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APPLICATION NUMBER:

22-393

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology Review

NDA	22-393
Submission Type	NDA-NME
Submission Date	12 January 2009; 4 April 2009
Brand Name	ISTODAX®
Generic Name	Romidepsin
Indication	Treatment of cutaneous T-cell lymphoma (CTCL), including relief of pruritus, in patients who have received at least one prior systemic therapy
Formulation	10 mg/vial, lyophilized powder for solution
Dosing Regimen	14 mg/m ² intravenously (IV) infusion over a 4-hour period on days 1, 8 and 15 of a 28-day cycle
Sponsor	Gloucester Pharmaceuticals, Inc.
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1 EXECUTIVE SUMMARY

Romidepsin, a new molecular entity, is an inhibitor of histone deacetylase (HDAC). The current submission is the original NDA for romidepsin for the treatment of cutaneous T-cell lymphoma (CTCL), including relief of pruritus, in patients who have received at least one prior systemic therapy.

Primary support for efficacy of romidepsin in CTCL is provided by two Phase 2, single arm, open-label studies of which one was pivotal and the other was supportive. In both studies, romidepsin was administered with the proposed dosing regimen: 14 mg/m² 4-hour intravenous (IV) infusion on Days 1, 8, 15 of a 28-day cycle. Objective disease response rate (ORR) was the primary efficacy endpoint in both studies. The ORR based on the investigators' evaluation was 34.4% with the lower bound of the 95% confidence interval (CI) at 25.0% for the pivotal study and 35.2 % with a lower bound of the 95% CI of 25% for the supportive study.

Romidepsin exhibited linear pharmacokinetics (PK). It is extensively metabolized by CYP3A4. Mild to severe renal impairment or mild hepatic impairment does not alter the PK of romidepsin based on a population PK analysis. The effect of moderate and severe hepatic impairment on the PK of romidepsin is unknown.

There was evidence of an exposure-response relationship for effectiveness following 14 mg/m² dose of romidepsin where higher exposure resulted in a higher proportion of responders and longer time to progression. No significant relationship could be identified between exposure and safety endpoints (thrombocytopenia, leucopenia and lymphopenia). There was experience with dose delaying and reduction in the pivotal and supportive trials. Therefore, if a patient experiences hematological toxicities, the dose of romidepsin should be delayed. If dose delaying does not resolve toxicities, and patient becomes intolerant to therapy, the dose should be reduced to 10 mg/m² and further to 8 mg/m².

1.1 RECOMMENDATIONS

This NDA is considered acceptable from a clinical pharmacology perspective provided that the Applicant agrees to the post-marketing studies:

1.2 PHASE 4 REQUIREMENTS

1. Conduct a drug interaction study to evaluate the effect of CYP3A4 inhibitor (e.g. ketoconazole) on the pharmacokinetics of romidepsin.
2. Conduct a drug interaction study to evaluate the effect of CYP3A4 inducer (e.g. rifampin) on the pharmacokinetics of romidepsin.
3. Conduct a study to determine the pharmacokinetics of romidepsin in patients with moderate and severe hepatic impairment.
4. Perform a study to determine the potential of ISTODAX to prolong QT.

1.3 PHASE 4 COMMITMENT

Conduct an *in vitro* study to determine whether romidepsin is an inducer of CYP enzymes including CYP3A4.

1.4 SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

Romidepsin is an antineoplastic agent that has been identified as a HDAC inhibitor. Romidepsin is being developed as a monotherapy for the treatment of cutaneous T-cell lymphoma (CTCL), including relief of pruritus, in patients who have received at least one prior systemic therapy. The proposed dosing regimen, 14 mg/m² administered IV over a 4-hour period on Days 1, 8, 15 of a 28-day cycle, was selected based on tolerability and was used in the pivotal and supportive trials.

Romidepsin exhibited linear PK across doses ranging from 1.0 to 24.9 mg/m² with 4-hour IV infusions in patients with advanced cancers. The t_{max} generally occurred at the end of infusion. The terminal half-life was approximately 3 hours in patients with CTCL. After repeated administration with the proposed dosing regimen, romidepsin PK did not change appreciably and no accumulation was observed.

A human mass balance study has not been conducted. Romidepsin was primarily eliminated by the liver in a rat mass balance study. No dedicated organ dysfunction studies have been conducted. The results of a population PK analysis show that mild to severe renal impairment or mild hepatic impairment did not affect romidepsin PK. The impact of moderate and severe hepatic impairment on the PK of romidepsin is unknown.

Romidepsin is extensively metabolized by CYP3A4. Co-administration of romidepsin with potent CYP3A4 inhibitors and inducers is expected to alter its PK. However, no *in vivo* drug-drug interaction studies have been conducted in humans. At the clinically relevant concentrations, romidepsin does not have any inhibitory effect on major CYP isozymes. It is a substrate of P-glycoprotein (P-gp) and multidrug resistance-associated protein 1 (MRP1).

There was an evidence of exposure-response relationship for effectiveness following 14 mg/m² dose of romidepsin where higher exposure resulted in a higher proportion of responders. The progression of the disease was also more rapid in patients with lower exposures. No significant relationship could be identified between exposure and safety endpoints (thrombocytopenia, leucopenia and lymphopenia). There was experience with dose delaying and reduction in the pivotal and supportive trials. Delaying the dose eventually resulted in recovery from the toxicities for most of the patients in these trials. Therefore, if the patient experiences hematological toxicities, the dose of romidepsin should be delayed. If delaying does not resolve toxicities and the patient becomes intolerant to romidepsin therapy, the dose should be reduced to 10 mg/m² and further to 8 mg/m².

2 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTITES

What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

The clinical development of romidepsin (depsipeptide, FK228, FR901228, and NSC 630176) was initiated in 1996 by Fujisawa Pharmaceutical Co, Ltd. (now Astellas Pharma Inc.) with the National Cancer Institute (NCI), under Investigational New Drug Application (IND) 51,810.

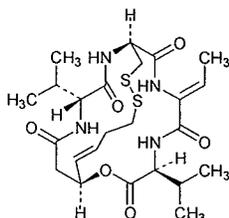
Astellas further developed romidepsin in the US in 2002 under IND 63,573. In 2004, Gloucester Pharmaceuticals, Inc. (Gloucester) acquired the license from Astellas to develop romidepsin.

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Romidepsin is a bicyclic depsipeptide produced by traditional fermentation as a secondary metabolite by a strain of *Chromobacterium violaceum*, a naturally occurring soil bacterium.

Physico-chemical properties

1 Structural formula:



- 2 Established name: Romidepsin
- 3 Molecular Weight: 540.71
- 4 Molecular Formula: $C_{24}H_{36}N_4O_6S_2$
- 5 Chemical Name: (1*S*,4*S*,7*Z*,10*S*,16*E*,21*R*)-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

2.1.2 What are the proposed mechanisms of action and therapeutic indications?

Romidepsin is an antineoplastic agent that has been identified as a HDAC inhibitor. HDAC inhibitors have been shown to induce hyperacetylation of histone and nonhistone proteins resulting in a variety of phenotypic changes. The mechanism of the antineoplastic effect of romidepsin observed in nonclinical and clinical studies has not been fully characterized.

The proposed indication is for the treatment of CTCL, including relief of pruritus, in patients who have received at least one prior systemic therapy.

2.1.3 What are the proposed dosage and route of administration?

The proposed dosing regimen is 14 mg/m² of romidepsin administered IV over a 4-hour period on days 1, 8 and 15 of a 28-day cycle. Treatment should continue as long as the patient continues to benefit.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The efficacy claim of romidepsin in CTCL was supported by the data from a Phase 2, pivotal study, GPI-04-0001, sponsored by Gloucester and a Phase 2, supportive study, NCI 1312, sponsored by NCI, in patients with CTCL.

The proposed dosing regimen was based on data from two Phase 1 studies and Study NCI 1312. This regimen was used in Study GPI-04-0001. In Phase 1 dose-escalation studies in advanced cancer sponsored by Fujisawa and NCI, the maximum tolerated dose (MTD) of romidepsin was determined to be 17.8 mg/m² administered on Days 1 and 5 every 21 days (Trial T95-0077) and 13.3 mg/m² administered on Days 1, 8, and 15 every 28 days (Trial T95-0022). In Trial T95-0077, responses were observed in patients with T-cell lymphoma. Based on these findings, study NCI 1312 in patients with CTCL and peripheral T-cell lymphoma (PTCL) was initiated with romidepsin at a dose of 18 mg/m² on Days 1 and 5 every 21 days. However, due to tolerability issues, the protocol was amended and the treatment regimen was changed to 14 mg/m² administered on Days 1, 8, and 15 every 28 days as done in Trial T95-0022. Interim data from study NCI 1312 demonstrated a manageable safety profile and meaningful responses for romidepsin administered at this dose and schedule. Based on these observations, the same dose and schedule were adopted for the pivotal study GPI-04-0001. The study confirmed the clinical activity and tolerability of romidepsin at this dosing regimen in patients with CTCL. The studies used to support dosing regimen or labeling are summarized in Table 1.

Table 1 Studies in support of dosing or labeling of romidepsin

Study Identifier	Study Description	Patient Population	Objectives	No. of Patients Enrolled	Test Product, Dosage, Regimens, Route of Admin
Clinical studies to support indication in CTCL					
GPI-04-0001	Open-label, single-arm, multicenter, uncontrolled Phase II study	Patients with confirmed Stage IB, IIA, IIB, III, or IVA CTCL who had failed at least 1 prior systemic therapy	Evaluate ORR (CR+Cru+PR), rate of objective disease control, duration of response, time to disease progression, safety, PK	96	14 mg/m ² (4-hr infusions on Days 1, 8, & 15 of 28-day cycles)
NCI 1312**	Open-label, single-arm, multicenter, uncontrolled Phase II study	CTCL (with all stages) and relapsed PTCL	Evaluate treatment response and rate of response, safety, PK	104/71*	14 mg/m ² (4-hour infusions on Days 1, 8, and 15 of 28-day cycles)**
MTD Determining Trials					
T-95-0022	Open-label, dose escalation, single-center, uncontrolled Phase I study	Advanced cancers, solid tumors	Determine MTD; evaluate safety and PK	33	1.0-17.7 mg/m ² (4-hr infusions on Days 1, 8, & 15 of 28-day cycles)
T-95-0077	Open-label, dose escalation, uncontrolled Phase I study	Refractory neoplasms, solid tumors	Determine MTD; evaluate tolerance and PK	48	1.0-24.9 mg/m ² (4-hr infusions on Days 1 & 5 of 21-day cycles)

* number of CTCL patients

** The initial 3 patients with CTCL and one patient with PTCL received romidepsin at a dose of 18 mg/m² on Days 1 and 5 every 21 days.

Additional phase 1 and 2 studies were conducted but do not pertain to the CTCL indication (Table 2). The Applicant used data from these additional phase 1 and phase 2 studies along with the data from the previously mentioned studies: GPI-04-0001, NCI 1312, T-95-0077, for population PK analyses to examine the effect of covariates (i.e. age, race, gender), renal impairment and hepatic impairment on the PK of romidepsin. In addition, the sponsor has developed a population PK model using ECG and PK data from studies NCI 1312 and GPI-06-0005 to characterize the relationship between romidepsin concentration and heart-rate corrected QTc interval. See Section 2.2.4.3 for more details.

Table 2 Phase 1 and 2 studies of romidepsin for other cancer indications

Study Identifier	Study Description	Patient Population	Objectives	No. of Patients Enrolled	Dosing Regimen
FJ-228-0001	An exploratory Phase 2, multicenter, open-label trial	Metastatic renal cell carcinoma	Evaluate rate of objective disease response, time to disease response, duration of response; assess safety and PK	29	13 mg/m ² (4-hr infusions on Days 1, 8, & 15 of 28-day cycles)
FJ-228-0002	An exploratory Phase 2, multicenter, open-label trial	androgen-independent metastatic prostate cancer	Evaluate rate of disease control for at least 6 mos; evaluate PSA decline; safety	35	13 mg/m ² (4-hr infusions on Days 1, 8, & 15 of 28-day cycles)
GPI-06-0005	an ongoing Phase 1, single center, single arm, bioavailability study	Advanced malignancies	Determine the oral bioavailability of romidepsin following a single oral dose	10	14 mg/m ² (4-hr infusions on Days 1, 8, & 15 of 28-day cycles)

2.2.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

Primary support for efficacy is provided by the pivotal study, GPI-04-0001, with additional support from Study NCI 1312. The primary efficacy endpoint in both studies was objective disease response rate (ORR) that was evaluated according to an investigator-assessed composite endpoint that included assessments of skin involvement, lymph node and abnormal circulating T-cells (“Sézary cells”) and was defined as the proportion of patients with complete response (CR) or partial response (PR). CR was defined as no evidence of disease and PR as $\geq 50\%$ improvement in disease.

For Study GPI-04-0001, it was prospectively defined that the primary efficacy endpoint would be met if the 95% confidence interval was entirely above 15% (i.e., the lower bound of the 95% confidence interval was $>15\%$).

Secondary endpoints in both studies included duration of response, time to response, and time to progression, rate of stable disease for ≥ 90 days (SD₉₀), and the disease control rate (CR+PR+SD₉₀). Additionally, in Study GPI-04-0001, pruritus relief was assessed and analyzed as a key indicator of clinical benefit.

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

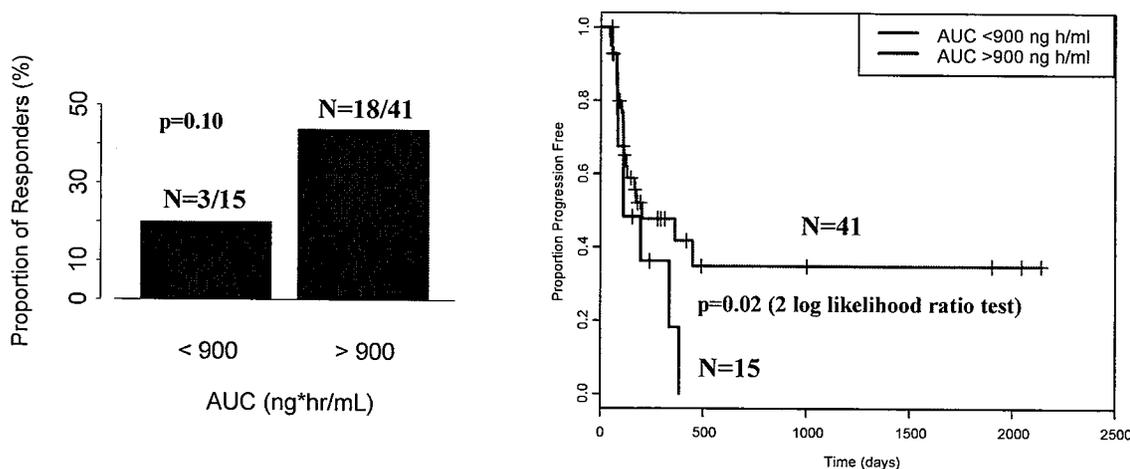
In clinical studies, metabolites were not measured. The relative contribution of metabolites to efficacy and safety is unknown. The performance of the bioanalytical methods is reviewed in Section 2.6.

2.2.4 Exposure-response

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

There is evidence of an exposure-response relationship for effectiveness seen in the supportive efficacy trial NCI-1312 following 14 mg/m² dose of romidepsin. CART (Classification and regression tree) analysis was performed to assess the exposure-response relationship for effectiveness based on the primary efficacy endpoint. The aim was to select an optimal AUC breakpoint which maximally distinguished the response. It can be seen from Figure 1 (left panel) that the proportion of responders was twice (43%) within the group of patients with AUC > 900 ng*hr/mL when compared to patients with AUC < 900 ng*hr/mL (20%). The odds ratio for subjects with AUC < 900 ng*hr/mL to respond is 0.32 (95% CI: 0.08-1.3, p=0.10). This AUC cutoff point was utilized to explore the time to progression which is one of the secondary endpoints of the trial. The progression of the disease is faster in patients with lower exposure (AUC < 900 ng h/ml). However, it is not clear why the separation between the two survival curves does not happen until 250 days. As a result, median time to progression is similar between groups (Figure 1, right panel).

Figure 1 Exposure-response relationship for romidepsin using objective disease response (left panel) and time to progression (right panel)



2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

No exposure-safety relationship could be discerned. Logistic regression models were used to explore the relationship between exposure (AUC) and treatment emergent adverse events. Blood/bone marrow disorders as a whole (thrombocytopenia, leucopenia and lymphopenia) was explored for a relationship with romidepsin exposure. Thrombocytopenia, leucopenia, lymphopenia and neutropenia were also explored individually for their relationship to romidepsin exposure. No exposure-response relationship could be established for safety. This is probably due to the large variation in exposure (AUC) and low number of patients.

The sponsor proposes the dose reductions to 10 and 8 mg/m² for patients experiencing thrombocytopenia, leucopenia or anemia. However, none of the patients had dose reductions in the pivotal trial experiencing these toxicities (Table 3). The dose was delayed for five patients. In other three patients, the dose was discontinued. All of the patients for whom the dose was delayed recovered from their toxicities.

There was experience with dose delaying and reduction in the pivotal and supportive trials. Delaying the dose eventually resulted in recovery for most of the patients in these trials. Therefore, if the patient experiences hematological toxicities, the dose of romidepsin should be delayed. If delaying does not resolve toxicities and the patient becomes intolerant to romidepsin therapy, the dose should be reduced to 10 mg/m² and further to 8 mg/m².

