

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-393**

**STATISTICAL REVIEW(S)**



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Translational Science  
Office of Biostatistics

## STATISTICAL REVIEW AND EVALUATION

### CLINICAL STUDIES – TEAM LEADER’S MEMO

**NDA/Serial Number:** 22-393 / N-000

**Drug Name:** Istodax ® (Romidepsin)

**Indication:** Cutaneous T-cell lymphoma in patients who have received at least one prior systemic therapy

**Applicant:** Gloucester Pharmaceuticals

**Date(s):** Submission Date: January 12, 2009  
PDUFA Date: November 12, 2009

**Review Priority:** Standard

**Biometrics Division:** V

**Primary Reviewer:** Huanyu Chen, Ph.D.

**Secondary Reviewer:** Kun He, Acting Team Leader

**Concurring Reviewer:** Rajeshwari Sridhara, Ph.D., Deputy Division Director

**Medical Division:** Division of Drug Oncology Products

**Clinical Team:** Qin Ryan, M.D., Ph. D., Clinical Reviewer  
Virginia E. Maher, M.D., Team Leader

**Project Manager:** Ms. Lisa Skarupa

**Keywords:** CTCL, response rate, confidence interval

The applicant is seeking an approval for Romidepsin in the treatment of patients with confirmed cutaneous T-cell lymphoma (CTCL) who have failed at least 1 prior systemic therapy and submitted two single arm studies GPI-04-0001 and NCI 1312 to support the application.

The romidepsin application is based on efficacy and safety results from two studies: study GPI-04-0001 and study NCI 1312. The pivotal study, GPI-04-0001, was conducted under IND 63,573, as a Special Protocol Assessment (SPA). It was an ongoing, international, multicenter, single arm, single agent phase II trial in the treatment of CTCL. The supportive study NCI 1312 was an ongoing, phase II, international, multicenter, non-randomized trial with 5 single arms (including 3 CTCL arms) sponsored by the NCI in 1996 under IND 51,810. It was designed to evaluate the efficacy and safety of romidepsin in patients with T-cell lymphomas, including CTCL. The protocol specified primary endpoint in both studies was investigator-assessed objective response rate (ORR), defined as complete response (CR), complete clinical response (CCR), and partial response (PR) based on the investigator's evaluations. The secondary endpoint was Duration of Response (DoR). For study GPI-04-0001, the ORR was 34.4% (95% CI: 25.0% - 44.8%) based on the Investigator's (INV) evaluations and 29.2% (95% CI: 20.3% - 39.3%) based on the Independent Response Review Committee (IRRC)'s evaluations. Similarly, the ORR in the study NCI 1312 was 35.2% (95% CI: 25.4% - 49.3%) based on INV's evaluations and 25.4% (95% CI: 16.5% - 38.6%) based on IRRC's evaluations. All of the ORRs' 95% CI lower bound (using exact method) was greater than the pre-specified 15% minimum efficiency of ORR. The median duration of response (DoR) was 454 and 336 days using INV assessment for study GPI-04-0001 and NCI 1312, respectively. However, the median DoR was not estimable and 392 days using IRRC assessment for study GPI-04-0001 and NCI 1312, respectively. For further details regarding the design, data analyses, and results, please refer to the statistical review by Dr. Huanyu Chen (September 21, 2009).

This (acting) Team Leader concurs with the recommendations and conclusions of the primary statistical reviewer (Dr. Huanyu Chen) of this application.

On September 2, 2009, the Oncologic Drugs Advisory Committee (ODAC) discussed this NDA 22,393's efficacy and safety results. The voting results were 10 Yes, 0 No, and 1 Abstain, for the question "Do the results of the two romidepsin single arm studies represent a favorable risk-benefit profile for patients with previously treated CTCL?" The committee also voted 7 Yes, 3 No, and 1 Abstain for the question "FDA has approved drugs in CTCL on the basis of single-arm trials. Should randomized studies be required for future approvals?"

This (acting) Team Leader's overall conclusion is that whether the data and analyses from the current submission demonstrate a favorable risk-benefit profile is deferred to the clinical team reviewing this submission.

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

NDA-22393

ORIG-1

GLOUCESTER  
PHARMACEUTICA  
LS INC

ROMIDEPSIN FOR INFUSION

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/s/

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KUN HE  
09/22/2009

RAJESHWARI SRIDHARA  
09/22/2009



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Translational Science  
Office of Biostatistics

## STATISTICAL REVIEW AND EVALUATION

### Clinical Studies

**NDA/Serial Number:** 22-393 / 000  
**Drug Name:** Istodax® (Romidepsin) Injection  
**Indication:** Cutaneous T-cell lymphoma in patients who have received at least one prior systemic therapy  
**Applicant:** Gloucester Pharmaceuticals  
**Date:** Submission: 1/12/2009  
**Review Priority:** Standard

**Biometrics Division:** V (HFD 711)  
**Statistical Reviewer:** Huanyu Chen, Ph.D.  
**Concurring Reviewers:** Kun He, Ph.D., Acting Team Leader  
Rajeshwari Sridhara, Ph.D., Deputy Division Director

**Medical Division:** Oncology Drug Products (HFD 150)  
**Clinical Team:** Qin Ryan, M.D., Clinical Reviewer  
Virginia E. Maher, M.D., Team Leader

**Project Manager:** Ms. Lisa Skarupa

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## **1. EXECUTIVE SUMMARY**

### **1.1 Conclusions and Recommendations**

The applicant is seeking an approval for Romidepsin in the treatment of patients with confirmed cutaneous T cell lymphoma (CTCL) who have failed at least 1 prior systemic therapy and submitted two single arm studies GPI-04-0001 and NCI 1312 to support the application.

The data and analyses from the submission indicated that the response rate in patients with CTCL treated with romidepsin was 34% and 35% in the GPI-04-0001 and NCI 1312 studies, respectively. The median duration of response was 454 and 336 days in the GPI-04-0001 and NCI 1312 studies, respectively. Whether the data and analyses from the current submission demonstrate a favorable risk-benefit profile is deferred to the clinical team reviewing this submission.

On September 2, 2009, the Oncologic Drugs Advisory Committee (ODAC) discussed this NDA 22,393's efficacy and safety results. The voting results were 10 Yes, 0 No, and 1 Abstain, for the question "Do the results of the two romidepsin single arm studies represent a favorable risk-benefit profile for patients with previously treated CTCL?" The committee also voted 7 Yes, 3 No, and 1 Abstain for the question "FDA has approved drugs in CTCL on the basis of single-arm trials. Should randomized studies be required for future approvals?"

