	4	6
Neurology	24	34	4	6	0	0	0	0
Cardiovascular (Arrhythmia)	22	31	3	4	0	0	0	0
Renal/Genitourinary	14	20	0	0	1	1	0	0
Pulmonary	12	17	3	4	1	1	1	1
Hemorrhage	8	11	1	1	0	0	0	0
Allergy/Immunology	6	8	1	1	0	0	0	0
Lymphatic	4	6	1	1	0	0	0	0
Coagulation	3	4	1	1	0	0	0	0
Endocrine	3	4	0	0	0	0	0	0
Ocular/Visual	3	4	0	0	0	0	0	0
Sexual/Reproductive Function	3	4	0	0	0	0	0	0
Musculoskeletal	1	1	0	0	0	0	0	0
Syndromes	1	1	1	1	0	0	0	0

Source: NDA 22393

The AEs observed from safety update are summarized in the table below.

**Table 55: Safety updates of common and grade 3/4 adverse events**

Adverse Reactions n (%)	Study GPI-04-0001 (n=102)		Study NCI 1312 (n=83)	
	All	Grade 3 or 4	All	Grade 3 or 4
<i>Any adverse reaction</i>	99 (97)	36 (35)	83 (100)	68 (82)
Nausea	57 (56)	3 (3)	71 (86)	5 (6)
Asthenia/fatigue	54 (53)	8 (8)	64 (77)	12 (14)
Infections	47 (46)	11 (11)	45 (54)	27 (33)
Vomiting	35 (34)	1 (<1)	43 (52)	8 (10)
Anorexia	23 (23)	1 (<1)	45 (54)	3 (4)
Hypomagnesemia	22 (22)	1 (<1)	23 (28)	0
Diarrhea	20 (20)	1 (<1)	22 (7)	1 (1)
Pyrexia	20 (20)	4 (4)	19 (23)	1 (1)
Anemia	19 (19)	3 (3)	60 (72)	13 (16)
Thrombocytopenia	17 (17)	0	54 (65)	12 (14)
Dysgeusia	15 (15)	0	33 (40)	0
Constipation	12 (12)	2 (2)	32 (39)	1 (1)
Neutropenia	11 (11)	4 (4)	47 (57)	22 (27)
Hypotension	7 (7)	3 (3)	19 (23)	3 (4)
Pruritus	7 (7)	0	26 (31)	5 (6)
Hypokalemia	6 (6)	0	17 (20)	2 (2)
Dermatitis/Exfoliative dermatitis	4 (4)	1 (<1)	22 (27)	7 (8)
Hypocalcemia	4 (4)	0	43 (52)	5 (6)
Leukopenia	4 (4)	0	38 (46)	18 (22)
Lymphopenia	4 (4)	0	47 (57)	31 (37)
Alanine aminotransferase increased	3 (3)	0	18 (22)	2 (2)
Aspartate aminotransferase increased	3 (3)	0	23 (28)	3 (4)
Hypoalbuminemia	3 (3)	1 (<1)	40 (48)	3 (4)
Electrocardiogram ST-T wave changes	2 (2)	0	52 (63)	0
Hyperglycemia	2 (2)	2 (2)	42 (51)	1 (1)
Hyponatremia	1 (<1)	1 (<1)	17 (20)	2 (2)
Hypermagnesemia	0	0	22 (27)	7 (8)
Hypophosphatemia	0	0	22 (27)	8 (10)
Hyperuricemia	0	0	27 (33)	7 (8)

Source: NDA 22393

## 6.4.2 Laboratory Findings

### 6.4.2.1 Hematology

Hematological adverse events were more common in the NCI study. The number of abnormal laboratories in the GPI study was substantially lower than in the NCI study. This increase was not only due to increased reporting of abnormal laboratory values as adverse events by NCI, but also due to more frequent laboratory testing and an increased number of serious adverse events.

Hematology tests in the GPI study were obtained on the day of dosing, whereas in the NCI study, they were obtained on the day of dosing and the day after dosing. Further, the number of serious adverse events in the NCI study was approximately twice that of the GPI study, in part, due to in hospital treatments, increased hospitalizations and resulting laboratory testing. Less than half of the grade 3-4 neutropenia in the NCI study occurred on the day of dosing; whereas most occurred the day after dosing or in association with a serious adverse event.