Table 3 Adverse Event (Blood/bone marrow disorders, All grades) in the pivotal trial GPI-04-0001

	GPI-04-0001 (N=96)	Recovered (%)
Patients with AE (%)	26 (27.1)	-
Dose Reduced (%)	0 (0)	-
Dose Delayed (%)	5 (19.2)	5 (100)
Dose Stopped (%)	3 (11.5)	2 (66.6)

2.2.4.3 Does romidepsin prolong the QTc interval?

A thorough QTc study was not performed. ECG data were collected from 3 clinical studies: Study GPI-04-0001 in patients with CTCL; Study 1312 in patients with CTCL, PTCL, or other T-cell lymphomas; Study GPI-06-0005 in patients with advanced solid tumors or hematologic malignancies. The sponsor performed an exposure response analysis using PK and ECG data to characterize the relationship between romidepsin concentration and heart-rate corrected QTc interval.

Limitations in the ECG data collection limit the interpretation of the results. The limitations in ECG data collection include:

- In study GPI-04-001, triplicate ECGs were collected at screening, at baseline, and within 2 hours after completion of administration of romidepsin. An ECG was not acquired at maximum plasma concentrations. ECGs were not collected at later time points to rule out any delayed drug effects on QT prolongation. Sparse PK were only collected for ten subjects (10.4% of the total population) ; There were no controls (positive or negative).
- In study NCI 1312, single ECGs were collected at baseline, within 2 hours after completion of administration of romidepsin and at 24 and 48 hours post-dose. Time matched PK was not obtained.
- In study GPI-06-0005, triplicate ECGs and PK samples were collected prior to infusion and at 0.25, 0.5, 1, 2, 3, 4, 6, 8, and 24 hours post-infusion. There are only 7 patients with available data. The number of patients to be evaluated may be too low to obtain any meaningful results from the exposure-response analysis.

Review of the QT data for this submission was performed by the *CDER Interdisciplinary Review Team* (IRT). Please refer to Appendix 4.3 for IRT-QT review for further details.

2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The dose and dosing regimen were selected on the basis of tolerability and clinical evidence of efficacy (see Section 2.2.1 of this review). The Applicant reported that the 14 mg/m² dosing regimen employed in the pivotal Phase 2 trial and the supportive Phase 2 trial proved to be acceptable based on both efficacy and safety.

2.2.5 Pharmacokinetic characteristics of the drug and its major metabolites

2.2.5.1 What are the single dose and multiple dose PK parameters?

Phase 1: Refractory Neoplasm

In Phase 1 dose escalation Study T-95-0077, a 4-hour IV infusion of romidepsin was administered on Days 1 and 5 of a 21-day cycle to patients with refractory neoplasm. The doses tested ranged from 1.0 to 24.9 mg/m². Blood samples were collected extensively on Day 1 for more than one cycle with additional blood samples collected on Day 5 at trough, end of infusion, and 3 hours post infusion for more than one cycle.

PK parameters of romidepsin are summarized in Table 4. Following a single administration of romidepsin, the median values of t_{max} ranged from 2 to 4 hours with a median value of 2.5 hours and then concentration decreased poly-exponentially. Despite the high inter-subject variability, the C_{max} and $AUC_{0-\infty}$ of romidepsin generally increased as dose increased.

Following multiple administrations, the mean values of the PK parameters obtained on Day 1 of Cycle 2 were generally similar to those obtained in Cycle 1. Across the dose range studied, the clearance was approximately 26 L/h.

Table 4 Mean ± SD (CV%) pharmacokinetic parameters of romidepsin following a 4-hour intravenous infusion on Day1 during cycle 1 and cycle 2 in patients with refractory neoplasm

Dose (mg/m ²)	Cycle	No of Subjects	C _{max} (ng/mL)	AUC _{0-∞} (hr*ng/mL)	t _{1/2} (hr)	CL (L/hr)	V _{ss} (L)
1	1	3	37.8 ± 30.0 (79.3%)	137.7 ± 89.7 (65.1%)	2.2 ± 0.8 (36.4%) n = 2	24.8 ± 22.5 (90.0%) n = 2	16.9 ± 12.7 (75.3%) n = 2
	2	2	32.2 ± 11.3 (35.0%)	109.6 ± 41.6 (38.0%)	1.3 ± 0.9 (69.2%)	23.8 ± 12.3 (51.5%)	16.4 ± 1.31 (8.0%)
1.7	1	3	37.7 ± 12.4 (46.4%)	156.8 ± 69.2 (44.1%)	14.8 ± 9.8 (66.2%)	21.7 ± 9.96 (46.0%)	67.1 ± 38.9 (57.9%)
	2	2	50.7 ± 34.0 (67.1%)	182.7 ± 135.1 (74.0%)	5.8 ± 5.8 (100%)	20.3 ± 15.1 (74.0%)	26.2 ± 9.07 (34.7%)
2.5	1	3	40.0 ± 35.6 (88.9%)	105.6 ± 87.4 (82.7%)	2.4 ± 2.9 (121%)	71.3 ± 45.1 (63.3%)	72.3 ± 62.5 (86.4%)
	2	3	59.1 ± 31.2 (52.9%)	147.8 ± 53.2 (36.0%)	2.0 ± 1.5 (75.0%)	37.3 ± 13.2 (35.3%)	71.0 ± 28.1 (39.5%)
3.5	1	1	81	230.5	11.5	27.3	73.5
	2	1	200.1	558.1	6.93	11.3	27.9
6.5	1	3	185.7 ± 62.6 (33.7%)	510.4 ± 66.7 (13.1%)	8.2 ± 3.6 (43.9%)	22.7 ± 4.51 (19.9%)	34.0 ± 8.54 (25.1%)
	2	2	251.0 ± 104.0 (41.4%)	669.3 ± 27.9 (4.2%)	8.9 ± 3.7 (41.6%)	16.5 ± 1.85 (11.2%)	50.5 ± 12.7 (25.1%)
9.1	1	4	177.1 ± 40.7 (23.0%)	569.6 ± 175.3 (30.8%)	10.5 ± 6.2 (88.2%)	35.1 ± 26.9 (76.6%)	64.6 ± 74.5 (73.5%)
	2	3	153.1 ± 68.4 (44.7%)	406.0 ± 234.0 (59.1%)	7.5 ± 5.6 (74.7%)	49.6 ± 21.2 (42.7%)	90.8 ± 76.5 (84.3%)
12.7	1	1	187.6	345.7	5.8	76.4	173.8
	2	3	622.6 ± 961.5 (154.4%)	1081.2 ± 1527.4 (141.3%)	5.6 ± 2.6 (47.2%)	96.0 ± 77.8 (81.0%)	146.5 ± 117.3 (80.1%)
17.8	1	7	632.3 ± 402.4 (63.6%)	1451.7 ± 492.5 (34.0%)	10.9 ± 7.2 (65.7%)	23.3 ± 12.9 (55.5%)	90.0 ± 79.7 (88.6%)
	2	7	421.5 ± 160.6 (38.1%)	1541.4 ± 613.6 (39.8%)	15.9 ± 14.5 (91.2%)	23.7 ± 9.20 (38.7%)	74.7 ± 61.7 (82.6%)
24.9	1	8	491.6 ± 350.7 (71.3%)	1854.8 ± 1519.1 (81.9%)	6.3 ± 4.7 (74.3%)	32.8 ± 28.3 (86.2%)	39.5 ± 38.1 (96.3%)
	2	4	451.9 ± 280.7 (62.1%)	1722.7 ± 1013.8 (58.9%)	5.3 ± 3.60 (68.5%)	39.0 ± 26.0 (66.7%)	29.5 ± 12.2 (41.5%)

Phase 2: T Cell Lymphoma including CTCL

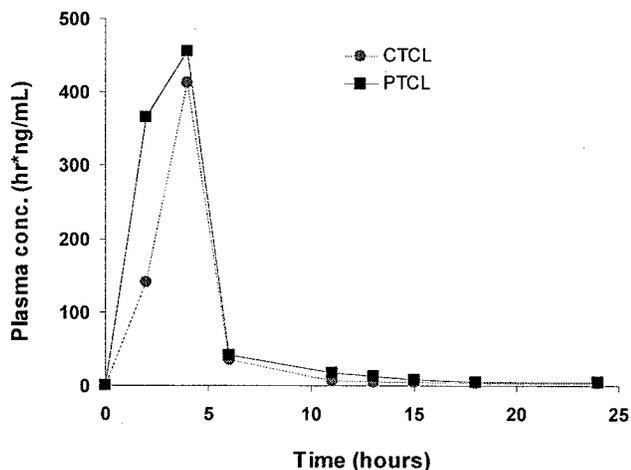
In Study NCI 1312, romidepsin was given to 94 patients with CTCL or PTCL. Initially three CTCL patients and one PTCL patient were administered with 18 mg/m² on days 1 and 5 of a 21-day cycle. Due to tolerability issues, the rest of the patients were on the proposed dosing regimen: 14 mg/m² administered as a 4-hour IV infusion on days 1, 8 and 15 of a 28-day cycle. Blood samples were collected on Day 1 in Cycle 1.

Since 14 mg/m² is the proposed dose in the label, the PK results presented below are only for this dose. Following a 4-hour IV infusion, the t_{max} generally occurred at the end of infusion. Due to rapid drug distribution and/or clearance, plasma concentrations were below the limit of detection (2.0 ng/mL) at ≤ 11 hours (representing a total of 3 time-points after the start of the infusion) for a number of patients and, as a result, estimation of the terminal half-life was not possible for all patients. Table 5 summarizes the PK parameters for both CTCL and PTCL patient populations. Their concentration time profiles are illustrated in Figure 2.

Table 5 Summary of romidepsin pharmacokinetics parameters (mean ± SD) following 4-hour infusion at 14 mg/m² by disease

	CTCL	PTCL
C _{max} (ng/mL)	413.7 ± 205.2 (n=61)	459.1 ± 233.4 (n=33)
AUC _{last} (hr*ng/mL)	1411.3 ± 740.7 (n=61)	1859.4 ± 1758.2 (n=33)
AUC _{0-∞} (hr*ng/mL)	1621.3 ± 744.3 (n=42)	2094.3 ± 1272.1 (n=17)
CL (L/hr)	20.9 ± 12.6 (n=42)	17.5 ± 10.5 (n=17)
V _{ss} (L)	58.3 ± 48.7 (n=42)	43.4 ± 24.7 (n=17)
t _{1/2} (hr)	3.7 ± 2.8 (n=42)	3.5 ± 1.8 (n=17)

Figure 2 Mean concentration time profiles of romidepsin following 4-hour infusion at 14 mg/m² in patients with CTCL or PTCL



As the PK parameters for CTCL patients were comparable to those with PTCL, plasma concentration data from both CTCL and PTCL patient populations were pooled together and the

PK parameters are summarized in Table 6.

Table 6 Summary of pooled romidepsin pharmacokinetics parameters (mean \pm SD) following 4-four infusion at 14 mg/m² in patients with T cell lymphoma

	Number of Subjects (n)	Arithmetic Mean \pm SD	Geometric Mean (CV%)
C _{max} (ng/mL)	94	429.4 \pm 215.1	376.6 (58.4%)
AUC _{last} (hr*ng/mL)	94	1565.5 \pm 1202.2	1283.6 (69.1%)
AUC _{0-∞} (hr*ng/mL)	59	1756.5 \pm 939.8	1548.5 (56.0%)
T _{max} (hr)*	59	4.0 (2.1 to 4.7)	
CL (L/hr)	59	20.0 \pm 12.1	17.2 (59.0%)
V _{ss} (L)	59	54.0 \pm 43.5	44.8 (62.3%)
t _{1/2} (hr)	59	3.6 \pm 2.6	3.0 (60.6%)

*Values are median (range) for Tmax

In the pivotal Study GPI-04-0001, sparse PK samples from ten patients were collected at 3 and 4 hours after the initiation of the infusion for more than one cycle. The plasma concentrations of romidepsin on Days 1, 8, 15 in the first and subsequential cycles were all comparable.

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

Not applicable. Romidepsin has only been administered and evaluated in cancer patients.

2.2.5.3 What are the characteristics of drug absorption?

Following a 4-hour IV infusion of 14 mg/m², the C_{max} of romidepsin was observed by the end of infusion period in patients with CTCL.

2.2.5.4 What are the characteristics of drug distribution?

In-vitro plasma protein binding

The protein binding of romidepsin was investigated *in-vitro* using serum and plasma samples from four healthy volunteers (Study CRD040011). Protein binding for radiolabeled romidepsin was 94% to 95% in human serum and 92% to 94% in human plasma over the concentration range of 50 to 1000 ng/mL. The percentage of protein bound tended to decrease at the highest concentration tested, 5000 ng/mL, and was determined to be approximately 82% in both human serum and plasma. In addition, radiolabeled romidepsin was 19.9% bound to human albumin and 93.5% bound to human α_1 -acid glycoprotein (AAG), suggesting that the principal binding protein in human serum is AAG.

Blood/Plasma Ratio

The extent of blood partitioning of romidepsin was determined in rat, dog and human whole blood (Report CRD040012). At a drug concentration ranging from 50 ng/mL to 5000 ng/mL, blood/plasma ratios were 0.68 to 0.75 in rats, 0.58 to 0.65 in dogs and 0.56 to 0.61 in humans.

Volume of Distribution

The volume of distribution on average in patients with T cell lymphoma was estimated to be 54 liters.

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

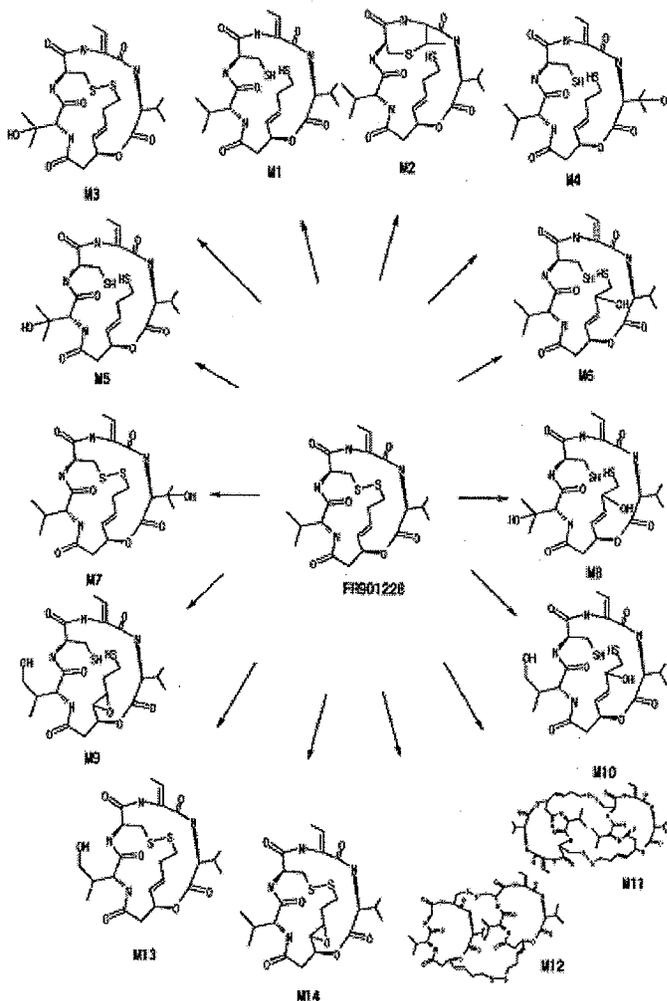
No mass balance study was conducted in humans. The mass balance study in rat suggests that romidepsin was primarily excreted into feces (Report CRD040009).

Following a single 0.3 mg/kg intravenous dose of [¹⁴C]-romidepsin to three rats, approximately 97.8% of the total administered dose was recovered in excreta during the collection interval of 0-168 hours. The majority of the administered radioactivity, 79.4%, was observed in the feces and 16.5%, and 0.1% were observed in urine and expired air, respectively.

2.2.5.6 What are the characteristics of drug metabolism?

[¹⁴C]-romidepsin metabolism was investigated *in vitro* using liver S9 and microsomal fractions from rats, dogs and human (Report CRD030200). Romidepsin underwent extensive metabolism and at least 20 metabolites were detected by radioactivity measurement. Among the metabolites formed, M3 and M7 (mono oxidation metabolites), M8 and M10 (di-oxidation and reduction of disulfide metabolites (DOH)), and VMH-1 and VMH-2 (structurally unidentified metabolites) were found to be the major metabolites in humans. Romidepsin reacted rapidly and nonenzymatically with glutathione by exchanging its disulfide bond with the thiol of glutathione and produced a reduced form of romidepsin (M1) under neutral conditions. This reaction occurred more rapidly than metabolism of romidepsin by liver microsomes. The enzymatic kinetics were evaluated based on romidepsin disappearance and formation of the major metabolites (M3, M8, M10, and VMH-1) in pooled human liver microsomes (Report CRD030201). K_m and V_{max} values for romidepsin disappearance were 20.3 $\mu\text{mol/L}$ and 561.9 pmol/min/mg , respectively. The intrinsic clearance value (Cl_{int} , calculated as V_{max}/K_m) was estimated to be 27.6 $\mu\text{L/min/mg}$. All metabolites detected in humans were also observed in either rats or dogs. Based on the metabolites characterized *in vitro*, a general biotransformation scheme is proposed in Figure 3.

Figure 3 Postulated biotransformation pathways for romidepsin *in vitro* (Applicant's figure)



In a separate study, the chemical structures of the metabolites of unlabeled romidepsin with human liver microsomes were elucidated using LC/electrospray ionization multi-stage mass spectrometry (LC/ESI-MSⁿ) (Report CRD040013). In addition to the metabolites observed in study CRD030200, new metabolites M17 and M21 through M28 were detected among which M17 was present in bile samples collected in the rat mass balance study. The structures of those newly formed metabolites are listed below. Romidepsin was also found to undergo a conjugation with glutathione.