### **1.2 Brief Overview of Clinical Studies**

The romidepsin application is based on efficacy and safety results from two studies, study GPI-04-0001 and study NCI 1312. The pivotal study, GPI-04-0001, was conducted under IND 63,573, as a Special Protocol Assessment (SPA). It was submitted by Astellas Pharma on April 30, 2002 and subsequently transferred to Gloucester Pharmaceuticals. It was an ongoing, international, multicenter, single arm, single agent phase trial in the treatment of CTCL. The data cut-off for the current submission was May, 2008 for efficacy evaluation and Oct. 2007 for safety evaluation, respectively. There were 96 as treated patients in the GPI-04-0001 study.

The supportive study NCI 1312 was an ongoing, phase II, international, multicenter, non-randomized, 5 single arm trial (including 3 CTCL arms) sponsored by the NCI in 1996 under IND 51,810. It was designed to evaluate the efficacy and safety of romidepsins in patients with T-cell lymphomas, including CTCL. The data cut-off for the current submission was March, 2007 for efficacy evaluation and Dec. 2007 for safety evaluation. There were 71 as treated CTCL patient in the NCI 1312 study.

The designed primary endpoint in both studies was investigator-assessed objective response rate (ORR), defined as complete response (CR), complete clinical response (CCR), and partial response (PR) on the Evaluable Patient (EP) analysis set. The secondary endpoint was Duration of Response (DoR)

### 1.3 Statistical Issues and Findings

#### Statistical Issues

There were two issues in the submission.

- A request for Special Protocol Assessment for GPI-04-0001 was submitted on August 18, 2004. Agreement/non-agreement letters were not sent by the Division at that time. The reviewer noted that the primary endpoint would be assessed using the Objective Primary Disease Response Evaluation Criteria (OPDREC), and stated that the primary endpoint should only include all complete and partial responses. The reviewer also noted that the primary endpoint would be assessed in both as treated population (TP, all patients who received at least 1 dose of study drug) and efficacy evaluable population. A statistical analysis plan (SAP) was submitted on March 24, 2008. The statistical reviewer stated that “Use of the evaluable patient population for the primary analysis may be problematic if a significant difference exists between the evaluable and the as treated population.” On the final SAP, the designed primary endpoint in both studies was investigator-assessed ORR on the Evaluable Patient (EP) analysis set. The efficacy results on the EP analysis were consistently better than the TP analysis. The population of treated patients (TP) is the typical primary population for single-arm study. Use of EP may be problematic, if a significant difference exists between EP and TP. Therefore, this review is limited to results on TP analysis set.
- During a pre-NDA meeting held on September 10, 2007, the applicant stated that the Independent Response Review Committee (IRRC) evaluations for GPI-04-0001 and NCI 1312, using the International Working Group criteria, would be considered secondary assessments of the primary endpoint. At a pre-NDA meeting held on May 7, 2008, the Agency requested a more mature assessment of response duration. Whether IRRC assessment would provide additional clinical value in the evaluation of efficacy of romidepsin will be deferred to the clinical judgment.

#### Findings

The primary endpoint ORR results are summarized in Table 1 for study GPI-04-0001 and NCI 1312. For study GPI-04-0001, the ORR was 34.4% (95% CI: 25.0% - 44.8%) based on the Investigator’s (INV) evaluations and 29.2% (95% CI: 20.3% - 39.3%) based on IRRC’s evaluations. Similarly, the ORR in the study NCI 1312 was 35.2% (95% CI: 25.4% - 49.3%) based on the Investigator’s evaluations and 25.4% (95% CI: 16.5% - 38.6%) based on IRRC’s evaluations. All of the ORRs’ 95% CI lower bound (using exact method) was greater than *the 15% pre-specified minimum efficiency of ORR*.

**Table 1 Objective Disease Response Rate Using OPDREC on the TP Analysis Set**

	GPI-04-0001 (N=96) n (%) [95% CI]		NCI 1312 (N=72) n (%) [95% CI]	
	Inv	IRRC	Inv	IRRC
ORR(CR+CCR+ PR)	33 (34.4) [25.0, 44.8 ]	28(29.2) [20.3,39.3]	25 (35.2) [25.4, 49.3]	18 (25.4) [16.5, 38.6]
CCR	6 (6.3) [2.3, 13.1 ]	7 (7.3) [3, 14.5]	4 (5.6) [1.6, 14.4]	4 (5.6) [1.6, 14.4]
PR	27 (28.1) [19.4, 38.2 ]	21 (21.9) [14.1, 31.5]	21 (29.6) [20.2, 43.3]	14 (19.7) [11.7, 32.1]

INV: Investigators' evaluations; IRRC: IRRC's evaluation;  
95% CI constructed using exact methods based on the binomial distribution

Table 2 presents the Kaplan Meier estimates of DoR, by studies using INV and IRRC assessment. The median duration of response (DoR) was 454 and 336 days using investigator assessment for study GPI-04-0001 and NCI 1312, respectively. However, the median DoR was not estimable and 392 days using IRRC assessment for study GPI-04-0001 and NCI 1312, respectively.

**Table 2 Summary of Kaplan Meier Estimates of DoR (Days)**

	GPI-04-0001		NCI 1312	
	INV N = 33	IRRC N = 28	INV N = 25	IRRC N = 18
Median Confirmed Response Duration (95% CI)	454 Days (454, NE)	NE (NE, NE)	336 Days (148, NE)	392 Days (170, NE)

## **2. INTRODUCTION**

### **2.1 Overview**

The applicant is seeking an approval for Romidepsin in the treatment of patients with confirmed CTCL who have failed at least 1 prior systemic therapy. Romidepsin was administered as 14 mg/m<sup>2</sup> intravenous injection over a 4-hour period on days 1, 8 and 15 of a 28-day cycle. Cycles has repeated every 28 days provided that the patient continued to benefit from and tolerated the drug. If a patient was intolerant to therapy, dose reduction to 10 mg/m<sup>2</sup> and further to 8 mg/m<sup>2</sup> was considered.

### **2.2 Background**

#### **Romidepsin**

Romidepsin is a novel compound in a new class of antineoplastic agents known as histone deacetylase (HDAC) inhibitors, which increase acetylation of histones and other proteins. HDAC inhibition is associated with anti-tumor activities, including cell cycle arrest, antiangiogenesis, growth inhibition and apoptosis. Romidepsin is a pan-HDAC inhibitor showing potent inhibition of Class I, II and IVHDACs. Unlike the hydroxamic acid structure common to many of the other HDAC inhibitors in development, romidepsin is a naturally occurring cyclic peptide.