**Table 56: Hematological AEs observed in either CTCL study**

Hematologic Event	Study GPI-04-0001 (N=96)		NCI Study 1312 (n=71)	
	All (%)	≥Grade 3 (%)	All (%)	≥Grade 3 (%)
Anemia	17 (18)	3 (3)	51 (72)	13 (18)
Thrombocytopenia	13 (14)	0	44 (62)	11 (16)
Lymphopenia	3 (3)	0	39 (55)	27 (38)
Neutropenia	8 (8)	2 (2)	37 (52)	18 (25)
Leukopenia	1 (1)	0	34 (48)	17 (24)

Source: NDA 22393

Hematological adverse events were also reported more often in the NCI study. This is likely due to differences in laboratory collection schedules and adverse event reporting.

### 6.4.2.2 Chemistry

Among the chemistry adverse events, hypomagnesemia was frequent on both studies while hypokalemia and hypocalcemia were less common on the GPI study. Both magnesium and potassium were supplemented on the NCI study prior to dosing; hence hypermagnesemia occurred in some patients.

Also note that none of the patients with grade 2-4 AST or ALT had an increase in bilirubin.

**Table 57: Chemistry AEs observed in either CTCL study**

Clinical Chemistry Event	Study GPI-04-0001 (N=96)		NCI Study 1312 (n=71)	
	All (%)	≥Grade 3 (%)	All (%)	≥Grade 3 (%)
Hypocalcemia	4 (4)	0	41 (58)	5 (7)
Hypoalbuminemia	4 (4)	1 (1)	37 (52)	3 (4)
Hypomagnesemia	20 (21)	1 (1)	18 (25)	0
Hyperglycemia	4 (4)	1 (1)	33 (47)	1 (1)
Hyperuricemia	0	0	25 (35)	6 (9)
AST increased	3 (3)	0	20 (28)	2 (3)
ALT increased	3 (3)	0	15 (21)	2 (3)
Hypophosphatemia	0	0	18 (25)	7 (10)
Hypermagnesemia	0	0	18 (25)	6 (8)
Hyponatremia	1 (1)	1 (1)	16 (23)	2 (3)
Hypokalemia	5 (5)	0	12 (17)	2 (3)

Source: NDA 22393

More chemistry adverse events were also observed in the NCI study. Again, this appears to be the differences in the laboratory schedule.

#### 6.4.3 Electrocardiograms (ECGs)

See section 6.1.4.1.

#### 6.4.4 Special Safety Studies

Adequate QT Studies of romidepsin has not been conducted.

#### 6.4.5 Safety Data Comparison of CTCL studies versus Solid Tumors

The toxicity of romidepsin observed in CTCL patients was compared to that observed in the patients with malignancies other than CTCL, as shown below.

**Table 58: Romidepsin AE comparison between patients with CTCL and with other malignancies**

Adverse Event	CTCL All (N=167)	Solid Tumor at 14 ± 2mg/m <sup>2</sup> (N=481)
	N (%)	N(%)
Nausea	114 (68)	303 (63)
Fatigue/asthenic conditions	107 (64)	298 (62)
Hemoglobin/hemoglobin decreased/anemia	68 (41)	176 (37)
Vomiting NOS	64 (38)	182 (38)
Anorexia	61 (37)	168 (35)
Thrombocytopenia/platelet count decreased	57 (34)	181 (38)
ECG T-wave amplitude decreased	49 (29)	46 (10)
Hypocalcemia/blood calcium decreased	45 (27)	103 (21)
Neutrophil count/neutropenia/ neutrophil count decreased	45 (27)	97 (20)
Lymphopenia/lymphocyte count decreased	42 (26)	94 (20)
Hypoalbuminemia/blood albumin decreased	39 (23)	97 (20)
Diarrhea	38 (23)	90 (19)
Dysgeusia	38 (23)	90 (19)
Hypomagnesemia	38 (23)	59 (12)
Constipation	37 (22)	126 (26)
Pyrexia	37 (22)	76 (16)
Leukopenia/WBC count decreased	35 (21)	99 (21)
Hyperglycemia NOS	34 (20)	108 (22)
Headache	30 (18)	88 (18)
Pruritus	30 (18)	37 (8)
Hyperuricemia	25 (15)	35 (7)
Infection NOS	25 (15)	32 (7)
Aspartate aminotransferase increased	23 (14)	62 (13)
Hypotension NOS	22 (13)	37 (8)
Alanine aminotransferase increased	18 (11)	64 (13)
Exfoliative dermatitis NOS	18 (11)	24 (5)
Hypermagnesemia	18 (11)	41 (9)
Hypophosphatemia	18 (11)	37 (8)
ECG QT corrected interval prolonged	17 (10)	37 (8)
Hyponatremia	17 (10)	24 (5)

Source: NDA 22393

At the time of the safety update, romidepsin has been investigated in peripheral T-cell lymphoma (PTCL) and other T-cell lymphomas (n=91), hematological malignancies (n=82), and solid tumors (n=512). All have shown a safety profile that is similar with that observed in CTCL clinical trials. However, in patients with CTCL, there was at least a two-fold increase in the reported incidence of T wave depression, hypomagnesemia, pruritus and overall infections when compared to patients with other malignancies.