Figure 4 Newly identified mono oxidation metabolites

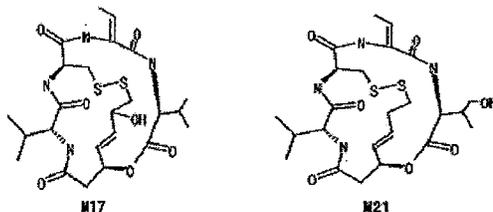


Figure 5 Newly identified mono oxidation and reduction of disulfide metabolites

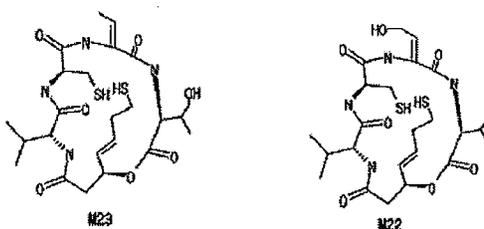


Figure 6 Newly identified di-oxidation metabolites

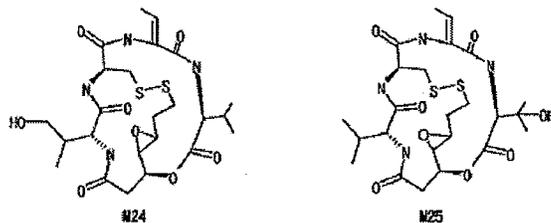
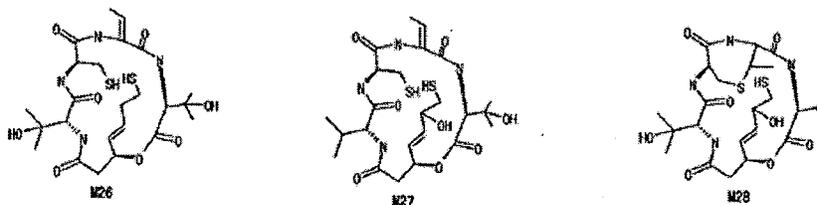


Figure 7 Newly identified di-oxidation and reduction of disulfide metabolites



In vivo, more than 30 kinds of metabolites were detected in the bile with no single metabolite being predominate in the rat mass balance study (Reports CRD040009 and CRD040010).

The role of cytochromes P450 (CYP450) isozymes in metabolism of romidepsin was examined by incubating [¹⁴C]romidepsin with either recombinant human CYP enzymes or with human liver microsomes (Report CRD030201). Of the 14 CYP enzymes examined, romidepsin disappearance was greatest in the presence of CYP3A4, followed to a much lesser extent by 3A5, 1A1, 2B6, and 2C19. In human liver microsomes from 12 individuals, romidepsin disappearance activities strongly correlated with testosterone 6β-hydroxylase activities and disappearance was inhibited by >90% by an anti-CYP3A4 antibody. When 0.1, 1, and 10 μM of ketoconazole was added, romidepsin disappearance activity was 41.2%, <10%, and <10% of the control value, respectively. These data indicate that romidepsin is primarily metabolized by CYP 3A4 in human liver microsomes *in vitro*.

2.2.5.7 What are the characteristics of drug excretion?

No mass balance study was conducted in humans. Results from the rat mass balance study (Report CRD040009) suggests that romidepsin was primarily excreted into feces via bile. Over 90% of the radioactive dose was excreted within 48 hours.

In the study following a single 0.3 mg/kg intravenous dose of [¹⁴C]-romidepsin to three rats, approximately 97.8% of the total administered dose was recovered in excreta during the collection interval of 0-168 hours with the majority of the administered radioactivity recovered in the feces (79.4% ± 1.1%) and the urine accounting for 16.5% ± 0.8%. Within 48 hours post-dose, approximately 91.2% of total radioactivity was excreted. Seventy five percentage of the radioactivity was recovered in the feces, and 15.9% was excreted in urine. Of the urinary recovery, 4.2% was as the parent compound.

Clearance

The mean systemic clearance of romidepsin following 4-hour IV administration at 14 mg/m² was approximately 20 L/h in patients with T cell lymphoma and was approximately 26 L/h in patients with refractory neoplasm.

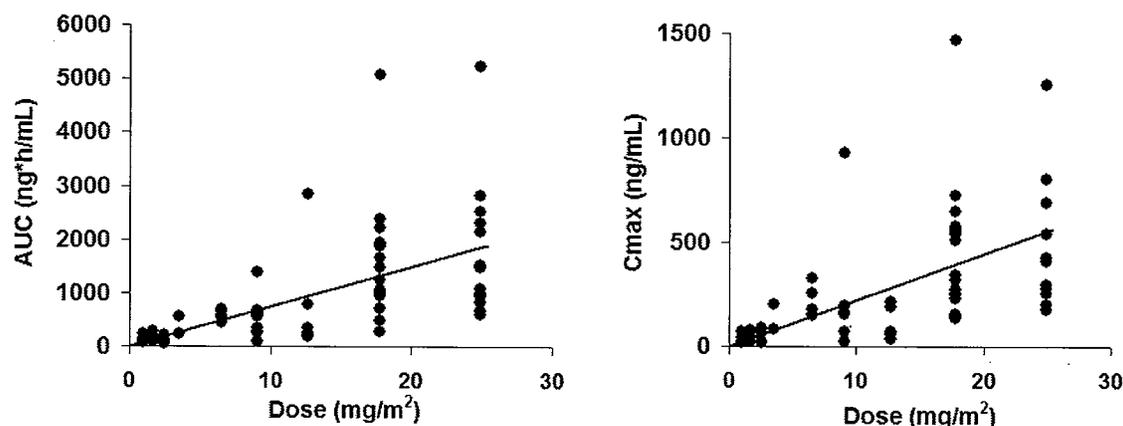
Half-life

The elimination half-life of romidepsin from plasma was approximately 3 hours in patients with T cell lymphoma.

2.2.5.8 Based on PK parameters, what is the degree of linearity or non-linearity based in the dose-concentration relationship?

Study T-95-0077 was a phase 1 dose escalation trial with dose ranging from 1.0 to 24.9 mg/m² in patients with refractory neoplasms. Despite moderate to high inter-patient variability at a given dose, the increase in romidepsin C_{max} and AUC was generally dose-proportional over the dose range studied (Figure 8). This was also confirmed by a power model analysis fitting log-AUC_{0-∞} and log-C on log-dose with the regression slope of 0.86 (95% CI, 0.638-1.09) for AUC and 0.90 (95% CI 0.703-1.09) for C_{max}.

Figure 8 Dose proportionality following 4-hour IV infusions of romidepsin in patients with refractory neoplasms



2.2.5.9 How do the PK parameters change with time following chronic dosing?

After repeated administration, romidepsin PK did not change appreciably and no accumulation was observed. Refer to Section 2.2.5.1 for more information on the PK of romidepsin following multiple doses.

2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Based on subjects in study T-95-0077 with more than one treatment at the same dose level, the intra-subject variability of romidepsin exposure in the patients with refractory neoplasm is moderate to high, with the CV% for Cmax and AUG generally in the range of 30% - 80%. The inter-subject variability in the T cell lymphoma patients was generally in the range from 50% to 70% for exposures (Table 6) and this level of variability in exposure was also seen in patients with refractory neoplasm. The major causes of variability seen in patients may include variability in the intrinsic factors of the patients (such as hepatic function, disease stage) and extrinsic factors such as concomitant medications as well as practice variability.

2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

The integrated population PK analysis with romidepsin in patients with advanced cancers, including CTCL, demonstrated that age, gender, race, and mild to severe renal impairment had no effect on romidepsin PK. The clearance of romidepsin does not depend upon age (range: 27-81 years). There is no difference in romidepsin clearance between males (n = 90) and females (n = 47). Race also does not affect romidepsin PK. Most of the subjects were white (n = 114) and a few were black (n = 17), therefore the results are applicable to these races only. There was no

effect of mild to severe renal function (CRCL range: 0.23 -198 ml/min) on the clearance of romidepsin. Refer to Appendix 4.2 (Pharmacometric Review) for details.

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

No dose adjustments for specific populations are recommended. The Applicant proposed in the label that the dose reduction from 14 to 10 and then to 8 mg/m² can be considered if a patient is intolerant to therapy. There was experience with dose delaying and reduction in the pivotal and supportive trials. Delaying the dose eventually resulted in recovery from the toxicities for most of the patients in these trials. Therefore, if the patient experiences hematological toxicities, the dose of romidepsin should be delayed. If delaying does not resolve toxicities and patient becomes intolerant to romidepsin therapy, the dose should be reduced to 10 mg/m² and further to 8 mg/m² (see Section 2.2.4 of this review).

2.3.2.1 Elderly

The results of the population PK analysis show that romidepsin disposition is not affected by age (see Section 2.3.1 of this review). Therefore, no dose adjustment will be required for the elderly. The Applicant states in the label that “Of the 167 patients with CTCL in trials, 23% were >65 years old. No overall differences in safety or effectiveness were observed between these subjects and younger subjects; however, greater sensitivity of some older individuals cannot be ruled out.”

2.3.2.2 Pediatric patients

There were no pediatric studies included in the current submission.

2.3.2.3 Gender

The results of the population PK analysis show that romidepsin disposition was similar in men and women (see Section 2.3.1 of this review). No dose adjustment is recommended with regard to gender.

2.3.2.4 Race

Based on the population PK analysis, race (white vs. black) had no affect the PK of romidepsin (see Section 2.3.1 of this review).

2.3.2.5 Renal impairment

No dedicated renal impairment study has been conducted. Based on the population PK analysis, mild to severe renal impairment was not found to affect the PK of romidepsin (see Section 2.3.1 of this review).

2.3.2.6 Hepatic impairment

No dedicated hepatic impairment study has been conducted. The Applicant employed a population PK approach to evaluate the effect of hepatic impairment on the PK of romidepsin

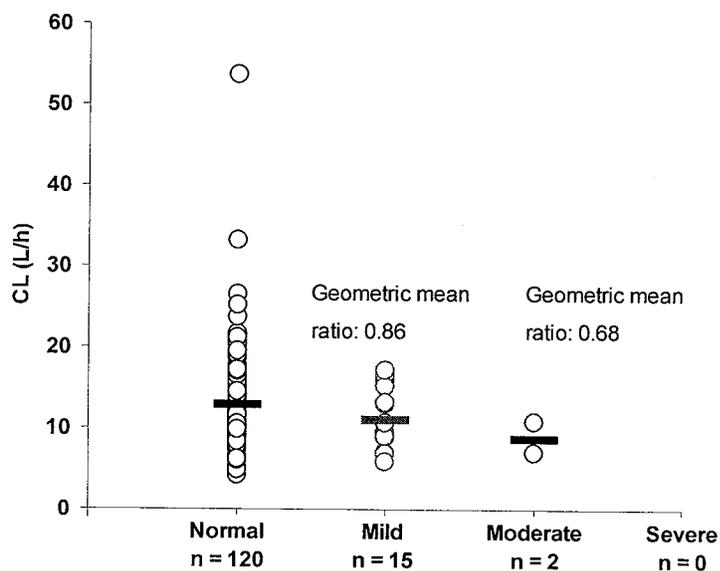
using data from 3 studies (1312, FJ-228-0001, GPI-06-0005). The hepatic function of the patients were categorized by the National Cancer Institute Organ Dysfunction Working Group Liver Function Classification.

Based on the population PK analysis, the Applicant concluded that mild [total bilirubin (TB) \leq upper limit of normal (ULN) and aspartate aminontransferase (AST) $>$ ULN; or TB $>$ 1.0x - 1.5x ULN and any AST] (n=15) and moderate (TB $>$ 1.5x – 3x ULN and any AST) (n=2) hepatic impairment had no influence on romidepsin disposition compared to the subjects with normal liver function (n=120).

However, the data that the Applicant analyzed is limited, which contained only two subjects with moderate hepatic impairment and none with severe hepatic impairment. Even so, there seems to be a trend of decreased CL in the two patients with moderate hepatic impairment compared to that of the normal and mild hepatically impaired patients.

Given the adequate number of subjects with mild hepatic impairment and a similar clearance between the patients with normal hepatic function and patients with mild hepatic impairment, a dose adjustment does not appear to be necessary in patients with mild hepatic impairment.

Figure 9 Romidepsin clearance by hepatic impairment grouping



Overall, due to the limited number subjects with moderate hepatic impairment and the absence of subjects with severe hepatic impairment, a recommendation on dose adjustment in this specific patient population cannot be provided. Thus, a post marketing study to evaluate the impact of moderate and severe hepatic impairment on PK and safety of romidepsin is required.

2.3.2.7 What pharmacogenetics information is there in the application and is it important or not?

There are no pharmacogenetics data in the application and no issues have been identified so far.

2.3.2.8 What pregnancy and lactation use information is there in the application?

There is no information on the excretion of romidepsin in the milk of humans or animals in the application.

2.4 EXTRINSIC FACTORS

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

No dedicated studies were conducted to evaluate the impact of extrinsic factors on the PK and/or pharmacodynamics of romidepsin.

2.4.2 Drug-drug interactions

2.4.2.1 Is there an *in vitro* basis to suspect *in vivo* drug-drug interactions?

Yes. The ability of CYP450 enzymes to metabolize romidepsin is discussed in Section 2.2.5.6. Since CYP3A4 is the major CYP isozyme responsible for the metabolism of romidepsin, inhibitors and inducers of CYP3A4 are expected to affect its PK. Thus, post marketing studies to evaluate the effects of a strong CYP3A4 inhibitor and an inducer on the PK of romidepsin are required.

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

As discussed in Section 2.2.5.6, romidepsin is primarily metabolized by CYP3A4, with lesser contributions from CYP3A5, 1A1, 2B6, and 2C19. There are no data indicating that metabolism is influenced by genetics.

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

In the clinically relevant concentration range, romidepsin does not exhibit any inhibitory effects on CYP isozymes.

The *in vitro* inhibition study was conducted using pooled human liver microsomes and enzyme-specific probe substrates (Report CRD030209). Romidepsin did not inhibit the activity of CYP1A2, CYP2C9 or CYP2E1 at any concentration tested. At concentrations of 10 μM or less, romidepsin did not appear to inhibit the activity of CYP2C19, CYP2D6, CYP3A4 (nifedipine oxidase), or CYP3A4 (testosterone 6 β -hydroxylase). At a concentration of 100 μM , these enzyme activities decreased to 36.5%, 76.2%, 38.2%, and 30.3% of their respective control activities, with values for the concentration resulting in 50% inhibition (IC_{50}) of 58.1 μM for CYP2C19, >100 μM for CYP2D6, 59.8 μM for CYP3A4 (nifedipine oxidase), and 42.7 μM for CYP3A4 (testosterone 6 β -hydroxylase).

Using the average maximum blood concentration of 429 ng/mL (approximately 0.9 μM) after IV infusion of romidepsin at the proposed clinical dose of 14 mg/m², the reviewer calculated the ratios of C_{max}/K_i by assuming the competitive inhibition. The values are listed below in Table 7.

Table 7 Ability of romidepsin to inhibit CYP enzymes

	IC ₅₀ (μM)	K _i (μM)*	C _{max} /K _i
CYP2C19	58.1	29.05	0.03
CYP2D6	>100		
CYP3A4	59.8	29.9	0.03
CYP3A4	42.7	21.4	0.04

*not determined, estimated assuming competitive inhibition

Based on the data, romidepsin does not appear to competitively inhibit the metabolic clearance of drugs that are substrates of CYP3A4, 2C9, and 2C19 at clinically relevant dose.

No information regarding the induction potential of romidepsin on the activity of CYP enzymes was submitted in the application.

2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes? Are there other metabolic/transporter pathways that may be important?

Romidepsin is a substrate of the efflux transporters P-glycoprotein (P-gp) and multidrug resistance-associated protein 1 (MRP1) (Xiao 2005).

At its clinically relevant concentration range, romidepsin showed an unidirectional flux across the Caco-2 cell monolayer, with basolateral to apical (BL→AP) apparent permeability coefficient (P_{app}) 32 times that of apical to basolateral (AP→BL) without apparent saturation. With P-gp inhibitors cyclosporine (5 μM) and verapamil (100 μM), the efflux ratio was reduced from 32 to 1.65 and 2.47, respectively. In the presence of MK571, a known MRP inhibitor (50 μM), the romidepsin efflux ratio was reduced to near unity. However, in the presence of another MRP inhibitor, indomethacin at 20 or 40 μM , no significant effect on romidepsin transport was observed in either direction.

As MRP1 is highly expressed in red blood cell (RBC) membrane, an *in vitro* uptake study was conducted for romidepsin at 1.8 and 18 μM with human RBCs from eight healthy volunteers. RBCs showed a concentration-dependent uptake and saturable efflux of romidepsin. In addition, on the cell lines of HL60 cells [Pgp(-)/MRP1(-)] and HL60Adr cells [Pgp(-)/MRP1(+)], HL60Adr cells were 4-fold more resistant to romidepsin than HL60 cells, and the resistance was reversed by MRP inhibition using MK571. These data confirmed that romidepsin was a substrate of MRP1.

Romidepsin was not found to be a P-gp inhibitor *in vitro* (Scala et al. 1997). In the study, P-gp over-expressing SW620 Ad300 human colon carcinoma cells were incubated in rhodamine-123 (a fluorescent indicator) - containing media for 30 minutes in the presence or absence of romidepsin or positive controls (verapamil and cyclosporin A). The cells were then washed and

incubated in rhodamine-123 free medium, continuing in the presence or absence of romidepsin for 60 minutes. The amount of rhodamine remaining in the cells after the 60 minutes efflux period was quantified by flow cytometric analysis. At tested concentrations of 1, 10, or 100 μM , romidepsin did not inhibit rhodamine efflux and did not increase rhodamine accumulation.