#### **Cutaneous T Cell Lymphoma**

Mycosis fungoides is the most common type of cutaneous T cell lymphoma (CTCL). Early stages of mycosis fungoides form patches, plaques, and tumors. Advanced stages involve the lymph nodes, blood, bone marrow, and visceral organs while Sezary syndrome includes generalized erythroderma with circulating Sezary cells (large, CD4+ cells with a cerebriform nucleus). There are stages IA, IB, IIA, IIB, III, IVA, and IVB in CTCL. The disease tends to be slowly progressive while advanced stages have a poor prognosis.

#### **Clinical Trials**

This NDA submission was based on data from two ongoing, phase 2, open-label, multicenter, international studies, GPI-04-0001 and NCI 1312.

The pivotal study, GPI-04-0001, was conducted under IND 63,573, as a SPA. It was submitted by Astellas Pharma on April 30, 2002 and subsequently transferred to Gloucester Pharmaceuticals. It was an ongoing, international, multicenter, single arm, single agent phase II trial in the treatment of CTCL. The data cut-off for the current submission was May, 2008 for efficacy evaluation and Oct. 2007 for safety evaluation, respectively. There were 96 as treated patients in the GPI-04-0001 study.

The supportive study NCI 1312 is an ongoing, phase II, international, multicenter, non-randomized, 5 single arm trial sponsored by the NCI in 1996 under IND 51,810. It was designed to evaluate the efficacy and safety of romidepsins in patients with T-cell lymphomas, including

CTCL. The data cut-off for the current submission was March, 2007 for efficacy evaluation and Dec. 2007 for safety evaluation. There were 71 as treated patient in the NCI 1312 study.

The pre-specified primary endpoint in both studies was investigator-assessed ORR, defined as CR, CCR, and PR on the EP analysis set. The secondary endpoint was DoR.

### **2.3 Data Sources**

The path to the CDER Electronic Document Room (EDR) is:

\\Cdsub1\evsprod\NDA022393\

## **3. STATISTICAL EVALUATION**

### **3.1 Evaluation of Efficacy**

Part of the text, and tables presented in this section are adapted from the applicant's Clinical Study Report (CSR).

#### **3.1.1 Study GPI-04-0001**

##### **3.1.1.1 Objective of Study GPI-04-0001**

The primary objective of this study was to confirm the efficacy of romidepsin in patients with CTCL whose disease was no longer controlled by skin-directed therapy and who had received at least 1 prior systemic therapy.

##### **3.1.1.2 Study Design**

Study GPI-04-0001 is a ongoing Phase 2, open-label, single-arm, international study designed to assess the efficacy of romidepsin in the treatment of patients with confirmed CTCL. Eligible patients were required to have failed at least 1 prior systemic therapy. The efficacy cut off date was May, 2008. However, the safety cutoff date was October, 2007.

Patients received romidepsin 14 mg/m<sup>2</sup> intravenously (IV) over 4 hours on Days 1, 8, and 15 of each 28-day cycle for six cycles. Responding patients and patients who had achieved at least stable disease (SD) had the option of continuing treatment beyond 6 cycles at the discretion of the investigator and based on local regulations.

The main inclusion criteria included males or non-pregnant female  $\geq 18$  years of age with histologically confirmed Stage IIA, IIB, III or IVA CTCL at study entry, who were no longer controlled on standard skin-directed therapy and had received at least 1 course of prior systemic therapy. Patients with Stage IB CTCL also were eligible provided they had relapsed following previous therapy and in the Investigator's opinion the potential benefit of treatment with romidepsin outweighed the possible risks. Patients also were required to have a life expectancy of  $>6$  months, ECOG PS  $\leq 1$ , and no known cardiac abnormalities.

### **3.1.1.3 Efficacy Measures**

The primary efficacy endpoint was the confirmed ORR, defined as the proportion of patients with confirmed CR, CCR, or PR, based on OPDREC. The primary efficacy objective would be considered met if the 95% confidence interval (CI) for ORR were entirely above 15% (i.e., the lower bound of the CI was >15%). To support primary efficacy endpoint, IRRC's evaluation of response was used as a secondary endpoint.

One of the secondary efficacy endpoints was duration of objective disease response, which was measured from the first dose date to the first date of later confirmed objective disease response of a later confirmed PR or CCR. Other secondary efficacy endpoints included changes in pruritus VAS scores, time to response, time to progression, and safety were not included in this report.

### **3.1.1.4 Sample Size Considerations**

The sample size was calculated based on a 1-stage design to test: Ho: ORR  $\leq$  15 % vs. Ha: ORR  $\geq$  30 %, using the exact binomial distribution with a 2-sided significance level of 0.05. A total of 64 evaluable patients would have provided 84% power. Adjusted by 28% of inevaluability rate, approximately 90 patients were needed. Enrollment was to be continued until at least 64 patients satisfied the criteria for evaluability. Upon advice from the Agency, additional patients were enrolled. The primary data cut-off for this report was based on the 96th patient reaching Cycle 4, Day 1 of the study. Based on advice from Agency at the pre-NDA meeting, additional disposition, exposure, and efficacy data were captured through 05 May 2008 for the 11 patients who were ongoing on treatment or in the follow-up phase as of the October 2007 data cut-off.

### **3.1.1.5 Statistical Analysis Plan**

#### Analysis Sets

Three analysis sets, the as-treated patients (TP) analysis set, the evaluable patients (EP) analysis set, and the modified evaluable patients (MEP) analysis set, were to be used to summarize study data.

TP analysis set included patients who received at least 1 dose of romidepsin. This population was to be used for the analyses of patient characteristics, treatment administration, safety endpoints, and supportive analyses of efficacy endpoints.

EP analysis set included patients who received 2 consecutive cycles of study treatment, with at least 2 of the 3 doses received in each cycle, and who had disease assessments performed, at baseline and after the last of the 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. Review of concomitant medications for patient exclusion from the EP was to be performed prior to database lock. The EP was designed to be used for the primary analyses of efficacy endpoints by Applicant.

MEP analysis set included patients who received 2 consecutive cycles of study treatment, with at least 2 of the 3 doses received in each cycle, and who had disease assessments performed at Baseline and after the last of the 2 consecutive cycles. The MEP was to be used for supportive summaries of selected efficacy endpoints.

Reviewer's Comments:

*The Applicant used different analysis sets on different analyses. There is no SPA agreement with agency on using EP as the primary analysis set. The population of TP is the typical primary population for single-arm study. Use of EP may be problematic, if a significant difference exists between EP and TP. In this review, TP analysis set will be used.*

Primary Efficacy analysis:

The primary efficacy endpoint was the confirmed objective response rate (ORR) assessed by investigator. A 2-sided 95% confidence interval (CI) of ORR would be constructed using exact methods based on the binomial distribution. The primary analysis would be performed on the EP, with supportive analysis performed on the TP and MEP analysis sets.