Reviewer: Comparing CTCL study database (from the GPI and NCI study) with the non-CTCL studies database (studies of romidepsin in other tumor types), at least a two-fold increase in the reported incidence of T-wave depression, hypomagnesemia, pruritus, and overall infections was noted in CTCL patients.

## 7 Postmarketing Experience

None

## 8 Appendices

### 8.1 Literature Review/References

This reviewer performed a literature review on the following topics:

- The natural history of CTCL,
- Available treatments for CTCL, and
- Published studies of CTCL using romidepsin or other chemotherapies.

No additional information regarding the efficacy or safety of romidepsin was obtained via literature review. This clinical review used the following references in addition to the references provided in the applicant's NDA submission.

1. Whittaker SJ, Marsden JR, Spittle M, Jones RR. Joint British Association of Dermatologists and UK Cutaneous Lymphoma Group guidelines for the management of primary cutaneous T-cell lymphomas. *B J Derm* 2003;149:1095- 1107.
2. Zolanza (vorinostat) prescribing information. Merck and Co., Inc., 2006.
3. ONTAK (denileukin diftitox) prescribing information. Seragen, Incorporated, 2006.
4. Olsen E, Duvic M, Frankel A, Kim Y, Martin A, Vonderheid E, et al. Pivotal phase III trial of two dose levels of denileukin diftitox for the treatment of cutaneous T-cell lymphoma. *J Clin Oncol* 2001;19(2):376-88.
5. Saleh MN, LeMaistre CF, Kuzel TM, Foss F, Platanius LC, Schwartz G, et al. Antitumor activity of DAB389IL-2 fusion toxin in mycosis fungoides. *J Am Acad Dermatol* 1998;39(1):63-73.
6. Targretin (bexarotene) capsules prescribing information. Ligand Pharmaceuticals Incorporated, 2003.
7. Wong SF. Oral bexarotene in the treatment of cutaneous T-cell lymphoma. *Ann Pharmacother* 2001;35(9):1056-65.

## 8.2 Labeling Recommendations

For details please see the final label. Briefly, the label states that romidepsin 14 mg/m<sup>2</sup> IV should be given on days 1, 8, and 15 every 28 days. This is the dosing regimen that was used in studies GPI-04-0001 and NCI 1312. The treatment dose modification guideline was adapted from study GPI-04-0001, since fewer AEs were observed in this study. Per FDA recommendation, the response rates of all enrolled patients in both studies (34% and 35%), response duration, and time to response were used to describe the efficacy of romidepsin. The safety update results were used to describe the adverse event profile of romidepsin in the label. The safety warnings included the following:

- cardiac arrhythmias with a recommendation for close monitoring of magnesium, potassium and ECGs,
- neutropenia and thrombocytopenia with a recommendation for close monitoring of CBCs,
- pregnancy, and
- the efficacy of contraception.

## 8.3 Advisory Committee Meeting

On September 2, 2009, the ODAC committee discussed the efficacy and safety data in CTCL patients for romidepsin, NDA 022-393. Most ODAC members felt the responses seen were encouraging and were not overly concerned with the safety profile. They felt that some of the adverse events reported could have been due to the disease course. Most members felt that randomized controlled trials should be done to better evaluate the efficacy and safety of romidepsin and the benefit/risk ratio. However, many also felt that there were compelling reasons why a randomized controlled trial was not necessary such as the rarity of the disease and the data presented. A few members stated that, if approved, the long term safety of romidepsin should be evaluated. The ODAC concluded that the results of the two single arm studies represent a favorable risk-benefit profile for the use of romidepsin in previously treated CTCL patients.

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22393

-----  
ORIG-1

-----  
GLOUCESTER  
PHARMACEUTICA  
LS INC

-----  
ROMIDEPSIN FOR INFUSION

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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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QIN C RYAN  
10/22/2009

VIRGINIA E MAHER  
10/23/2009