2.4.2.5 Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

The label does not specify co-administration of any other drugs.

As indicated in the Integrated Summary of Safety in the application, the serious adverse event of coagulation abnormalities was reported in a subject who received romidepsin 22 mg/m^2 IV over 4 hours on days 1, 8, and 15 every 28 days concomitantly with 7.5 mg of warfarin sodium orally daily. After two doses of romidepsin, this patient's prothrombin time (PT) was elevated from 58.3 seconds (pre-study) to greater than 200 seconds and International Normalized Ratio (INR) was increased from pre-study value of 1.6 to greater than 15.

Although the interaction potential between romidepsin and coumadin or coumadin derivatives has not been formally studied, in Study GPI-04-001, concomitant use of warfarin was prohibited. The Applicant proposed in the label that ‘

b(4)

2.4.2.6 What other co-medications are likely to be administered to the target patient population?

Because of the toxicities associated with the regimen, antiemetics are likely to be co-administered.

2.4.2.7 Are there any *in vivo* drug-drug interaction (DDI) studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

No dedicated clinical DDI studies have been conducted for romidepsin. As addressed in Section 2.4.2.1, *in vivo* DDI studies should be conducted for romidepsin with strong CYP3A4 inhibitor and inducer in humans.

2.5 GENERAL BIOPHARMACEUTICS

2.5.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

Not applicable.

2.5.2 What is the composition of the to-be-marketed formulation?

Romidepsin is an injection, powder, lyophilized, for solution dosage form. Drug Product is manufactured as a lyophilized, sterile finished product containing romidepsin, 10 mg/vial and 20 mg/vial of the bulking agent, Povidone, USP. It is supplied in a dual-pack configuration with a diluent vial containing 2 mL of a reconstitution solution composed of 80% propylene glycol, USP, and 20% dehydrated alcohol, USP. The composition of the Drug Product is presented in Table 8.

Table 8 Romidepsin drug product composition

Component	Function	Quantity per Vial	Reference to Quality Standard
Romidepsin	Active ingredient	10 mg	In-house specification
Povidone		20 mg	USP
		Trace	NF/EP
		N/A	NF/EP
		N/A	USP/EP
		N/A	ACS

¹ Removed during lyophilization

b(4)

2.5.3 What moieties should be assessed in bioequivalence studies?

Not applicable.

2.5.4 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Not applicable.

2.5.5 Has the applicant developed an appropriate dissolution method and specification that will assure *in vivo* performance and quality of the product?

Not applicable.

2.6 ANALYTICAL SECTION

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

In all the clinical studies, romidepsin was measured in plasma by validated analytical methods. Please see Section 2.6.4 for details.

2.6.2 Which metabolites have been selected for analysis and why?

No metabolites were measured and the NDA dose not address the reason as to why the metabolites were not measured.

2.6.3 For all moieties measured, is free, bound or total measured? What is the basis for that decision, if any, and is it appropriate?

Total drug was measured for all moieties. The rationale of choosing to measure total drug was not presented in the NDA.

At therapeutic concentrations of romidepsin, *in vitro* experiments show that the extent of romidepsin binding to plasma proteins is not saturated and independent of drug concentration (see Section 2.2.5.4 of this review). This suggests that measurement of total drug is appropriate and may have been the reason of the Applicant's decision to measure total drug.

2.6.4 What bioanalytical methods are used to assess concentrations?

Two validated analytical methods were used for the measurement of romidepsin concentrations in the six clinical studies that contributed most to pharmacokinetics decision (See Section 2.2.1 for more details of these studies). For both methods, romidepsin was extracted from human plasma by liquid/liquid extraction prior to assay. The specificity of the assay was established and no trace of interference substance was found at the same retention time as romidepsin. The accuracy of the analytical methods were within $100 \pm 15\%$ and precision expressed as the coefficients of variation (% CV) was $< 15\%$. In plasma, the freeze thaw stability was 3 cycles, short term stability was 4 hours (the longest time evaluated) at room temperature, and long term stability at -20°C was 12 months. It was stable in extracted samples for 24 hours at 4°C . As romidepsin was observed to be unstable at room temperature in human whole blood, it was suggested that human whole blood should be cooled on ice immediately after withdrawal and the centrifugation and separation into plasma were done through under the cooling. The current practice of sample processing appears acceptable.

The two methods are summarized in the following sections, along with reference to the clinical studies they supported. Validation summary of bioanalytical methods for romidepsin in clinical studies is presented in Table 9.

2.6.4.1 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used? What are the lower and upper limits of quantification (LLOQ/ ULOQ)? What are the accuracy, precision and selectivity at these limits? What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)? What is the QC sample plan?

HPLC-MS/MS Method to Determine Romidepsin in Human Plasma (1 to 100 ng/mL)

The method for the determination of romidepsin in human plasma was validated over the range 1 to 100 ng/mL using HPLC-MS/MS. Prior to assay, romidepsin and the internal standard (IS) in human plasma samples were extracted by ethyl acetate, evaporating to dryness under nitrogen gas stream at 40°C , and dissolved in mobile phase containing methanol/12 mM/ ammonium acetate solution/acetonitrile (60:30:10, v/v/v). An aliquot of the reconstituted solution was then injected to HPLC/MS/MS system. Romidepsin and IS were detected by multiple reaction monitoring (MRM) mode at mass transition m/z 541.0 – 272.0 for romidepsin and m/z 510.0 - 217.0 for the IS.

The accuracy of the assay was determined by comparing the nominal concentrations with the

corresponding calculated concentrations via linear regression. The within-run and between run precision values were expressed as the coefficients of variation (% CV).

This method is used for the studies, GPI-04-0001, GPI-06-0005, FJ-228-0001, FJ-228-0002, and T-95-0077.

HPLC-MS Method to Determine Romidepsin in Human Plasma (2 to 1000 ng/mL)

Prior to assay, romidepsin and the IS in human plasma samples were extracted by ethyl acetate, evaporating to dryness under desiccated air in a water bath at 40°C, and dissolved in a mixture of methanol/0.2% formic acid (55:45, v/v) and vortex mixed. Then the reconstituted solution is analyzed using LC/MS. Selected-ion monitoring was accomplished at *m/z* 541.2 for romidepsin and *m/z* 213.1 for the IS.

The accuracy of the assay was evaluated by the percentage deviation (DEV) from the nominal or theoretical concentration. This method is used for the study, NCI 1312.

Table 9 Validation summary of bioanalytical methods for analytes in clinical studies

Study No.	GPI-04-0001, FJ-228-0001, FJ-228-0002, GPI-06-0005	T-95-0077		NCI 1312
Analyte	Romidepsin			
Matrix/Anticoagulant	Human Plasma/Heparin			
Assay Vol Required	500 µL			240 µL
Detection Method	LC/MS/MS			LC/MS
Standard Curve Range	0.1-100 ng/mL			2-1000 ng/mL
Regression Type	Linear			
Quantification Method	Peak area ratio			
LLOQ	0.1 ng/mL			2 ng/mL
LLOQ Validation Sample				
Precision (≤%CV)			Precision (≤%CV)	
Intra-Assay	10.0	11.9%	Inter-Assay	9.82
Inter-Assay	10.0	10.2%		
Accuracy (% of the nominal concentrations)			Accuracy (≤± %deviation)	
Intra-Assay	110.0	101.0	Inter-Assay	5.8
Inter-Assay	100.0	107.3		
Precision (≤%CV)			Precision (≤%CV)	
Intra-Assay	8.3	8.2	Inter-Assay	3.7
Inter-Assay	3.8	8.3		
Accuracy (% of the nominal concentrations range)			Accuracy (≤± %deviation)	
Intra-Assay	104.0 -112.0	99.3 - 110.7	Inter-Assay	6.39
Inter-Assay	104.0 – 110.1	98.9 – 103.0		
Dilution Integrity	(1:50) 2000 ng/mL	Not reported		Not reported

3 DETAILED LABELING RECOMMENDATIONS

8 Page(s) Withheld

Trade Secret / Confidential (b4)

X Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

Withheld Track Number: Clin Pharm/Bio Review Section- 1

4 APPENDICES

4.1 Applicant's Proposed Package Insert

4.2 Pharmacometric review

4.3 QT review

Appendix 4.1 Applicant's Proposed Package Insert

7 Page(s) Withheld

Trade Secret / Confidential (b4)

X Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

Appendix 4.2 Pharmacometric review

OFFICE OF CLINICAL PHARMACOLOGY:

PHARMACOMETRIC REVIEW

Application Number	22393
Submission Number (Date)	January 12, 2009
Compound	Romidepsin (Depsipeptide: 14 mg/m ²)
Clinical Division	DDOP
Primary PM Reviewer	Nitin Mehrotra, Ph.D.
Secondary PM Reviewer	Christoffer W. Tornoe, Ph.D.

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1 SUMMARY OF FINDINGS

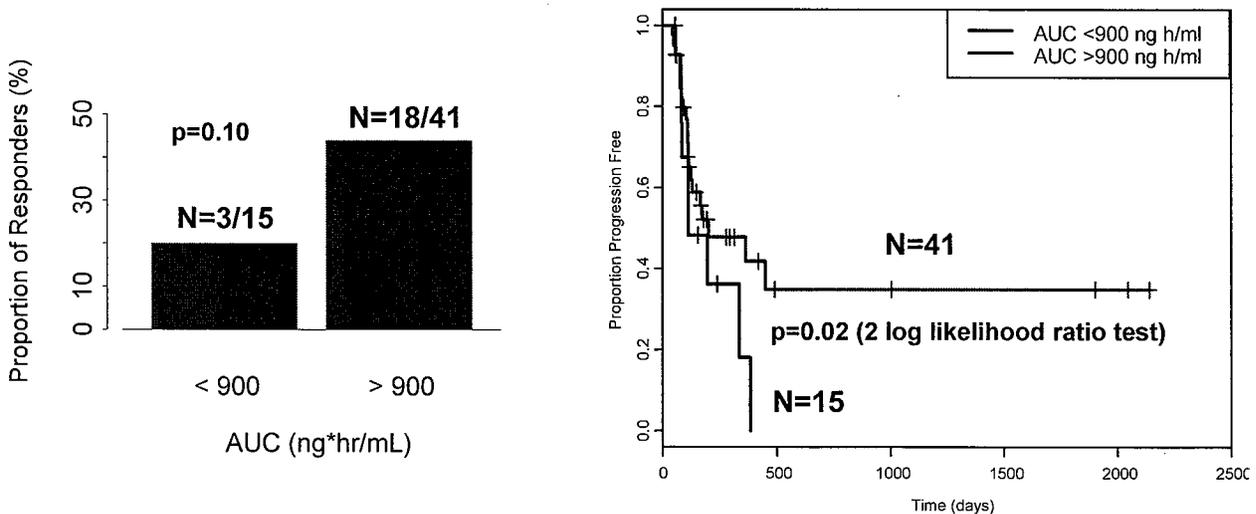
1.1 Key Review Questions

The following key questions were addressed in this pharmacometrics review.

1.1.1 Is there evidence of exposure-response for effectiveness?

Yes, there is evidence of exposure-response for effectiveness seen in the supportive efficacy trial NCI-1312 following 14 mg/m² dose of romidepsin. CART (Classification and regression tree) analysis was performed to assess the exposure-response relationship for effectiveness based on the primary efficacy endpoint- objective disease response (ODR). The aim was to select an optimal AUC breakpoint which maximally distinguished the response. It can be seen from **Figure 1** (left panel) that the proportion of responders were twice (43%) within the group of patients with AUC > 900 ng*hr/mL when compared to patients with AUC < 900 ng*hr/mL (20%). The odds ratio for subjects with AUC < 900 ng h/mL to respond is 0.32 (95% CI: 0.08-1.3, p=0.10). This AUC cutoff point was utilized to explore time to disease progression, which is one of the secondary endpoints of the trial. The progression of the disease is faster in patients with lower exposure (AUC < 900 ng h/ml). However, it is not clear why the separation between the two survival curves does not happen until 250 days. As a result median PFS is similar between groups (**Figure 1**, right panel). Even though there are few patients contributing to this analysis, it provides a supportive evidence that romidepsin exhibits pharmacological effect.

Figure 1: Exposure-response relationship for romidepsin using ODR (left panel) and time to progression (Right panel). Black and red vertical lines on the time to disease progression plot (Right Panel) are censored observations in the two groups.



1.1.2 Are the proposed dose reductions of 10 and 8 mg/m² adequate to reduce risk of toxicities (blood/bone marrow disorders)?

No, dose reductions may cause loss in response without significantly reducing toxicities (Blood/bone marrow disorders). Sponsor proposes dose reductions to 10 and 8 mg/m² for patients experiencing thrombocytopenia, leucopenia or anemia. However, none of the patients had dose reductions in the pivotal trial experiencing these toxicities (**Table 1**). The dose was delayed for five patients. In other three patients dose was discontinued. Hundred percent of patients for whom the dose was delayed recovered from their toxicities. For 66% of the patients who experienced blood/bone marrow disorders, no action was taken.

Logistic regression models were used to explore the relationship between exposure (AUC) and treatment emergent adverse events. Blood/bone marrow disorders which is combination of thrombocytopenia, leucopenia and lymphopenia was explored for relationship with romidepsin exposure. Thrombocytopenia, leucopenia, lymphopenia and neutropenia were also explored individually for their relationship to romidepsin exposure. Exposure-response relationship could not be established for safety. This is probably due to large variation in exposure (AUC) and also relatively few subjects.

The sponsor had experience with delaying the dose which eventually resulted in recovery for most of the patients. Therefore, if patient experiences hematological toxicities, consider delaying the dose of romidepsin since there is evidence of exposure-efficacy relationship and reducing the dose may cause loss in response. However, it is possible that lack of exposure-safety relationship could be due to low number of subjects and/or high variability in AUC. The sponsor had experience with dose reduction in NCI trial which did result in reduction in toxicities. Therefore, if delaying does not resolve toxicities and patient becomes intolerant to romidepsin therapy, dose should be reduced to 10 and further to 8 mg/m².

Table 1: AE (Blood/bone marrow disorders, All grades) in the pivotal trial GPI-04-0001

	GPI-04-0001 (N=96)	Recovered (%)
Patients with AE (%)	26 (27.1)	-
Dose Reduced (%)	0 (0)	-
Dose Delayed (%)	5 (19.2)	5 (100)
Dose Stopped (%)	3 (11.5)	2 (66.6)
Concomitant Medications (%)	4 (15.3)	2 (50)
Non Medication Treatment	3 (11.5)	3 (100)
Other	2 (7.6)	3 (100)
None	17 (65.8)	15 (88.2)

1.1.3 Which intrinsic factors influence romidepsin pharmacokinetics?

Body weight was the only intrinsic factor found to influence romidepsin pharmacokinetics (also see Section 1.1.4).

The clearance of romidepsin dose not depend upon age (Age range: 27-81 years, **Figure 3**, left panel)). There is no difference in romidepsin clearance between males and females (**Figure 2**, left panel). Race also does not affect romidepsin PK (**Figure 2**, right panel). Most of the subjects were white and few were black, therefore the results are applicable to these races only. There was no effect of mild to severe renal function (CRCL range: 0.23-198 ml/min) on the clearance of romidepsin (**Figure 3**, right panel). It is expected as romidepsin is primarily eliminated via hepatic route.

Figure 2: No effect of (Left) gender and (Right) race on clearance of romidepsin. Each red dot represents a subject.