Secondary analyses:

Similar to primary efficacy analysis, ORR, based on the IRRC's evaluations, was assessed as part of secondary endpoints on EP analysis set. The secondary endpoint of duration of objective disease response was analyzed by Kaplan-Meier product limit estimates using the EP Analysis Set.

Reviewer's Comments:

*This reviewer will report efficacy endpoints by investigator and IRRC evaluations. Since skin disease is difficult to assess with photographs, the investigator assessments are considered primary and the independent assessment to provide corroboration of the investigator assessment.*

### **3.1.1.6 Applicant's Results and Statistical Reviewer's Findings/ Comments**

#### **3.1.1.6.1 Study Population**

A summary of the data analysis sets is provided in Table 3 (adapted from CSR P. 88).

**Table 3 Analysis Sets**

<b>Analysis Set:</b>	<b>Patient No.</b>	<b>All Patients N (%)</b>
As-Treated Patients (TP) Analysis Set		96 (100.0)
Evaluable Patients (EP) Analysis Set		72 (75.0)
Reasons for exclusion from the EP Analysis Set		
Minimum dosing not met and efficacy response data not available	02029, 02047, 08025, 45053, 47036, 48040, 51057, 52046, 52061, 56079, 94083	11
Minimum dosing not met	02052, 03016, 23081, 28091, 38033, 45092, 54049	7
Received prohibited potentially effective concomitant medication	02037, 32038, 46096, 47062	4
Efficacy response data not available	55075, 91084	2
<b>Modified Evaluable Analysis Set<sup>1</sup></b>		<b>76 (79.2)</b>

Source: Section 14.1, Table 14.1.1B, Appendix 16.2.2, Listing 16.2.3.1.

<sup>1</sup> Excludes the 20 patients who did not meet minimum dosing requirements or who did not have efficacy response data available and does not exclude those 4 patients who received prohibited medication.

Reviewer's Comments:

*A total of 96 patients were enrolled at 33 study centers in the US and Europe with at least one dose of romidepsin. However, a quarter (24) of TP patient was excluded from EP. Eighteen of those twenty four excluded patients are due to minimum dosing not met and efficacy response data unavailable. These patients should be considered as progressed (failure) on the first dose data of study drug or intolerance of study drug.*

**3.1.1.6.2 Disposition of Patients**

Table 4 (adapted from CSR P. 84) presents an overview of patient disposition in the study as of the efficacy cut off date.

**Table 4 Major Disposition for Enrolled Patient as of Efficacy Cut-Off Date**

<b>Patient Disposition</b>	<b>Patients N (%)</b>
Enrolled	96
Treated	96 (100.0)
Early discontinuation of treatment during cycles 1 to 6	61 (63.5)
Completed 6 cycles of treatment	35 (36.5)
Received treatment beyond 6 cycles	10 (10.4)
Ongoing on treatment beyond 6 cycles	4 (4.2)
Discontinuation of Treatment beyond 6 cycles	6 (6.3)
Major reason for discontinuation:	
Disease progression:	21 (21.9)
Evidence of disease progression for 2 consecutive cycles	15 (15.6)
In the Investigator's opinion, there has been significant disease progression	6 (6.3)
Informed consent withdrawn	21 (21.9)
Adverse event	17 (17.7)

Reviewer's comments:

*There are 61 (63.5%) patients had discontinued treatment during Cycle 1-6. Six patients among ten patients, who got treatment beyond cycle 6, discontinued treatments. The common reasons for discontinuation were disease progression and withdrawal of consent (21 patients each, 22%), and adverse events (17, 18%).*

**3.1.1.6.3 Demographic and Other Baseline Characteristics**

Demographic and baseline characteristics are summarized in Tables 5.

**Table 5 Demographic and Baseline Characteristics**

Parameter	N=96
Sex	
Male, n (%)	59 (61%)
Female	37 (39%)
Age	
Mean ( $\pm$ Std Dev)	56.9 (12.0)
Median (25-75)	57.0 (51-64)
Range (min, max)	(21, 89)
Race	
Caucasian	90 (94%)
Black	5 (5%)
Other	1 (1%)
Performance Status	
0	49 (51%)
1	47 (49%)
$\geq 2$	0
Missing	0
Geographic Region	
America	18 (19%)
Australia	0
Europe	78 (81%)

Reviewer's Comments:

*The majority of patients were Stage IIB (tumors) or higher. All of the patients on GPI-04-0001 received at least one prior systemic therapy. Most patients had received multiple prior systemic therapies; the median number of prior therapies was 2.0.*

Baseline disease characteristics are summarized in Tables 6.

**Table 6: Baseline Disease Characteristics**

Parameter	GPI-04-0001 N=96
Disease Stage at Study Entry	
IA	0
IB	15 (16%)
IIA	13 (14%)
IIB	21 (22%)
IIIA or B	23 (24%)
IV/IVA	24 (25%)
IVB	0

Prior therapy for CTCL are summarized in Tables 7.

**Table 7 Prior therapy for CTCL**

Parameter	GPI-04-0001 N=96
Number of Patients with Any Prior CTCL Therapy	96 (100.0%)
Number of Prior CTCL Therapies	
N	96
Mean ( $\pm$ Std Dev)	4.6 (2.40)
Median	4.0
Range	1.0, 11.0
Number of Prior Systemic CTCL Therapies	
N	96
Mean ( $\pm$ Std Dev)	2.7 (1.70)
Median	2.0
Range	1.0, 8.0
Type of Prior Systemic Therapy	
Chemotherapy	74 (77.1%)
Immunotherapy	36 (37.5%)
Bexarotene	32 (33.3%)
Denileukin diftitox	14 (14.6%)
Steroids	12 (12.5%)
Monoclonal antibodies	4 (4.2%)
Vorinostat	2 (2.1%)
Other Retinoids	9 (9.4%)
Other Systemic Therapy	2 (2.1%)
Number of Prior Skin Directed Therapies	
N	90
Mean ( $\pm$ Std Dev)	2.1 (1.22)
Median	2.0
Range	1.0, 6.0
Type of Prior Skin Directed Therapy	
Phototherapy	51 (53.1%)
Skin directed Radiotherapy	36 (37.5%)
Steroids	35 (36.5%)
Other Skin Directed Therapy	18 (18.8%)
Photopheresis	18 (18.8%)

### 3.1.1.6.4 Efficacy Analyses

#### Primary efficacy endpoint- ORR

Table 8 presents the ORR using INV and IRRC assessment in GPI study. The ORR was 34.4% (95% CI: 25.0% - 44.8%) based on the Investigator's (INV) evaluations and 29.2% (95% CI: 20.3% - 39.3%) based on IRRC's evaluations.