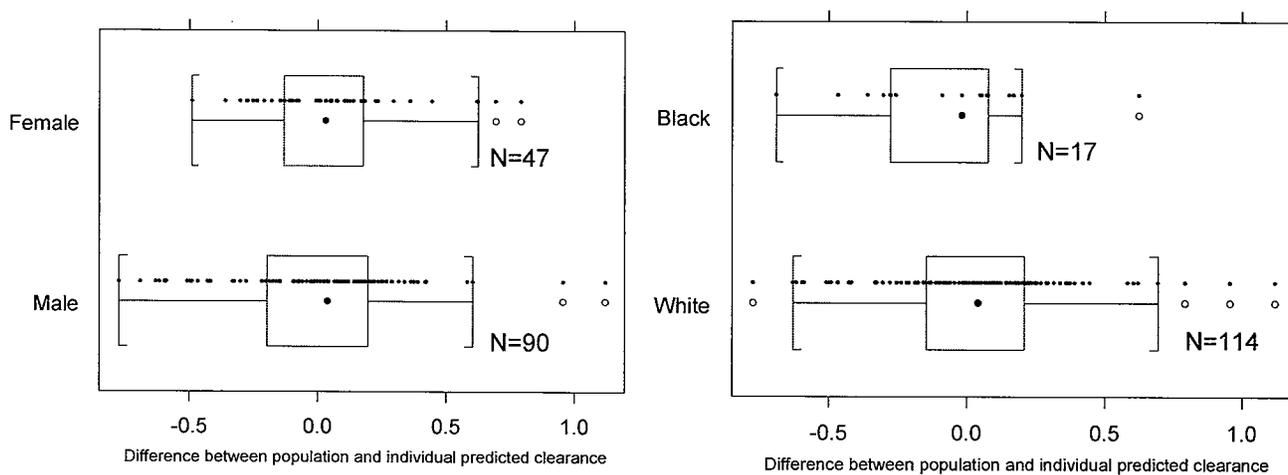
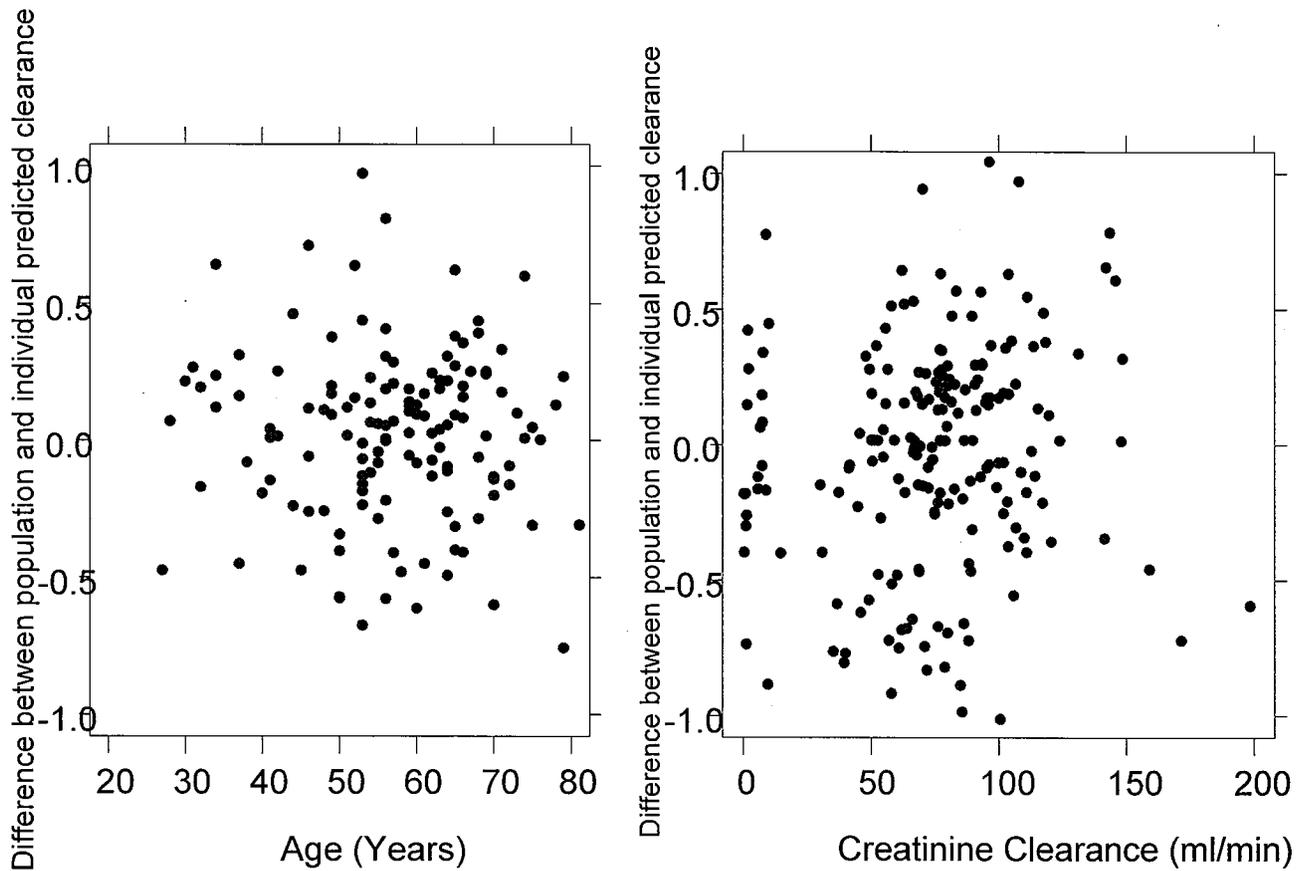


Figure 3: No effect of (Left) age and (Right*) renal function on clearance of romidepsin. Each red dot represents a subject.

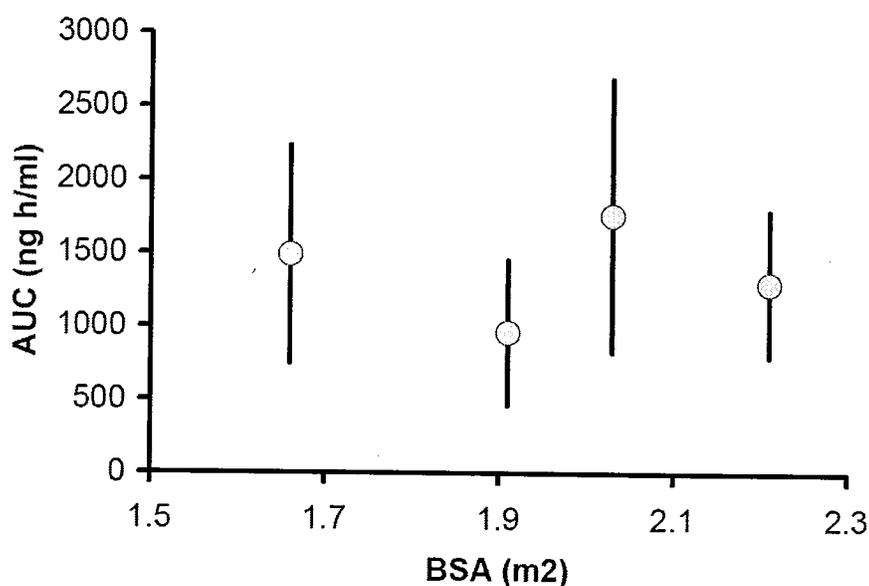


*Integrated population model which pooled 6 studies was utilized so as to include severe renal impaired subjects (CRCL < 30 ml/min)

1.1.4 Does proposed dose of 14 mg/m² produce similar exposures across patients?

Since body weight affected romidepsin PK and body weight and body surface area (BSA) were highly correlated, it is reasonable to conclude that BSA also affects romidepsin PK. Therefore, BSA-based dosing normalizes AUC across patients (Figure 4).

Figure 4: Exposure is similar across BSA when dosed at 14 mg/m².



1.1.5 Does romidepsin prolong QT?

A thorough QTc study was not performed. ECG data were collected from 3 clinical studies: Study GPI-04-0001 in patients with CTCL; Study 1312 in patients with CTCL, PTCL, or other T-cell lymphomas; Study GPI-06-0005 in patients with advanced solid tumors or hematologic malignancies. The sponsor performed an exposure response analysis using PK and ECG data to characterize the relationship between romidepsin concentration and heart-rate corrected QTc interval.

Limitations in the ECG data collection limit the interpretation of the results. The possibility of QT prolongation cannot be excluded since this class of compounds (Histone deacetylase inhibitors) has been associated with class effect for prolonging QT.

The limitations in ECG data collection include:

- In study GPI-04-001, triplicate ECGs were collected at screening, at baseline, and within 2 hours after completion of administration of romidepsin. An ECG was not

acquired at maximum plasma concentrations. ECGs were not collected at later time points to rule out any delayed drug effects on QT prolongation. Sparse PK were only collected for ten subjects (10.4% of the total population) ; There were no controls (positive or negative).

- In study NCI 1312, single ECGs were collected at baseline, within 2 hours after completion of administration of romidepsin and at 24 and 48 hours post-dose. Time matched PK was not obtained.
- In study GPI-06-0005, triplicate ECGs and PK samples were collected prior to infusion and at 0.25, 0.5, 1, 2, 3, 4, 6, 8, and 24 hours post-infusion. There are only 7 patients with available data. The number of patients to be evaluated may be too low to obtain any meaningful results from the exposure-response analysis.

Review of the QT data for this submission was performed by the *CDER Interdisciplinary Review Team* (IRT). Please refer to Appendix 4.3 for IRT-QT review for further details.

1.2 Recommendations

Division of Pharmacometrics finds the NDA acceptable from a clinical pharmacology perspective.

1.3 Label Statements

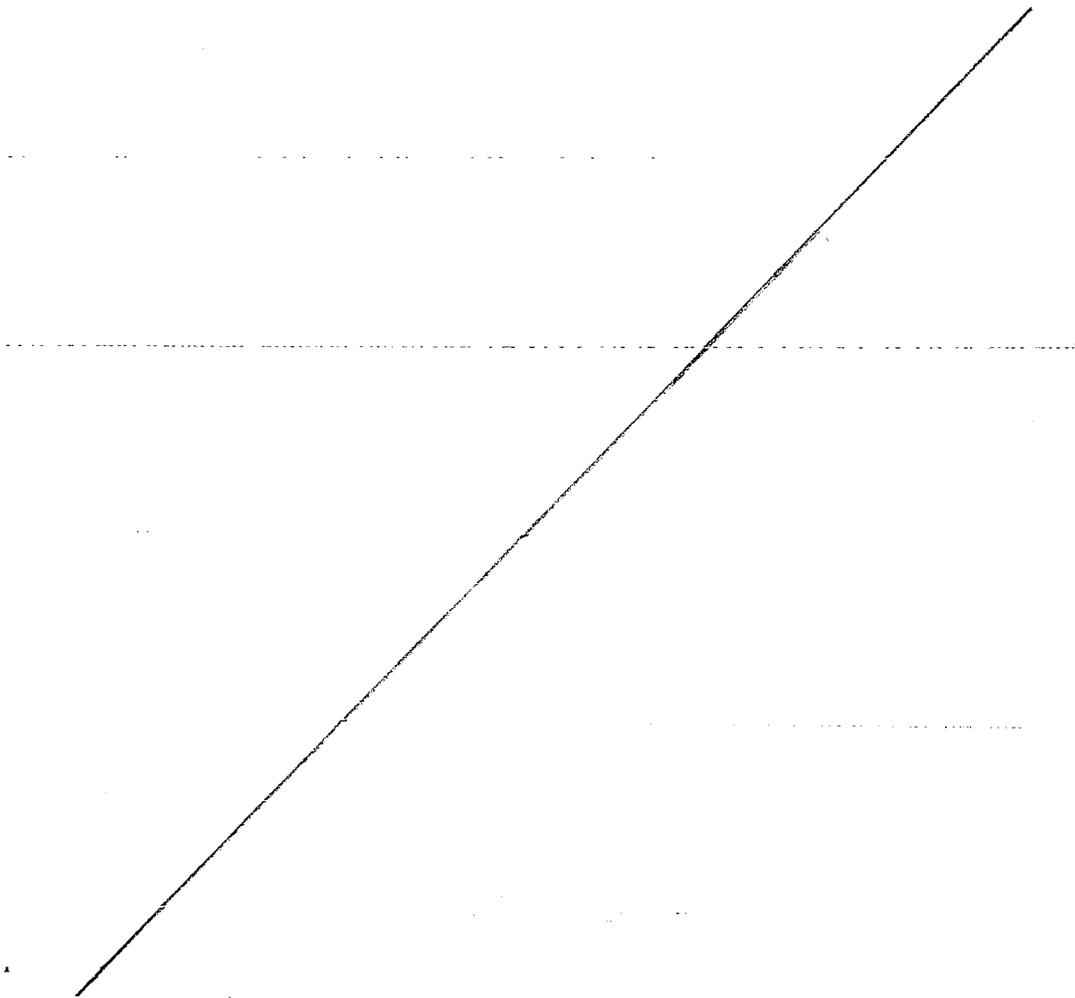
The following are the labeling recommendations relevant to clinical pharmacology for NDA 22393. The ~~red-strikeout font~~ is used to show the proposed text to be deleted and underline blue font to show text to be included or comments communicated to the sponsor.

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2 Pertinent Regulatory Background

Romidepsin is a unique bicyclic depsipeptide originally isolated from *Chromobacterium violaceum* strain 968. Romidepsin is an antineoplastic agent that has been identified as a novel histone deacetylase (HDAC) inhibitor. The proposed indication is for the treatment of cutaneous T-cell lymphoma (CTCL), including relief of pruritus, in patients who have received at least one prior systemic therapy. Currently, three systemic therapies are approved by US FDA. Vorinostat which belongs to the same class as romidepsin, Denileukin diftitox (fusion protein) and bexarotene (Retinoid X-receptor activator). Primary support for efficacy is provided by the pivotal study, GPI-04-0001, with additional support from Study NCI-1312. Primary end point for both these trials was objective disease response while progression free survival, duration of response and time to response were some of the secondary endpoints. NCI trial included both CTCL and

Peripheral T Cell lymphoma (PTCL) patients while GPI-04-0001 trial comprised of CTCL patients only.

3 Results of Sponsor's Analysis

Sponsor performed population PK modeling utilizing data from six studies which evaluated romidepsin in advanced cancer. Primary objective of the population PK analysis was to describe the PK of romidepsin. Secondary objective was to evaluate the effect of various covariates (age, gender, race, renal function, hepatic function) on romidepsin PK and to develop separate predictive population models for PK data from studies NCI 1312 and GPI-06-0005 to support exposure – QTc analysis.

3.1 Methods

PK Data from a total of 217 patients was available from the six Phase 1 and 2 studies. Description of the studies with other relevant information is provided in **Table 2**. Sponsor first utilized studies with rich PK sampling scheme to develop the structural model. After structural model was identified three of the studies were pooled (NCI1312, FJ-228-0001, GPI-06-0005) based on the prespecified criteria to develop the final covariate model.

Table 2: Study characteristics.

Study No.	Number of cycles	Sample size	Nominal doses studied (mg/m ²)	Indication	Sample collection
NCI-1312	1	96 4	14 18	CTCL & PTCL	Rich
FJ-228-0001	1-6	27	13	Metastatic renal cell carcinoma	Sparse
FJ-228-0002	1-6	35	13	Androgen independent metastatic prostate cancer	Sparse
GPI-04-0001	1-6	10	14	CTCL	Sparse
GPI-06-0005	1	10	14	Advanced malignancies	Rich
T-95-0077	1-4	35	1.0, 1.7, 2.5, 3.5, 6.5, 9.1, 12.7, 17.8, and 24.9	Refractory neoplasms	Rich

3.2 Conclusions

- The PK of romidepsin was best described by a three compartment model parameterized in terms of clearances and volumes of distribution.
- Weight and study type were identified as covariates on central clearance.
- There was no effect of age, race, sex, renal function and hepatic impairment on PK of romidepsin.

Parameter estimates for fixed effect and random effects with uncertainty are presented in **Table 3** and **Table 4**, respectively.

Table 3: Summary of NONMEM/Bootstrap Fixed Effect Population Pharmacokinetic Parameter Estimates with Uncertainty for the Integrated Analysis of Studies NCI 1312, FJ-228-0001, and GPI-06-0005.

Statistic	Parameter									
	θ_1	θ_2	θ_3	θ_4	θ_5	θ_6	θ_7	θ_8	θ_9	θ_{10}
	NONMEM									
	8.23	5.55	12.90	0.45	2.14	1.02	0.0009	0.06	1.15	1.58
	Bootstrap									
Mean	8.43	5.55	10.50	0.43	2.09	1.03	0.0009	0.06	1.16	1.60
Median	8.17	5.55	8.62	0.42	2.08	1.04	0.0007	0.06	1.13	1.60
Bootstrap SE (BSE)	1.32	0.33	4.73	0.06	0.20	0.11	0.0007	0.02	0.20	0.24
%Relative BSE	15.69	5.93	45.09	12.99	9.54	10.46	77.12	29.82	17.03	15.19
Bootstrap 95% CI by BSE										
Lower limit	5.85	4.90	1.27	0.32	1.70	0.82	-0.0004	0.03	0.77	1.12
Upper limit	11.00	6.19	19.72	0.54	2.48	1.24	0.0021	0.09	1.54	2.07

θ_1 : typical value of CL(L/hr)

θ_2 : typical value of V1 (volume of distribution of the central compartment (L))

θ_3 : typical value of V2 (volume of the first peripheral compartment (L))

θ_4 : typical value of Q2 [intercompartmental clearance between the central compartment (i.e., compartment 1) and the first peripheral compartment (i.e., compartment 2) (L/hr)]

θ_5 : typical value of V3 [volume of distribution of the second compartment (i.e., compartment 3) (L)]

θ_6 : typical value of Q3 [intercompartmental clearance between the central compartment (i.e., compartment 1) and the second peripheral compartment (i.e., compartment 3) (L/hr)]

θ_7 : scaling parameter for epsilon, σ^2

θ_8 , θ_9 , and θ_{10} are regression coefficient for the effects of weight, Studies FJ-228-0001 (coded 2 in the NONMEM dataset\data-a23.xpt) and NCI 1312 (coded 1 in the NONMEM dataset\data-a23.xpt).

125 bootstrap NONMEM runs were used to obtain the bootstrap estimates. (Source: Appendix I-4 (NONMEM output file) and Appendix B-3 (PSN output table))

Source: AN10022-pop-pk-report, Table 10, Page 65

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Table 4: Summary of NONMEM/Bootstrap Random Effects Population Pharmacokinetics Parameter Estimates with Uncertainty for the Integrated Analysis of

Statistic	Parameter											
	ω_{CL}	ω_{V1}	ω_{V2}	ω_{Q2}	κ_1	κ_2	κ_3	σ_1^2	σ_2^2	σ_3^2	σ_4^2	σ_5^2
	NONMEM											
	0.12	0.22	0.00002	0.20	0.01	0.01	0.01	0.14	0.00008	0.02	4400	1990
	Bootstrap											
Mean	0.11	0.22	0.05	0.23	0.01	0.01	0.01	0.19	0.00004	0.02	4257.77	1994.67
Median	0.11	0.22	0.00002	0.22	0.01	0.01	0.01	0.18	0.00005	0.02	4240.00	1920.00
Bootstrap SE (BSE)	0.02	0.07	0.08	0.08	0.01	0.01	0.01	0.15	0.00003	0.01	1416.06	693.22
%Relative BSE	15.16	31.83	167.87	36.54	51.81	51.81	51.81	75.20	85.28	32.46	33.26	34.75
Bootstrap 95% CI by BSE												
Lower limit	0.08	0.08	-0.10	0.06	0.00	0.00	0.00	-0.09	0.00	0.01	1482.29	635.95
Upper limit	0.15	0.36	0.20	0.39	0.02	0.02	0.02	0.48	0.00	0.03	7033.26	3353.39

ω_{CL} : variance of the intersubject variability in CL

ω_{V1} : variance of the intersubject variability in V1

ω_{V2} : variance of the intersubject variability in V2

ω_{Q2} : variance of the intersubject variability in Q2

κ_1, κ_2 interoccasion variability for occasions 1, 2, 3 representing cycle 1, 2, and cycles ≥ 3

* σ_2^2 was infinitely small, and either removing it or leaving it in the NONMEM model did not alter the objective function.