**Table 8: Objective Disease Response Rate by INV and IRRC**

	INV		IRRC	
	n (%)	[95% CI]	n (%)	[95% CI]
ORR(CR + PR)	25 (35.2)	[25.4, 49.3]	18 (25.4)	[16.5, 38.6]
CR	4 (5.6)	[1.6, 14.4]	4 (5.6)	[1.6, 14.4]
PR	21 (29.6)	[20.2, 43.3]	14 (19.7)	[11.7, 32.1]

#### Reviewer's Comments:

*The majority of the ORR was PR. Although ORR using IRC was lower than that by INV assessment, the 15% pre-specified minimum efficiency of ORR has been met for both assessments.*

#### Secondary efficacy endpoint- DoR

Table 9 summarized Kaplan-Meier estimates of DoR based on the Investigators' and IRRC's evaluations. The median duration of response (DoR) was 454 days based on INV assessment. However, the median DoR was not estimable based on IRRC assessment.

**Table 9 Summary of Kaplan Meier Estimates of Duration of Objective Disease Response**

Duration of Response	TP (N=96)	
	INV	IRRC
N	33	28
Censored Observations, n (%)	25 (75.8%)	28 (100.0%)
Number of Events, n (%)	8 (24.2%)	0
25th Percentile (95% CI)	217 (64, NE)	NE
Median (95% CI)	454 (454, NE)	NE
75th Percentile (95% CI)	NE	NE
Minimum, maximum	1+, 603+	43+, 603+

Source: Adapted from Tabel 11-9 and 11-10 in the Sponsor's study report

Note: + denotes censored value; NE = not estimated.

### 3.1.2 Study NCI 1213

#### 3.1.2.1 Objective of Study NCI 1312

The primary objective of this study was to evaluate the response to treatment with romidepsin in patients with CTCL (enrolled in Arm 1, 3, and 5) and PTCL (enrolled in Arm 2 and 4). To match

study GPI-000-004's inclusion criteria, only patients with CTCL were considered in this NDA review. Therefore, patients with a primary diagnosis of CTCL enrolled in Arms 1, 3, and 5 were evaluated in this review.

### **3.1.2.2 Study Design**

Study NCI 1312 is an ongoing, phase 2, multi-center, six arms, open-label study designed to evaluate the activity and tolerability of romidepsin in patients with CTCL, PTCL, or other mature T-cell lymphomas. Arms 1 and 5 enrolled patients with stage IA-IIA disease who were refractory or intolerant to 2 prior non-steroid therapies as well as patients with stage IIB-IVB disease who had received  $\leq 2$  two prior systemic therapies. Arm 3 enrolled stage IA-IVB patients who had received  $> 2$  prior systemic therapies. The efficacy cut off date was March, 2008. The safety cutoff date was Dec, 2007.

The main inclusion criteria included patients aged  $\geq 18$  years with Stage IA to IVB CTCL, had written informed consent, an ECOG performance status of 0-2, no other serious or intercurrent illness, a life expectancy of  $>12$  weeks, no more than 2 systemic cytotoxic chemotherapeutic regimens (Arms 1 and 5) or experienced disease progression after receiving more than 2 prior systemic cytotoxic chemotherapies (Arm 3). Additionally, patients were to have disease that was measurable by radiographic imaging, by assessment of skin lesions, or by quantification of abnormal circulating T-cells. The laboratory values were required within 14 days before registration. Females were to have a negative pregnancy test within 4 weeks before baseline and use effective contraception. Sexually active male patients were to use effective contraception.

### **3.1.2.3 Efficacy Measures**

The primary efficacy end point was confirmed objective response rate (ORR), defined as the proportion of patients with confirmed objective disease response (confirmed CR or PR) as determined by a standardized assessment based on a composite of changes in skin involvement as determined by investigators, lymph node and visceral/extranodal involvement, where applicable, and abnormal circulating T-cells, where applicable.

The secondary efficacy endpoint were the duration of objective disease response, which was calculated as the time from the initial date of the response (CR or PR) to the first date of observed PD.

### **3.1.2.4 Sample Size Considerations**

A total of 88 patients with CTCL were planned to be enrolled into the 3 study arms in 10 study centers in the US and Australia, based on the patients' primary diagnosis, the number of prior therapies they had received, and the time of enrollment. Sample sizes were determined separately for each study arm; the sample size rationales for the 3 arms that enrolled CTCL patients are given below.

The study objective for arm 1 and 3 were to rule out an unacceptable response rate of 5% in favor of a targeted 25% response rate, which was in the range of response other agents were able

to produce, according to a Simon optimal 2-stage design. A probability of a Type I error (alpha) = 0.1 and probability of a Type II error (beta) = 0.1 were used. Using similar inclusion criteria as Arm 1, up to 50 patients with CTCL, who received  $\leq 2$  prior lines of cytotoxic chemotherapy, were enrolled in Arm 5. However, patients with Stage IA disease were excluded from enrollment Arm 5 by protocol amendment. As of 21 March 2007, a total of 71 patients (Arm 1: 27, Arm 3: 15, and Arm 5: 29) with CTCL were enrolled in this ongoing study.

### **3.1.2.5 Statistical Analysis Plan**

#### Analysis Sets

Two patient analysis sets, the as treated patients (TP) analysis set and the evaluable patients (EP) analysis set, were to be used to summarize study data.

The TP analysis set included patients with CTCL who were enrolled in the study, and had received at least 1 dose of study drug was included in this NDA submission.

The EP analysis set included all enrolled patients with a diagnosis of CTCL 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 response assessment on or after Cycle 2.

#### Reviewer's Comments:

*This reviewer will report results on TP analysis set, per comments in Section 3.2.1.*

#### Primary efficacy analysis:

A 2-sided 95% confidence interval (CI) of the ORR, using Investigator assessment, would be constructed using exact methods based on the binomial distribution. The primary analysis was to be performed on the EP Analysis Set, with supportive analysis conducted on the TP Analysis Set.

#### Secondary analyses:

ORR based on IRRC's evaluation would be assessed as part of secondary endpoints on EP and TP analysis set.

#### Reviewer's Comments:

*Please refer to reviewer's comment in section 3.1.1.5.*

### **3.1.2.6 Applicant's Results and Statistical Reviewer's Findings/ Comments**

#### **3.1.2.6.1 Study Population**

Table 10 presents the analysis sets in study NCI 1312. A total of 71 patients were enrolled at 10 study centers in the US and Australia with at least one dose of romidepsin. There are 63 (89%) in the EP analysis set.