σ_1^2 and σ_3^2 : residual error variances for Study NCI 1512

σ_2^2 and σ_4^2 : residual error variances for Study FJ-228-0001

σ_5^2 : residual error variances for Study GPI-06-0005

125 bootstrap NONMEM runs were used to obtain the bootstrap estimates.

Source: Appendix I-4 (NONMEM output file) and Appendix B-3 (PSN output table)

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Source: AN10022-pop-pk-report, Table 11, Page 67

Reviewer's comments:

- Sponsor's analysis followed a reasonable and thorough approach in describing the pharmacokinetics of romidepsin. Structural model was developed utilizing data from rich PK studies to establish that romidepsin was best described using a three compartment model. When reviewer ran both the base and final model supplied by the sponsor, NONMEM terminated due to rounding errors. Log transformation of the data along with modification in the ERROR model of the sponsor was performed before NONMEM runs for the base and final model were successful. The parameter estimates for fixed and random effects were similar to the sponsor's model. Reviewer removed the inter-individual variability for V2 from the model as it was negligible. Moreover, the conclusions drawn by the reviewer on lack of effect of age, gender, race and renal function are also in accordance with the sponsor.
- Randomization and percentile approach was utilized by the sponsor to conclude lack of effect of mild or moderate hepatic impairment on PK of romidepsin. It should be noted that there were only two subjects with moderate hepatic impairment in the dataset. Lack of effect of hepatic status (moderate to severe) on romidepsin PK is unlikely considering that romidepsin is primarily eliminated by liver. Therefore a dedicated hepatic impairment study will be requested as a post marketing requirement (See clinical pharmacology review by Dr. Lillian Zhang for details on effect of hepatic impairment on PK of romidepsin).

4 Reviewer's Analysis

4.1 Exposure-Response Analysis for Effectiveness

4.1.1 Objectives

Since both GPI-04-001 and NCI-1312 were single arm trials, it is important to explore the exposure-response relationship which could provide supportive evidence of effectiveness. The aim of the present analysis was to evaluate the exposure-response relationship for effectiveness with objective disease response and progression free survival (PFS) as the response variables for study NCI-1312.

4.1.2 Methods

The primary efficacy endpoint was the objective response rate (ORR), defined as the proportion of patients with confirmed ODR (confirmed response (CR) or partial response (PR)), as determined by the standardized investigator assessment based on a composite assessment of changes in skin involvement as determined by Investigators, lymph node and visceral / extranodal involvement, where applicable, and abnormal circulating T-cells, where applicable. Response rate was defined as the number of patients with CR or PR divided by the total number of evaluable patients. The Evaluable Patients (EP) analysis set was to include 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. Data from study GPI-04-0001 was not used in the analysis as it had sparse PK data from only 10 subjects. Rich PK was collected for most of the patients in the study NCI-1312 and the AUC obtained by non-compartmental analysis was used for exposure-response analysis. The exposure-response dataset comprised of 56 patients in the EP analysis set for whom both exposure and ODR information was available.

4.1.3 Datasets

The datasets utilized for the analysis are summarized below.

Study Number	Name	Link to EDR
NCI-1312	dataa11.xpt	\\cdsesub1\evsprod\NDA022393\0000\m5\datasets\an10022\analysis
NCI-1312	ainvrsp.xpt	\\cdsesub1\evsprod\NDA022393\0000\m5\datasets\nci-1312\analysis
NCI-1312	akeyvar.xpt	

4.1.4 Software

SAS 9.2 and S-PLUS were used for analysis.

4.1.5 Model

Logistic regression and CART analysis was performed to explore the exposure-ODR relationship. Kaplan-Meier analysis was performed to evaluate the time to disease progression (secondary endpoint) among subgroups identified based on CART analysis.

4.1.6 Results

Due to high variability in PK and few subjects, it was not possible to establish the continuous relationship between exposure and ODR using logistic regression. CART analysis revealed that response rate was twice (43%) within the group of patients with $AUC > 900 \text{ ng*hr/mL}$ when compared to patients with $AUC < 900 \text{ ng*hr/mL}$ (20%). The patients were divided into two groups based on this cutoff point of 900 ng*hr/mL . The odds ratio for subjects with $AUC < 900 \text{ ng h/mL}$ to produce response is 0.32 (95% CI: 0.08-1.3, $p=0.10$). Progression free survival was compared between these two groups using Kaplan-Meier analysis. It was seen that patients having $AUC < 900 \text{ ng*hr/mL}$ progressed faster when compared to patients with $AUC > 900 \text{ ng*hr/mL}$. Median PFS was similar between the two exposure groups as the separation does not happen until 250 days. The relationship between exposure and effectiveness based on both primary (ODR) and secondary endpoint (time to disease progression) supports the evidence of effectiveness of romidepsin (**Figure 1**). **Table 5** summarizes details of the survival (Kaplan-Meier) analysis.

Table 5. Statistics for time to disease progression analysis using $AUC > 900 \text{ ng*hr/mL}$ and $AUC < 900 \text{ ng*hr/mL}$ as two exposure strata's.

NCI-1312	AUC < 900	AUC > 900
Total	15	41
Event	9	20
Censored	6	21
% Censored	40	51
Strata Homogeneity Tests	2Log(LR) ($p=0.0183$) Log Rank ($p=0.16$)	

4.2 Exposure-Response Analysis for Safety

4.2.1 Objectives

The objective of this analysis was to explore if the proposed dose reductions from 14 mg/m² to 10 and 8 mg/m² are adequate to reduce toxicities. Toxicities here are referred to as blood/bone marrow disorders which comprise of thrombocytopenia, leucopenia (lymphopenia and neutropenia) and anemia. Sponsor recommends dose reduction to 10 and 8 mg/m² in patients who experience these adverse events. Exposure-safety was also assessed for constitutional symptoms (fatigue and asthenia) and infections.

4.2.2 Methods

There were few subjects in the specific categories of the blood/bone marrows disorders (Grade ≥ 3) i.e. thrombocytopenia, leucopenia or anemia (**Table 6**). Therefore, “blood/bone marrow disorders” which can be referred to as a composite safety end point was utilized for exposure-response analysis for safety. The exposure-safety dataset comprised of 64 patients from the NCI-1312 study for whom both exposure and safety information was available. Exposure-safety analysis for constitutional symptoms and infections was performed in a similar manner to hematological toxicities.

4.2.3 Datasets

The datasets utilized for the analysis are summarized below.

Study Number	Name	Link to EDR
NCI-1312	dataa11.xpt	\\cdsesub1\evsprod\NDA022393\0000\m5\datasets\an10022\analysis
NCI-1312	aaeder.xpt	\\cdsesub1\evsprod\NDA022393\0000\m5\datasets\nci-1312\analysis
GPI-04-0001	aae.xpt	\\cdsesub1\evsprod\NDA022393\0000\m5\datasets\gpi-04-0001\analysis

4.2.4 Software

SAS 9.2 and S-PLUS were used for analysis.

4.2.5 Model

Logistic regression was performed to explore the exposure-response relationship for safety for treatment emergent blood/bone marrow disorders (thrombocytopenia, leucopenia and anemia).

4.2.6 Results

Lack of exposure-response relationship for safety was indicated by a shallow mean logistic prediction (Figure 5). This may be attributed to high variability in AUC and fewer subjects. Table 6 shows the blood/bone marrow disorders (Grade ≥ 3) seen in trial NCI-1312 which was explored for exposure-safety analysis. Moreover, no exposure safety could be established for constitutional symptoms and infections.

Figure 5: Probability of patients experiencing blood disorders (hematologic adverse events)-AUC relationship for romidepsin. Solid black squares represent the observed percentage of patients experiencing blood disorders in each AUC quartile. The black bars represent the 95% confidence interval. The solid red line represents the mean logistic regression prediction. The shaded area represents the 95% confidence interval.

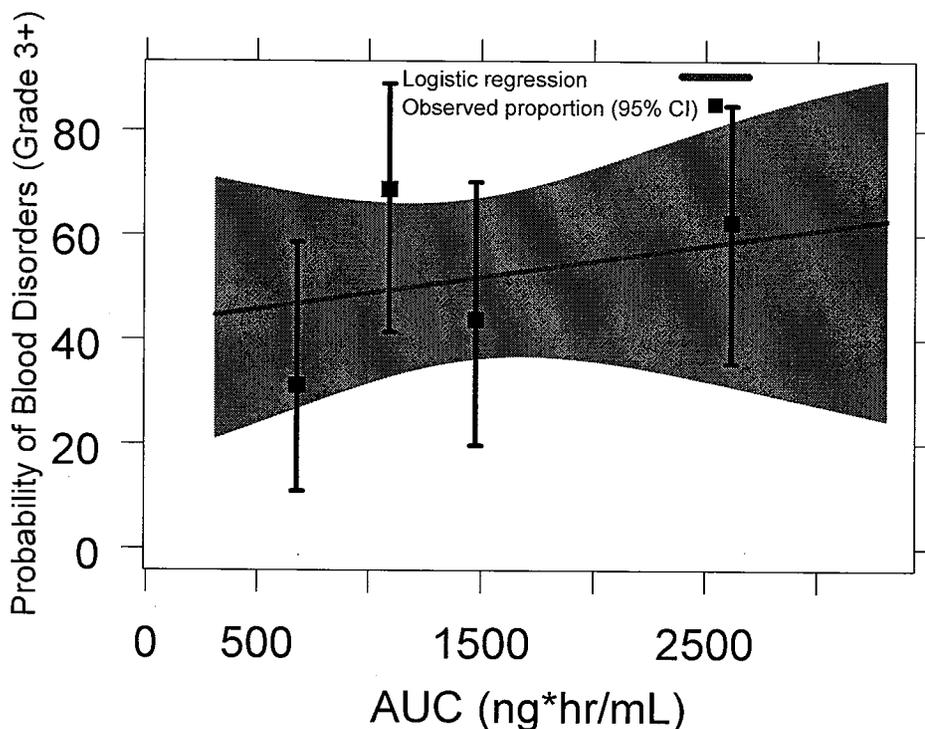


Table 6. Proportion of patients having hematological adverse events (Grade \geq 3).

AE (Grade \geq 3)	Total number of patients	Number of patients having adverse events (%)
Blood/Bone Marrow Disorders	64	33 (52)
Anemia	64	9 (14)
Thrombocytopenia	64	10 (16)
Neutropenia/Granulocytopenia	64	17 (27)
Lymphopenia	64	23 (36)
Leucopenia	64	16 (25)

Sponsor proposes dose modification scheme in patients who experience hematological toxicities in trial NCI-1312 (Table 7) and GPI-04-0001.

Table 7. Dose modification scheme utilized for trial NCI-1312

Dose Adjustment	ANC	Platelet Count
Hold Dose	$<0.5 \times 10^9/L$	$<50 \times 10^9/L$
Reduce Dose	$\geq 0.5 \times 10^9/L$, but $<1.0 \times 10^9/L$	≥ 50 , but $<75 \times 10^9/L$
Full Scheduled Dose	$\geq 1.0 \times 10^9/L$	$\geq 75 \times 10^9/L$

Source: NCI-1312-body, Table 9-4, Page 52

For, GPI-04-0001 the following modification scheme was followed:

“Hematologic toxicities

- Grade 3 or 4 neutropenia or thrombocytopenia: Subsequent doses of therapy were to be delayed until the specific cytopenia had returned to $ANC \geq 1.5 \times 10^9/L$ and/or platelet count $\geq 75 \times 10^9/L$; or Baseline.
- Grade 4 febrile ($\geq 38.5^\circ C$) neutropenia or thrombocytopenia that required platelet transfusion: Subsequent doses of therapy were to be delayed until the specific cytopenia returned to \leq Grade 1 or Baseline, and then the romidepsin dose was to be permanently reduced to 10 mg/m^2 .”

Source: GPI-04-001-body, Section 9.4.5.1, Page 49

The adverse event data from both the trials was explored to see how sponsor applied dose adjustment scheme in patients who had these adverse reactions. Doses were either delayed, reduced or stopped to reduce toxicities. Dose was not reduced in any of the subjects in GPI-04-0001 trial while it was reduced for only 2 patients in the NCI-1312 trial (**Table 8**). Sponsor delayed the doses for some subjects in these trials as a measure to reduce toxicities.

Table 8. Blood bone marrow disorders (Grade \geq 3) in GPI-04-0001 and NCI-1312 trial

	GPI-04-0001 (N=96)	NCI-1312 (N=71)
Patients with AE (%)	3 (2.8)	36 (50.7)
Dose Reduced (%)	0 (0)	2 (5.5)
Dose Delayed (%)	1 (33.3)	2 (5.5)
Dose Stopped (%)	1 (33.3)	0
Con Med (%)	1 (33.3)	-

The sponsor had experience with delaying the dose which eventually resulted in recovery for most of the patients. Therefore, if patient experiences hematological toxicities, consider delaying the dose of romidepsin since there is evidence of exposure-efficacy relationship and reducing the dose may cause loss in response. However, it is possible that lack of exposure-safety relationship could be due to low number of subjects and/or high variability in AUC. The sponsor had experience with dose reduction in NCI trial which did result in reduction in toxicities. Therefore, if delaying does not resolve toxicities and patient becomes intolerant to romidepsin therapy, dose should be reduced to 10 and further to 8 mg/m².

Appendix 4.3 QT review



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: July 1, 2009

From: QT Interdisciplinary Review Team and Division of Cardiovascular and Renal products

Through: Norman Stockbridge, M.D., Ph.D.
Division Director
Division of Cardiovascular and Renal Products /CDER

To: Lisa Skarupa
Regulatory Project Manager
Division of Drug Oncology Products

Subject: QT-IRT Consult to NDA 22-393

This memo responds to your consult to us dated April 10, 2009 regarding the QTc assessment of romidepsin submitted NDA 22-393, sponsored by Gloucester Pharmaceuticals, Inc. The QT-IRT received and reviewed the following materials:

- Your consult
- Romidepsin Cardiovascular Assessment Report
- QT-IRT review of QTc Clinical /Statistical Analysis Plan dated December 20, 2007
- Safety Report submitted by the sponsor dated June 11 2009 from GPI-06-0002

1 QT-IRT Comments to DDOP

1.1 QT effects

- There are several limitations to the ECG data collected in these studies which limit the interpretation of results. The limitations include:
 1. In study GPI-04-001, triplicate ECGs were collected at screening, at baseline, and within 2 hours after completion of administration of romidepsin. An ECG was not acquired at maximum plasma concentrations. ECGs were not collected at later time points to rule out any delayed drug effects on QT prolongation. Blood draws

for PK were not obtained; therefore, exposure-response analysis cannot be performed. There were no controls (positive or negative).

2. In study NCI 1312, single ECGs were collected at baseline, within 2 hours after completion of administration of romidepsin and at 24 and 48 hours post-dose.
 3. In study GPI-06-0005, triplicate ECGs and PK samples were collected prior to infusion and at 0.25, 0.5, 1, 2, 3, 4, 6, 8, and 24 hours post-infusion. There are only 7 patients with available data. The number of patients to be evaluated may be too low to obtain any meaningful results from the exposure-response analysis.
 4. Waveforms were not submitted to the ECG warehouse for review.
- The sponsor should perform a dedicated QT assessment in a sufficient number of patients, with triplicate ECGs and PK samples similar to GPI-06-0005 to adequately characterize the QT effect. The sample size for an ECG sub-study is mainly determined by: (1) the distance between the non-inferiority margin (20 ms for most of oncology products) and the true mean difference to be detected; (2) the variability of the study; (3) the number of time points; (4) the shape of the true mean difference to be detected over time; (5) type I error (0.05); (6) type II error and (7) correlation of the data. For example, assume that the data are independent with 4 time points and a constant mean effect of 5 ms (conservative assumptions) and type II error rate of 0.15 (=power 85%). With 24 subjects, the study can detect a difference of 5 ms between post-dose and baseline assuming SD = 15 ms and the non-inferiority margin of 20 ms (See table below). If the true mean difference is greater than 5 ms, more subjects are needed to maintain the same study power.

Table: Sample sizes for constant mean effect over time (4 time points, independent, $\alpha = 0.05$, $\beta = 0.15$)

	<i>Distance (non-inferiority margin, true mean difference to be detected)</i>		
σ	5 (20, 15)	10 (20, 10)	15 (20, 5)
9	75	19	9
11	112	28	13
13	157	40	18
15	208	52	24
17	267	67	30
19	334	84	38

1.2 Other Cardiac Effects

- Information from these uncontrolled clinical studies is limited and the information is confounded due to co-morbid illness and concomitant medications, but we cannot exclude myocardial toxicity due to romidepsin based on the following observations:
 - Sudden deaths have been observed in the clinical program

the drug.

Romidepsin, in initial Phase 1 dose-escalation studies was reported to prolong QTc, although the studies were not designed to rigorously assess this effect and the methodology used is not currently standard (i.e. usage of Bazett's rather than Frederica's correction method; performance of single rather than triplicate ECGs at designated time points). In 2001, based on results of Phase 1 clinical studies and in consultation with DODP, a cardiac monitoring plan was developed for romidepsin clinical studies. The extent of cardiac monitoring was subsequently reduced following discussions with DODP and review of additional nonclinical cardiac safety data and clinical findings (FDA Briefing Document SN 013, 26 January 2004, and FDA Meeting Minutes, 24 February 2004).

To address the recommendations in ICH E14, the sponsor developed a Romidepsin QTc Clinical/Statistical Analysis Plan. The QTc SAP was submitted to the Food and Drug Administration (FDA) for review (SN 096 1 November 2007). The QT-IRT reviewed the QTc SAP and provided DDOP with comments on December 20, 2007.

2.1 Nonclinical Experience

Source: Pharmacology Written Summary eCTD 2.6.2 and Cardiovascular Assessment report GLR030533: Safety Pharmacology Study of FR901228-hERG Assay

“The suppressive rate of the vehicle control (extracellular superfusion solution) on the hERG channel current was 8.3% 10 minutes after application. The value for romidepsin at 0.3 µg/ml was 7.9%, which was not significantly different from the vehicle control. Romidepsin at 1 and 10 µg/ml resulted in suppressive rates of 18% and 37.3% of the hERG current at 10 minutes, respectively. The differences in suppression relative to vehicle control were statistically significant ($P < 0.001$). The positive control, E-4031 at 0.10 µmol/L, suppressed the hERG channel by 82.5% 10 minutes after application. Romidepsin showed mild suppression of the hERG channel current at high concentrations (1 and 10 µg/ml), with maximal suppression of the hERG channel current calculated to be 37%. Clinically relevant concentrations of romidepsin concentrations (i.e. C_{max} of 377 ng/ml following administration of 14 mg/m² over a four hour infusion) have been shown to be approximately 20- fold less than the highest concentration, 10 µg/ml, used in the present study. Based on this data and the degree of protein binding noted with romidepsin, the drug is unlikely to have a biologically relevant effect on the hERG channel at concentrations used in the clinic.

“Romidepsin (0.3 and 1 µg/ml) showed no effects on APD₉₀, RP, APA, or dV/dt. At a concentration of 10 µg/ml, romidepsin significantly shortened APD₉₀ and significantly decreased APA, but had no significant effects on RP or dV/dt. The positive control, sotalol, prolonged APD₉₀ and showed significant differences in dV/dt when compared with the vehicle group, but had no significant effects on RP or APA.

“In summary, no cardiac lesions were noted in studies conducted in rat or the dog and no effects on blood pressure or ECGs were noted in repeat-dose studies in the dog. In a cardiovascular assessment of romidepsin in the dog, mild increases in heart rate were observed at all doses studied, and sporadic effects on QTc were observed at the highest dose tested; 1.0 mg/kg (20 mg/m²).”

Reviewer's Comments: Although no cardiac lesion were reported in the chronic repeat dose toxicity studies in the rat or the dog, romidepsin was cytotoxic to neonatal rat, dog, and human cardiac myocytes in Study SRI-CBE-93-362-8000-XLI.

2.2 Clinical Experience

Source: ISS-October 20, 2008

“A total of 783 patients have received romidepsin in 34 studies, 7 conducted under IND 63,573 by Gloucester and 27 conducted under IND 51,810 by the NCI. A total of 167 patients with CTCL have been treated in 2 phase 2 clinical studies, a pivotal study, Study GPI-04-0001, sponsored by Gloucester and a supportive study, NCI Study 1312, sponsored by the NCI.

“There were 12 deaths from adverse events among the 167 CTCL patients in Study GPI-04-0001 and NCI Study 1312. Three were considered possibly related to therapy: one due to cardiopulmonary failure, one due to infection and one sudden death (reported by the Investigator as cardiac ischemia-infarction; MedDRA preferred term myocardial ischemia).

“For the remaining 9 patients, the cause of death was considered unrelated to study drug; the cause of death among these 9 patients included progression of disease (4 patients), infection (3 patients), dyspnea (1 patient), and acute renal failure (1 patient).

“In addition to the patient who had a primary diagnosis of CTCL in NCI Study 1312 (Patient No. 900-00-4757), 6 unexpected deaths have occurred in the romidepsin clinical program involving >700 patients generally with advanced cancer. Overall, the unexpected death occurred within 1 day after the last study drug dose for 3 patients, 2 or 3 days after the last dose of study drug for 2 patients, and more than 1 week after the last dose of study drug for the remaining 2 patients. Of the 6 patients, 1 had PTCL and the remaining 5 had solid tumors (breast, renal, esophageal, neuroendocrine, and prostate + thyroid cancers). In 5 of these cases, significant cardiovascular risk factors were either present at the time of entry into the romidepsin study or developed during the course of the study. The sixth patient had a history of sarcoidosis and was simultaneously co-administered an antiemetic that has a 40-hour half life and is known to prolong the QTc interval. The role of romidepsin, if any, in these deaths is unknown. An independent medical panel was convened in July 2005 to discuss all study deaths that occurred by that time. (Five of these 6 cases had occurred.) As a consequence of these events, the cardiovascular inclusion/exclusion criteria were modified to exclude patients who had a history of significant cardiac disease.”

Summary of AE from Safety Report dated June 11 2009 from GPI-06-0002

A 58 yr old female with no pre-existing heart disease started the study drug at 14mg/m² for 3 months and at reduced dose of 15.1 mg for 4 months on days 1, 8 and 15 of a 28 day cycle for Peripheral T Cell Lymphoma (PTCL). One-half years after the first dose of the study drug and one year after the last dose of the study drug the patient was reportedly diagnosed with cardiac failure. A cardiac MRI reported a left ventricular ejection fraction of 35% (55-60% earlier). The differential diagnosis included CMV-myocarditis and graft-versus-host reaction. Myocardial

biopsy is pending. The investigator's causality assessment for the events was possibly related to the study drug.

Reviewer's Comment: Narratives for the 6 deaths in the advanced cancers program were reviewed. Association with romidepsin is unclear due to confounding by comorbidities including advanced malignancies, cardiac co-morbidities and concomitant medications. The patient with sarcoidosis and metastatic thyroid cancer received palonosetron which does not prolong the QT interval. QTc readings one week before death were normal. The medical panel report was not available for review.

2.3 Clinical Pharmacology Experiences

Source: Package Insert

Romidepsin exhibited dose proportional and linear pharmacokinetics across doses ranging from 1.0 to 24.9 mg/m² infused for 4 hours in a Phase 1 study in patients with advanced cancers.

The pharmacokinetics of romidepsin were also evaluated in a Phase 2 study of 94 patients with T-cell lymphomas who received 14 mg/m² of romidepsin infused for 4 hours on days 1, 8, and 15 every 28 days. Based on noncompartmental pharmacokinetic methodology, the mean maximum plasma concentration (C_{max}) of romidepsin was 377 ng/ml (95% CI: 337, 421), the mean area under the plasma concentration versus time curve (AUC_{inf}) was 1549 ng*hr/ml (n=59; 95% CI: 1349, 1777), and the terminal elimination half life (t_{1/2}) was estimated to be 2.92 hours (n=59; 95% CI: 2.54, 3.36).

Elimination in humans has not fully been characterized; however, in a population pharmacokinetics analysis of romidepsin pharmacokinetic data, CL was not affected by mild to severe renal impairment or mild to moderate hepatic impairment.

3 Sponsor's QTc Analysis

3.1 Overview

Sponsor's QTc analyses are based on data from 3 clinical studies of romidepsin:

- Study GPI-04-0001 in patients with CTCL
- Study 1312 in patients with CTCL, PTCL, or other T-cell lymphomas
- Study GPI-06-0005 in patients with advanced solid tumors or hematologic malignancies

3.2 Objectives

Primary objective was to evaluate the effect of romidepsin on the change from baseline in the corrected QT interval of the electrocardiogram using the Fridericia QT correction method (QTcF) during Cycle 1 Day 1 (C1D1) exposure to study drug

Secondary objectives included the evaluation of:

- the change from baseline in selected electrocardiogram (ECG) parameters following romidepsin treatment including QTcF changes from baseline from subsequent study drug administrations (e.g., C1D8, C1D15, C2D1), Bazett corrected QT intervals (QTcB), heart

rate, PR and QRS intervals, and morphological ECG patterns

- the correlation between QTcF interval change from baseline and plasma concentrations of romidepsin
- the effect of romidepsin on left ventricular ejection fraction
- the effect of romidepsin on myocardial perfusion as measured by serum troponin I
- cardiac specific adverse events and serious adverse events

3.3 Study Designs

Study GPI 04 0001 is a Phase 2, open label, single arm international study designed to determine the efficacy and to assess the safety of romidepsin in the treatment of patients with confirmed CTCL who had received at least 1 prior systemic therapy. The pivotal study, which is closed to accrual, was conducted at 33 sites in Europe and the United States (US). As of July 2007, a total of 96 patients were enrolled in this study. Patients received romidepsin 14 mg/m² intravenously (IV) over 4 hours on Days 1, 8, and 15 of each 28 day cycle. Six cycles of treatment were planned; responding patients and patients who achieved at least stable disease had the option of continuing treatment beyond 6 cycles at the discretion of the Investigator until progressive disease was documented or until toxicity or another withdrawal criterion was met.

NCI Study 1312 is a Phase 2, multi-center, open-label, non-randomized study designed to evaluate the activity and tolerability of romidepsin in patients with CTCL or PTCL. Patients with CTCL were enrolled in 3 arms of this study, based on the number of prior therapies they had received and the time of enrollment. Patients were enrolled at 10 study centers in the US and Australia. As of 31 March 2007, a total of 71 patients with CTCL were treated in this study which is closed to accrual. Patients eligible for the study, based on screening assessments, were enrolled in the study and started treatment with romidepsin at Baseline (C1D1). Initially, patients received romidepsin administered as an IV infusion over 4 hours at a starting dose of 18 mg/m² on Days 1 and 5 every 21 days. (The first 3 patients with CTCL enrolled in the study received romidepsin according to this dose schedule.) Based on findings in the current study as well as in another Phase 1 study, the dose regimen was changed by Amendment-2 to 14 mg/m² on Days 1, 8, and 15 every 28 days.

GPI-06-0005 is an ongoing, open-label, single-arm, exploratory Phase 1 bioavailability study that is being conducted at a single study center in the US in patients with histologically-confirmed advanced malignancies. The study is designed to determine the oral bioavailability of romidepsin as well as the safety and tolerability of both IV and oral romidepsin; intensive PK sampling and ECG monitoring are occurring in the study. Romidepsin administrations are via the IV route at 14 mg/m² on Days 1, 8, and 15 of each 28-day cycle, except C2D1 when patients receive a single oral dose of romidepsin. Patients continue to receive IV administration of romidepsin for a total of 6 cycles or until disease progression occurs. Patients with at least stable disease could continue treatment beyond 6 cycles.

3.4 ECG and PK Data

ECG and pharmacokinetic data assessments are summarized in Table 1 through Table 3.

Table 1: Summary of ECG and PK Assessments

Parameter	Clinical Study		
	Study GPI-04-0001	NCI Study 1312	Study GPI-06-0005
ECGs	X	X	X
Troponin		X	
LVEF		X	
Pharmacokinetics		X	X
Adverse events	X	X	X
Serious adverse events	X	X	X

Source: Table 4-1 from CV Assessment Report

Table 2: ECG Data Description

Study	No. of patients	No. of ECGs	Single / Triplicate	PK Correlation
GPI-04-0001	87	4249	Triplicate	No
NCI 1312	41	440	Single	Yes
GPI-06-0005	7	220	Triplicate	Yes

Source: Table 4-2 from CV Assessment Report

Table 3: Pharmacokinetic Sample Collection

Parameter	Study	
	Study NCI-1312	Study GPI-06-0005
Doses	14 mg/m ³ as 4 hour IV infusion (2 patients received 18 mg/m ³)	14 mg/m ³ as 4 hour IV infusion
PK sampling	Predose, end of the infusion, and 2, 7, 9, 11, 14, and 18 hours after completion of the infusion	0, 0.25, 0.5, 1, 2, 3, 4, 6, 8, and 24 hours after initiation of IV infusion
ECG collection	Before and after romidepsin infusion. An ECG was collected for some patients on Days 2 and 3 following the first dose	0.25, 0.5, 1, 2, 3, 4, 6, 8, and 24 hours after initiation of infusion
Patients	39	7
ECGs	144	199

Source: Table 4-3 from CV Assessment Report

3.5 Sponsor's Results

3.5.1 Study Subjects

A total of 216 patients, 96 patients in Study GPI-04-0001, 110 patients in NCI Study 1312, and 10 patients in Study GPI-06-0005, received at least 1 dose of study drug.

Approximately two-thirds (135 of 216 patients; 63%) of these patients, representing 91% (87 of 96 patients) of patients in Study GPI-04-0001, 37% (41 of 110 patients) of patients in NCI Study 1312, and 70% (7 of 10 patients) of patients in Study GPI-06-0005 are included in the ECG

evaluable population. Among all 135 patients in the ECG evaluable population, the majority was male (84 patients; 62%) and white (117 patients; 87%). The mean age of patients was 57 years, with a range of 27 to 89 years. The mean height and weight were 170 cm and 79 kg, respectively. Among the 135 patients in the ECG evaluable population, all had a malignant disease, either CTCL (113 patients), PTCL or another T-cell lymphoma (15 patients), or, less commonly, non-Hodgkin's lymphoma (NHL) or solid tumors (7 patients).

Cardiac exclusion criteria:

- Patients with known cardiac abnormalities such as:
 - Congenital long QT syndrome.
 - Corrected QT interval >480 milliseconds.
 - Any cardiac arrhythmia requiring anti-arrhythmic medication.
- Patients who had a myocardial infarction within 12 months prior to study entry.
- Patients with a history of coronary artery disease (CAD), e.g., angina Canadian class II to IV. In any patient in whom there was doubt, the patient was to have had a stress imaging study and exercise ECG and, if abnormal, angiography to define whether or not CAD was present.
- Patients with an ECG recorded at screening showing evidence of cardiac ischemia (ST depression of ≥ 2 mm). If in any doubt, the patient was to have had a stress imaging study and exercise ECG and, if abnormal, angiography to define whether or not CAD was present.
- Patients with congestive heart failure that met New York Heart Association class II to IV definitions and/or ejection fraction <40% by multiple gated acquisition scan or <50% by echocardiogram and/or magnetic resonance imaging (MRI).
- Patients with a history of sustained ventricular tachycardia (VT), ventricular fibrillation, Torsade de Pointes, or cardiac arrest, unless currently addressed with an automatic implantable cardioverter defibrillator.
- Patients with hypertrophic cardiomegaly or restrictive cardiomyopathy from prior treatment or other causes.
- Patients with uncontrolled hypertension, i.e., $\geq 160/95$ mmHg.
- Patients with Mobitz II second degree heart block and who did not have a pacemaker. (Patient with first degree or Mobitz I second-degree heart block, bradyarrhythmias, or sick sinus syndrome required Holter monitoring and a cardiology evaluation.)
- Patients with other cardiac disease could be excluded at the discretion of the Principal Investigator following consultation with cardiology.

Reviewer's Comments: Stress imaging, exercise ECG with cardiac catheterization (if required to confirm the diagnosis) was done to exclude patients with CAD.

3.5.2 Statistical Analyses

Because all patients in the ECG evaluable population had a malignant disease (CTCL in the majority of patients), they commonly received concomitant medications for the management of disease-related complications. Specifically, these patients were frequently exposed to anti-emetic treatment (e.g., dolasetron, granisetron, and ondansetron), which has been associated with a mild degree of QT prolongation. Consequently, QTc analyses were performed comparing changes in the QTc from pre-comedication baseline (i.e. pre-comed) to post-romidepsin infusion (i.e. post-infusion) and also from post-comedication baseline (i.e. post-comed) to post-infusion. In this way, any QTc prolongation attributable to anti-emetic comedication given prior to the romidepsin infusion could be detected.

3.5.2.1 Primary Analysis

The primary analysis for the QT/QTc data was the change from baseline to each subsequent time point (single delta approach). A 2-sided, 90% CI for the mean difference in the baseline-corrected QT, QTcF and QTcB was displayed at each time point, based on a paired t-test of the changes from baseline. The 90% CI for QTcF was considered the primary efficacy measure. The upper limit of the 90% CI was compared to the 20-ms bound for the active treatments. If the upper limit of the 90% CI fell below 20 ms, it was to be concluded that the romidepsin dose did not prolong the mean QTc interval to a clinically significant degree.

Among the 110 patients with pose-dose ECGs, the mean change from baseline (post-comed) to 2 hours post-infusion in QTcF was 2.7 ± 16.1 ms, with a 90% CI upper bound of 5.3 ms. A summary of change from baseline (post-comed) to 2 hours post-infusion in ECG interval data is presented in Table 4, overall and by study.