**Table 10. Analysis Sets in Study NCI 1312**

<i>Analysis Set</i>	<i>All Patients N(%)</i>
As Treated Patients (TP) Analysis Set	71 (100)
Evaluable Patients (TP) Analysis Set	63 (89)
Receiving <3 study drug doses in Cycles 1 & 2, and lack of efficacy evaluations on or after Cycle 2	6 (11)
Failure to receive 2 of 3 study drug doses in Cycles 1 and 2	1 (1)
Failure to receive 2 of 3 doses in Cycle 2	1 (1)

*Reviewer's Comments:*

*Seven of eight patients are excluded due to minimum dosing requirement and efficacy response data unavailable. These patients may be considered as progressed (failure) on the day of first dose administered on the study.*

**3.1.2.6.2 Patient Disposition in Study NCI 1312 by Treatment Arm**

Study NCI 1312 was initially designed to administer 6 cycles. However, an early amendment changed the study plan, so that romidepsin would be continued until progression or intolerable toxicity. The patient disposition is summarized in Table 11.

**Table 11. Patient Disposition NCI 1312 Arms 1, 3, and 5**

<b>Patient Disposition</b>	<b>All</b>
Enrolled	71
Treated	71
Ongoing Treatment	6
Completed 6 Cycles of Study	27
Discontinued During Cycles 1-6	44
Progressive Disease	27
Adverse Event	6
Informed Consent Withdrawn	4
Death on Study	2
Patient Decision	1
Other	4

*Reviewer's Comments:*

*Progressive disease 27(38%), adverse event 6(8%), and informed consent withdrawn 4 (6%) were the main reasons for early discontinuation. Despite the differences in entry criteria, discontinuation due to progressive disease or an adverse event occurred in approximately the same percentage of patients in each arm.*

### 3.1.2.7 Baseline Characteristics

The patient demographics are summarized in Tables 12.

**Table 12. Patient Demographics**

Parameter	TP N=71
Sex	
Male, n (%)	46 (68%)
Female	23 (32%)
Age	
Mean ( $\pm$ Std Dev)	56.0 (13.0)
Median (25-75)	57.0 (48-66)
Range (min, max)	(28.0, 84.0)
Race	
Caucasian	55 (78%)
Black	15 (21%)
Other	1 (1%)
Performance Status	
0	16 (23%)
1	41 (58%)
$\geq 2$	10 (14%)
Missing	4 (6%)
Geographic Region	
America	56 (79%)
Australia	15 (21%)
Europe	0

Reviewer's Comments:

*There were relatively more African-Americans in study NCI 1312 (21%), compared to 5% in GPI study. There were 20% patients who had ECOG PS score  $\geq 2$ , which was an exclusion criteria in GPI study. Furthermore, no study centers were from Europe. Therefore, the NCI study may have different population than that of GPI study.*

The baseline disease characteristics are summarized in Tables 13.

**Table 13. Duration since Diagnosis and Disease Stage at Baseline**

Study ID	NCI 1312 N=71
Disease Stage at Entry	N (%)
IA	1 (1)
IB	6 (9)
IIA	2 (3)
IIB	14 (20)
IIIA or B	8 (11)
IVA	27 (38)
IVB	12 (17)

Reviewer's Comments:

The majority of patients were in Stage IIB (tumors) or higher. There was none of stage IA to IIA patient who got CR. PR existed in all of the disease stage.

Prior treatment of CTCL are summarized in Tables 14.

**Table 14 Prior therapy for CTCL**

Parameter	NCI 1312 N=71
Number of Patients with Any Prior CTCL Therapy	68 (96%)
Number of Prior CTCL Therapies	
N	68 (89%)
Mean ( $\pm$ Std Dev)	3.4 (1.47)
Median	3.0
Range	1, 10
Number of Prior Systemic CTCL Therapies	
N	63
Mean ( $\pm$ Std Dev)	2.4 (1.47)
Median	2.0
Range	0, 7
Type of Prior Systemic Therapy	
Chemotherapy	48 (68%)
Immunotherapy	24 (34%)
Bexarotene	31 (44%)
Denileukin diftitox	13 (18%)
Steroids	17 (24%)
Monoclonal antibodies	9 (13%)
Vorinostat	n/a
Other Retinoids	6 (9%)
Other Systemic Therapy	5 (7%)
Number of Prior Skin Directed Therapies	
N	43
Mean ( $\pm$ Std Dev)	1.8 (0.80)
Median	2.0
Range	1, 3
Type of Prior Skin Directed Therapy	
Phototherapy	38 (54%)
Skin directed Radiotherapy	0
Steroids	8 (13%)
Other Skin Directed Therapy	18 (25%)
Photopheresis	12 (17%)

Reviewer's Comments:

Eighty nine percent of patients on NCI 1312 had received at least one prior systemic therapy. Most patients had received multiple prior systemic therapies; the median number of prior therapies was 3.0. Only 43 of 71 patients on NCI 1312 had received prior skin directed therapy compared to 90 of 96 in the GPI study.

### 3.1.2.8 Primary Efficacy Analyses

Table 15 presents DoR using INV and IRRC assessment in study NCI 1312. The ORR was 35.2% (95% CI: 25.4% - 49.3%) based on the Investigator evaluations, and 25.4% (95% CI: 16.5% - 38.6%) based on IRRC evaluations.

**Table 15 Objective Disease Response Rate using OPDREC**

	INV		IRC	
	n (%)	[95% CI]	n (%)	[95% CI]
ORR(CR+ PR)	25 (35.2)	[25.4, 49.3]	18 (25.4)	[16.5, 38.6]
CR	4 (5.6)	[1.6, 14.4]	4 (5.6)	[1.6, 14.4]
PR	21 (29.6)	[20.2, 43.3]	14 (19.7)	[11.7, 32.1]

INV: Investigators' evaluations; IRC: IRRC's evaluation; 95% CI constructed using exact methods based on the binomial distribution

#### Reviewer's Comments:

*The majority of the ORR was PR based on either INV or IRC assessments. Although IRRC has lower 95% CI than that of INV, the prespecified cut off of 15% for efficacy was observed.*

### 3.1.2.9 Secondary Efficacy Analyses –Duration of Response

Table 16 presents the Kaplan-Meier results for duration of response. The median duration of response (DoR) was 336 and 392 days based on INV assessment and IRRC assessment, respectively.

**Table 16 Summary of Kaplan Meier Estimates of Duration of Objective Disease Response**

Duration of Response	TP (N=72)	
	INV	IRC
N	25	18
Censored Observations, n (%)	13 ( 52.0)	9 ( 50.0)
Number of Events, n (%)	12 ( 48.0)	9 ( 50.0)
Median (95% CI)	336 [148, NE]	392 (170, NE)

Source: Adapted from CSR; NE = not estimated.

## 3.2 Evaluation of Safety

Please see the clinical review by Dr. Qin Ryan for the safety evaluation.

## 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Since the number of patients in some subgroups was very small, the results presented in this section are mainly for descriptive purpose.

### 4.1 Gender, Race and Age

Tables 17 and 18 present the ORR in the subgroup analysis for study GPI-04-0001 and NCI 1312, respectively. For some subgroups with small sample size, the lower 95% CI bound is less than 15%.

**Table 17 Subgroup Analysis on ORR in Study GPI-04-0001**

Subgroup	Category	GPI-04-0001 (N=96)			
		Inv		IRRC	
		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%

**Table 18 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%

## 4.2 Other Special/Subgroup Populations

### 4.2.1 Responders with or without Concomitant Anti-infective Therapies

Table 19 summarized the concomitant therapy in the ORR subgroup by IRRC assessment in the TP population. The use of antibiotics has a profound effect on patient response in both studies, but is more prominent in GPI-04-0001. This may be due to differences in skin care. In GPI-04-0001, this difference is confined to the use of anti-bacterial therapy while in NCI 1312. This is seen with all anti-infective therapies. Note that the lower limit of the 95% confidence interval for the response rate in patients who received systemic antibiotics in GPI-04-0001 is 14.5%. Two patients on GPI-04-0001 received steroids (a prohibited concomitant medication per protocol) during the study period. If these patients are excluded from the analysis, the INV response rate is 33.7%.

**Table 19. Concomitant Therapy in the ORR subgroup by IRRC assessment on the TP**

Concomitant Therapy	GPI-04-0001 N=96		NCI 1312 N=71	
	ORR (n=33)		ORR (n=25)	
	Use	No Use	Use	No Use
Systemic	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	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	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	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	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)

#### 4.2.2 Analysis of Response by Disease Stage

Table 20 provides response by disease stage. Response was not confined to patients with IB or IIA disease, but also occurred among patients with late stage disease.

**Table 20 Response Rate by Disease Stage**

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

#### 4.2.3 Analysis of Response by Prior Therapies

Table

21

**Table 21. Analysis of Response by Number of Prior Therapies** presents the response rate among all patients who had received at least one prior CTCL therapies and skin directed and systemic therapy. Response does not seem to be affected by the number of prior therapies, skin directed or systemic therapies. While it can be concluded that response is not confined to patients with one prior therapy, the number of patients is too small to infer that prior therapies is unrelated to response. Note that two patients on NCI 1312 had not received the required number of therapies and were ineligible for study entry criteria. After excluding these patients, the INV response rate was 33.3%.

**Table 21. Analysis of Response by Number of Prior Therapies**

Prior Treatments	GPI-04-0001 N=96	NCI 1312 N=71
No. of Prior Therapies	ORR/N	ORR/N
1	0/2	7/19
2	8/19	6/10
≥ 3	25/75	11/39
No. of Skin Directed Therapies		
1	12/36	8/19
2	9/28	4/14
≥ 3	11/26	3/10
No. of Systemic Therapies		
1	11/30	7/20
2	9/22	9/20
≥ 3	13/44	6/23
No. of Chemotherapies		
1	15/47	17/48
2	7/14	0/0
≥ 3	3/13	0/0
Type of Therapies		
Chemotherapy	25/74	17/48
Other Systemic Therapy	0/2	2/5
Immunotherapy	13/36	9/24
Retinoid	5/9	2/6
Ontak	5/14	4/13
Bexarotene	12/32	8/31
Monoclonal Antibody	1/4	2/9
Vorinostat	0/2	0/0
Steroid	2/12	8/17
Phototherapy	19/51	13/38
Photopheresis	8/18	5/12
Radiotherapy	12/35	0/0
Skin Directed Steroid	13/35	2/9
Other Skin Directed	8/18	5/18

Since a number of agents have been approved for use in CTCL, response was assessed in patients who received these agents. On GPI-04-0001, 32 patients received prior bexarotene. Among these patients, 12 responded to romidepsin. Outcome was similar on NCI 1312 with 8 of 31 patients with prior bexarotene responding to romidepsin. Deneleukin diftitox was used in fewer patients. Among these patients, 5 of 14 in GPI-04-0001 and 4 of 13 in NCI 1312 responded to romidepsin. Since these studies were initiated in 2005 and 2001, few patients had received vorinostat and response to the use of a second histone deacetylase inhibitor cannot be assessed.

## 5. SUMMARY AND CONCLUSIONS

### 5.1 Statistical Issues and Collective Evidence

## Statistical Issues

There were two issues in the submission.

- A request for Special Protocol Assessment for GPI-04-0001 was submitted on August 18, 2004. Agreement/non-agreement letters were not sent by the Division at that time. The reviewer noted that the primary endpoint would be assessed using the Objective Primary Disease Response Evaluation Criteria (OPDREC), and stated that the primary endpoint should only include all complete and partial responses. The reviewer also noted that the primary endpoint would be assessed in both as treated population (all patients who received at least 1 dose of study drug) and efficacy evaluable population. A statistical analysis plan was submitted on March 24, 2008. The statistical review stated that “Use of the evaluable patient population for the primary analysis may be problematic if a significant difference exists between the evaluable and the as treated population.” On the final SAP, the designed primary endpoint in both studies was investigator-assessed ORR on the Evaluable Patient (EP) analysis set. The efficacy results on the EP analysis were consistently lower than the TP analysis. The population of enrolled patients (TP) is the typical primary population for single-arm studies. Use of EP may be problematic, if a significant difference exists between EP and TP. Therefore, this review is limited to results on TP analysis set.
- During a pre-NDA meeting held on September 10, 2007, the applicant stated that the Independent Response Review Committee (IRRC) evaluations for GPI-04-0001 and NCI 1312, using the International Working Group criteria, would be considered secondary assessments of the primary endpoint. At a pre-NDA meeting held on May 7, 2008, FDA requested a more mature assessment of response duration. Whether IRRC assessment would provide additional clinical value in the efficacy evaluation of romidepsin will be deferred to the clinical judgment.

## Findings

The primary endpoint, ORR, based on INV and IRRC assessment, are summarized in Table 22 by study GPI-04-0001 and NCI 1312.

**Table 22 Objective Disease Response Rate using OPDREC on the TP Analysis Set**

	GPI-04-0001 (N=96) n (%) [95% CI]		NCI 1312 (N=72) n (%) [95% CI]	
	Inv	IRRC	Inv	IRRC
ORR(CR+CCR+ PR)	33 (34.4) [25.0, 44.8 ]	28(29.2) [20.3,39.3]	25 (35.2) [25.4, 49.3]	18 (25.4) [16.5, 38.6]
CCR	6 (6.3) [2.3, 13.1 ]	7 (7.3) [3, 14.5]	4 (5.6) [1.6, 14.4]	4 (5.6) [1.6, 14.4]
PR	27 (28.1) [19.4, 38.2 ]	21 (21.9) [14.1, 31.5]	21 (29.6) [20.2, 43.3]	14 (19.7) [11.7, 32.1]

INV: Investigators' evaluations; IRRC: IRRC's evaluation; n (%) [95% CI]  
95% CI constructed using exact methods based on the binomial distribution

For study GPI-04-0001, the ORR was 34.4% (95% CI: 25.0% - 44.8%) based on the Investigator's (INV) evaluations and 29.2% (95% CI: 20.3% - 39.3%) based on IRRC's evaluations. Similarly, the ORR in the study NCI 1312 was 35.2% (95% CI: 25.4% - 49.3%) based on the Investigator's evaluations and 25.4% (95% CI: 16.5% - 38.6%) based on IRRC's evaluations. All of the ORRs' 95% CI lower bound (using exact method) was greater than *the 15% pre-specified minimum efficiency of ORR*.

Table 23 presents the Kaplan Meier estimates of DoR, by studies using INV and IRRC assessment. The median duration of response (DoR) was 454 and 336 days using investigator assessment for study GPI-04-0001 and NCI 1312, respectively. However, the median DoR was not estimable and 392 days using IRRC assessment for study GPI-04-0001 and NCI 1312, respectively.

**Table 23 Summary of Kaplan Meier Estimates of DoR (Days)**

	GPI-04-0001		NCI 1312	
	INV N = 33	IRRC N = 28	INV N = 25	IRRC N = 18
Median Confirmed Response Duration (95% CI)	454 Days (454, NE)	NE (NE, NE)	336 Days (148, NE)	392 Days (170, NE)

## 5.2 Conclusions and Recommendations

The data and analyses from the submission indicated that the response rate in patients with CTCL treated with romidepsin was 34% and 35% in the GPI-04-0001 and NCI 1312 studies, respectively. The median duration of response was 454 and 336 days in the GPI-04-0001 and NCI 1312 studies, respectively. Whether the data and analyses from the current submission demonstrate a favorable risk-benefit profile is deferred to the clinical team reviewing the submission.

On September 2, 2009, the Oncologic Drugs Advisory Committee (ODAC) discussed this NDA 22,393's efficacy and safety results. The voting results were 10 Yes, 0 No, and 1 Abstain, for the question "Do the results of the two romidepsin single arm studies represent a favorable risk-benefit profile for patients with previously treated CTCL?" The committee also voted 7 Yes, 3 No, and 1 Abstain for the question "FDA has approved drugs in CTCL on the basis of single-arm trials. Should randomized studies be required for future approvals?"

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22393	ORIG-1	GLOUCESTER PHARMACEUTICALS INC	ROMIDEPSIN FOR INFUSION
NDA-22393	ORIG-1	GLOUCESTER PHARMACEUTICALS INC	ROMIDEPSIN FOR INFUSION
NDA-22393	ORIG-1	GLOUCESTER PHARMACEUTICALS INC	ROMIDEPSIN FOR INFUSION
NDA-22393	ORIG-1	GLOUCESTER PHARMACEUTICALS INC	ROMIDEPSIN FOR INFUSION
NDA-22393	ORIG-1	GLOUCESTER PHARMACEUTICALS INC	ROMIDEPSIN FOR INFUSION
NDA-22393	ORIG-1	GLOUCESTER PHARMACEUTICALS INC	ROMIDEPSIN FOR INFUSION
NDA-22393	ORIG-1	GLOUCESTER PHARMACEUTICALS INC	ROMIDEPSIN FOR INFUSION
NDA-22393	ORIG-1	GLOUCESTER PHARMACEUTICALS INC	ROMIDEPSIN FOR INFUSION
NDA-22393	ORIG-1	GLOUCESTER PHARMACEUTICALS INC	ROMIDEPSIN FOR INFUSION
NDA-22393	ORIG-1	GLOUCESTER PHARMACEUTICALS INC	ROMIDEPSIN FOR INFUSION
NDA-22393	ORIG-1	GLOUCESTER PHARMACEUTICALS INC	ROMIDEPSIN FOR INFUSION

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HUANYU CHEN  
09/21/2009

KUN HE  
09/21/2009

RAJESHWARI SRIDHARA  
09/21/2009

## STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Amended filing check list

**NDA Number: 22-393**

**Applicant: Gloucester  
Pharmaceuticals**

**Stamp Date: 1/12/2009**

**Drug Name: ISTODAX**

**NDA/BLA Type: Standard**

On initial overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	Yes			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	Yes			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	Yes			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	Yes			

**IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes**

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

No issue identified at this time. SAS efficacy analysis programs have been requested.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	Yes			Single arm
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	Yes			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			NA	Single arm
Appropriate references for novel statistical methodology (if present) are included.		No		
Safety data organized to permit analyses across clinical trials in the NDA/BLA.			NA	Single arm
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	Yes			

File name: 5\_Statistics Filing Checklist for a New NDA\_BLA110207

# STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Huanyu Chen	2/26/2008
Reviewing Statistician	Date
<hr/>	
Supervisor/Team Leader	Date

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/s/

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Huanyu Chen  
3/3/2009 01:28:44 PM  
BIOMETRICS

Kun He  
3/3/2009 01:32:31 PM  
BIOMETRICS

## STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

**NDA Number: 22-393**

**Applicant: Gloucester  
Pharmaceuticals**

**Stamp Date: 1/12/2009**

**Drug Name: ISTODAX**

**NDA/BLA Type: Standard**

On **initial** overview of the NDA/BLA application for RTF:

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comments</b>
1	Index is sufficient to locate necessary reports, tables, data, etc.	Yes			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	Yes			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	Yes			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	Yes			

**IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE?** Yes

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

<b>Content Parameter (possible review concerns for 74-day letter)</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
Designs utilized are appropriate for the indications requested.		No		
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.		No		
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.		No		
Appropriate references for novel statistical methodology (if present) are included.		No		
Safety data organized to permit analyses across clinical trials in the NDA/BLA.		No		
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.		No		

# STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Huanyu Chen  
Reviewing Statistician

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2/25/2008  
Date

Supervisor/Team Leader

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Date

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/s/

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Huanyu Chen  
2/27/2009 02:41:58 PM  
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Kun He  
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