Table 4: Change from Baseline (Post-Comed) to Post-Infusion QTcF

QTcF / Time point	Statistic	GPI-04-0001 ²		NCI 1312 ³		GPI-06-0005 ²		Total	
		Result	Change from Baseline	Result	Change from Baseline	Result	Change from Baseline	Result	Change from Baseline
Baseline	N	76	-	41	-	7	-	124	-
	Mean	415.1	-	394.8	-	385.1	-	406.7	-
	SD	18.09	-	21.87	-	24.03	-	22.39	-
	90% CI	411.7, 418.6	-	389.0, 400.5	-	367.4, 402.7	-	403.4, 410.0	-
Post-Dose	N	80	72	31	31	7	7	118	110
	Mean	415.3	1.3	399.8	4.5	394.1	9.1	410.0	2.7
	SD	17.77	14.94	22.74	17.21	20.06	22.31	20.69	16.10
	90% CI	412.0, 418.6	-1.6, 4.2	392.9, 406.8	-0.7, 9.8	379.4, 408.9	-7.3, 25.5	406.8, 413.1	0.2, 5.3

1 For GPI studies, Baseline values are those post- comedication (labeled as Pre-Romidepsin).

2 For GPI studies, post-romidepsin ECGs occurred at 2 hours after completion of romidepsin administration.

3 For NCI Study 1312, post-dose ECGs were stipulated per protocol to occur approximately 1 hour post dose.

Source: Section 16.1, Table 11.2.1.1B.

Source: Table 7-2 from CV Assessment Report

Mean change from baseline in QTcF for each post-dose time point is summarized in Table 5 through Table 7.

Table 5: Mean Change from Baseline (Post-Comed) in QTcF for Study GPI-04-0001

ECG (QTcF) Time point	Statistic	GPI-04-0001	
		Result	Change from Baseline
Baseline	N	76	
	Mean (\pm SD)	415.1 (18.09)	
	90% CI	411.7, 418.6	
C1D8 Pre-dose	N	71	62
	Mean (\pm SD)	411.8 (19.58)	-3.9 (18.94)
	90% CI	407.9, 415.7	-7.9, 0.1
C1D15 Pre-dose	N	65	57
	Mean (\pm SD)	410.5 (20.76)	-5.3 (18.35)
	90% CI	406.2, 414.7	-9.4, -1.3
C2D1 Pre-dose	N	68	61
	Mean (\pm SD)	408.7 (18.88)	-6.8 (16.30)
	90% CI	404.9, 412.5	-10.3, -3.3
C2D8 Pre-dose	N	64	57
	Mean (\pm SD)	410.3 (20.78)	-5.3 (17.48)
	90% CI	406.0, 414.7	-9.2, -1.4
C2D15 Pre-dose	N	64	57
	Mean (\pm SD)	406.0 (18.10)	-10.9 (18.23)
	90% CI	402.3, 409.8	-14.9, -6.8

C=Cycle; D=Day.

Source: Section 16.1, Table 11.2.1.2B.

Source: Table 7-3 from CV Assessment Report

Table 6: Mean Change from Baseline in QTcF for Study NCI 1312

ECG (QTcF) Time point	Statistic	NCI 1312	
		Result	Change from Baseline
Baseline	N	41	
	Mean (\pm SD)	394.8 (21.87)	
	90% CI	389.0, 400.5	
C1D1 Post-dose	N	31	31
	Mean (\pm SD)	399.8 (22.74)	4.5 (17.21)
	90% CI	392.9, 406.8	-0.7, 9.8
C1D1 24 Hours Post	N	39	39
	Mean (\pm SD)	398.3 (24.29)	4.6 (18.09)
	90% CI	391.8, 404.9	-0.3, 9.5
C1D1 48 Hours Post	N	29	29
	Mean (\pm SD)	387.1 (13.68)	-7.1 (19.77)
	90% CI	382.8, 391.4	-13.3, -0.8

C=Cycle; D=Day.

Source: Section 16.1, Table 11.2.1.2C.

Source: Table 7-6 from CV Assessment Report

Table 7: Mean Change from Baseline in QTcF for Study GPI-06-005

ECG (QTcF) Time point	Statistic	GPI-06-005	
		Result	Change from Baseline
Baseline	N	7	
	Mean (\pm SD)	385.1 (24.03)	
	90% CI	367.4, 402.7	
0.25 hours	N	6	6
	Mean (\pm SD)	385.2 (14.44)	2.6 (15.60)
	90% CI	373.3, 397.1	-10.2, 15.4
0.5 hours	N	7	7
	Mean (\pm SD)	384.7 (15.66)	-0.4 (19.18)
	90% CI	373.2, 396.2	-14.5, 13.7
1 hour	N	7	7
	Mean (\pm SD)	384.5 (15.24)	-0.6 (13.58)
	90% CI	373.3, 395.7	-10.6, 9.4
C1D1, 2 hours	N	7	7
	Mean (\pm SD)	382.5 (11.41)	-2.6 (19.25)
	90% CI	374.1, 390.8	-16.7, 11.5
C1D1, 3 hours	N	7	7
	Mean (\pm SD)	383.1 (10.11)	-2.0 (22.59)
	90% CI	375.6, 390.5	-18.6, 14.6
C1D1, 4 hours	N	6	6
	Mean (\pm SD)	385.8 (15.30)	0.0 (22.11)
	90% CI	373.3, 398.4	-18.1, 18.2
C1D1, 6 hours	N	7	7
	Mean (\pm SD)	394.1 (20.06)	9.1 (22.31)
	90% CI	379.4, 408.9	-7.3, 25.5
C1D1, 8 hours	N	7	7
	Mean (\pm SD)	388.5 (18.60)	3.4 (20.02)
	90% CI	374.8, 402.1	-11.3, 18.1
C1D1, 24 hours	N	6	6
	Mean (\pm SD)	382.2 (27.98)	-9.8 (26.29)
	90% CI	359.2, 405.2	-31.4, 11.9

C=Cycle; D=Day.

Source: Section 16.1, Table 11.2.1.2E.

Source: Table 7-7 from CV Assessment Report

3.5.2.2 Categorical Analysis

Categorical analyses were performed on C1D1 ECGs for studies GPI-04-0001, NCI-1312, and GPI-06-0005 as shown in Table

Table 8: Categorical Analysis of QTcF

Category	Study			Total N=135 n (%)
	Study GPI-04- 0001 N=87 n (%)	Study NCI 1312 N=41 n (%)	Study GPI-06- 0005 N=7 n (%)	
QTcF change from baseline¹				
No increase	31 (36)	10 (24)	2 (29)	43 (32)
1-29 msec increase	46 (53)	27 (66)	4 (57)	77 (57)
30-60 msec increase	2 (2)	4 (10)	1 (14)	7 (5)
>60 msec increase	0	0	0	0
QTcF not available	8 (9)	0	0	8 (6)
QTcF absolute value:				
>450 msec	2 (2)	2 (5)	0	4 (3)
>480 msec	0	0	0	0
>500 msec	0	0	0	0

Source: Section 16.1, Table 11.2.1.3a.

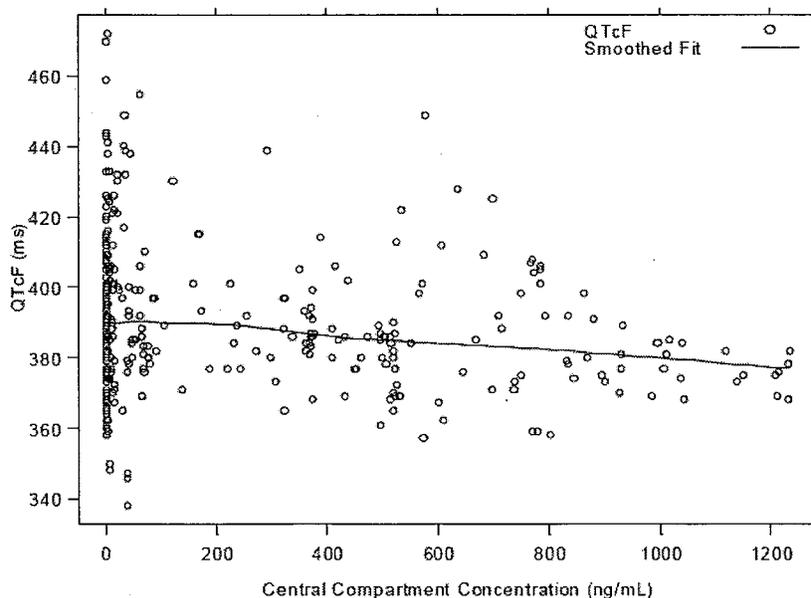
¹ For GPI studies, baseline values are those post-comedication, or if missing post-comedication, then pre-comedication baseline is used.

Source: Table 7-8 from CV Assessment Report

3.5.2.3 PKPD Analysis

Nonlinear mixed effects modeling was used to estimate the parameters of linear, power, E_{max}, and Simoidal E_{max} models to evaluate the effect of romidepsin concentration on the HR-corrected QT interval using Fridericia's correction and an individually-derived correction (Study GPI-06-0005 only). There was no evidence of a romidepsin concentration-QTcF relationship as shown in Figure 1 and Table 9.

Figure 1: QTcF vs. Romidepsin Plasma Concentration: Integrated Dataset



Source: Figure 8-1 from CV Assessment Report

Table 9: Summary of Results from Three C-QTcF Models

Model	Parameter					95% CI		
	Δ OFV	Conc.	Parameter	Units	Estimate	SE	Lower	Upper
Linear ¹	-20.988	Central	Slope	ms/ng/mL	-0.00249	0.00630	-0.0148	0.00986
E _{max} ²	-68.414	Central	E _{max}	ms	0.384	7.34	-14.0	14.8
E _{max} ³	-41.658	Periph. 2	E _{max}	ms	0.279	16.9	-32.8	33.4

Source: Anoxis Technical Report AN10019.

¹Model 001.1, ²Model 003.2, ³Model 023.2.

Conc.=romidepsin concentration in the indicated PK compartment, SE= asymptotic standard error

Source: Table 8-1 from CV Assessment Report

Reviewer's Comments: Time-matched PK and ECG samples were not obtained; therefore, the sponsor used a population PK-PD approach to evaluate the potential for QTc prolongation. This analysis is being reviewed by Dr. Nitin Mehrotra in the Division of Pharmacometrics, OCP.

3.5.3 Safety Analysis

3.5.3.1 Heart rate and ECG changes

For all studies, the sponsor reports that there was an increase in HR (with corresponding decrease in the RR interval) at the post-dose time point when compared to baseline which was consistent across studies. In the pooled analysis, the mean change in HR from baseline was 10.1 ± 9.0 bpm. The most common treatment-emergent T-wave abnormalities were T-wave flattening (11%), bi-phasic T-waves (11%), and T-wave inversion (8%) as shown in Table 10. The sponsor submitted shift tables for each of these groups to show that the treatment-emergent T-wave changes occurred in nearly the same frequency as the pre-dose T-wave abnormalities.

Treatment-emergent minor ST-segment depression was the most frequent abnormality identified in NCI Study 1312 (39%) and Study GPI-06-0005 (57%) as shown in Table 10; this abnormality was not analyzed for Study GPI-04-0001. The sponsor again submitted shift tables for each of these groups to show that the treatment-emergent T-wave changes occurred in nearly the same frequency as the pre-dose T-wave abnormalities.

Table 10: Treatment-emergent ECG Abnormalities on C1D1, Overall and by Study (ECG Evaluable Population)

Abnormality	Study			Total N=135 n (%)
	Study GPI- 04-0001 N=87 n (%)	NCI Study 1312 N=41 n (%)	Study GPI- 06-0005 N=7 n (%)	
Rhythm				
Sinus Tachycardia (>100 bpm)	5 (6)	7 (17)	2 (29)	14 (10)
Sinus Bradycardia (<50 bpm)	0	2 (5)	0	2 (2)
Sinus Arrhythmia	1 (1)	0	0	1 (1)
Ventricular Premature Complexes	0	1 (2)	1 (29)	3 (2)
Ectopic Atrial Rhythm	0	1 (2)	0	1 (1)
Atrial Premature Complexes	3 (3)	1 (2)	4 (57)	8 (6)
Conduction				
1st Degree AV Block	1 (1)	1 (2)	1 (14)	3 (2)
Intraventricular Conduction Delay, Nonspecific	3 (3)	0	0	3 (2)
Hypertrophy				
LVH w/ Secondary ST-T Abnormalities	1 (1)	1 (2)	0	2 (2)
Left Atrial Abnormality	2 (2)	3 (7)	1 (14)	6 (4)
T-Wave				
T-U Fusion	1 (1)	0	0	1 (1)
T-Wave Inversion	0	10 (24)	1 (14)	11 (8)
T-Wave Flattening	11 (13)	4 (10)	0	15 (11)
Biphasic T-Wave	4 (5)	9 (22)	2 (29)	15 (11)
U-Wave				
Prominent U-Waves	1 (1)	0	0	1 (1)
ST-Segment				
Major ST Depression	ND	1 (2)	0	1 (1)
Minor ST Depression	ND	16 (39)	4 (57)	20 (15)
Minor ST Elevation	ND	2 (5)	1 (14)	3 (2)

Source: Section 16.1 Table 11.2.1.5.

ND = Not done. Specific criteria were used in the ECG analysis of NCI 1312 and GPI-06-0005 to identify ST-segment changes; these criteria could not be applied to Study GPI-04-0001.

Source: Table 7-9 from CV Assessment Report

Reviewers Comments: Treatment emergent ST-T wave changes are clearly evident based on review of table 7-9. ST depression was not assessed in GPI-04-0001. The sponsors shift tables (Tables 7-10- 7-13 in the CV assessment report) are hard to interpret. Moreover, all these studies lacked a placebo or active control group.

The sponsor reports no clinically relevant effects on the PR and QRS intervals.

3.5.3.2 Cardiac AEs

Two patients experienced a CTCAE Grade 5 cardiac disorder, which were reported as study drug-related (cardiopulmonary failure in Patient No. 92097 [Study GPI-04-0001] and myocardial ischemia in Patient No. 900-00-4757 [NCI Study 1312]).

Study GPI-04-0001

Six (6%) patients discontinued study drug because of a cardiac/ECG event. Three patients (Patient No. 38033, Patient No. 48040, Patient No. 94082) discontinued due to prolongation of electrocardiogram QT/QTc interval (all < 500 ms), Patient No. 34013 discontinued due to angina

pectoris, Patient No. 23081 discontinued due to bradyarrhythmia and Patient No. 47036 discontinued due to atrioventricular block first degree, atrioventricular block second degree, cardiac failure congestive, cardiac tamponade, and ventricular tachycardia (see below).

No patient who had an ECG abnormality reported as an adverse event also experienced syncope during the study. Overall, 3 patients experienced syncope during the study. Syncope was assessed as Grade 1 or 2 in intensity for all 3 patients. All 3 patients recovered from this event and continued study treatment unchanged without a recurrence of this event.

Patient No. 92097, a 21-year-old Caucasian male with Stage IIB disease at screening developed pyrexia, hypotension, hepatomegaly, hyperbilirubinemia, left lobar pneumonia and pleuritis post-treatment. The patient was admitted to the ICU with signs of acute cardiovascular insufficiency and died due to cardiopulmonary insufficiency 10 days after his last study drug dose. The patient had received 3 complete cycles of romidepsin. Upon independent review of this case, carried out by another senior investigator at the request of his IRB, it appears more likely that the patient died of progressive disease with cardiopulmonary insufficiency as the terminal event.

Patient No. 47036 was a 52-year-old Caucasian female with Stage IIB disease at screening with cardiovascular history significant for hypertension and an anterior myocardial infarction. The patient died ~2 months post-study likely from pulmonary embolism which was associated with right ventricular failure in the setting of a mediastinal mass. This patient presented to the emergency room with shortness of breath 6 days after her initial dose of romidepsin (C1D8). A diagnosis of cardiac tamponade (Grade 4) was made, which at that time was considered to be secondary to hypoalbuminemia (lowest albumin value reported, 18 g/L; normal range 35 to 47 g/L) and Grade 4 tumor lysis syndrome. The patient was subsequently determined to be experiencing Grade 4 congestive heart failure; anasarca was reported. Grade 3 first and second degree heart block were apparent by ECG. Approximately 2 weeks later (D+21), CT revealed pulmonary embolism (Grade 4) and evidence of a possible mediastinal mass. Elevated troponin I (Grade 4; value not reported) also was noted around this time. The patient remained hospitalized, and approximately 1 month later (D+52), experienced right ventricular myocardial infarction; this event was considered to be unrelated to study drug. Cardiac catheterization was planned; however, the patient died 2 days later (D+54); the primary cause of death was considered to be right ventricular failure.

Patient 23081 was an 89-year-old white male with Mycosis Fungoides, diagnosed in _____, he had Stage IIB disease at study entry. During a routine examination 14 days after his last dose of study drug (D+14), the patient was noted to be in a poor general condition and had experienced orthostatic hypotension. His heart rate ranged between 48 and 59 bpm and an ECG revealed bradyarrhythmia with intermittent atrial fibrillation. The patient was diagnosed with Grade 4 bradyarrhythmia. On D+61, routine examination and ECG revealed tachyarrhythmia with atrial fibrillation. Bradyarrhythmia was considered resolved on D+64. In the opinion of the Investigator, Grade 4 bradyarrhythmia was probably related to study drug, and led to discontinuation from the study. All measures of the QT interval were within normal limits.

b(6)

Reviewers Comments: There were no reports of seizures or TdP in the CSR. For 1 patient (Patient No. 03019), syncope was considered by the Investigator to be study drug-related (associated with bradyarrhythmia).

NCI 1312

Patient No. 900-00-4757, a 69-year-old white male with Stage IB Mycosis Fungoides (MF) at Baseline, who had preexisting valvular disease and cardiomyopathy and had recent ECG evidence of atrial fibrillation, for which treatment with digoxin was started, experienced sudden death (reported by the Investigator as cardiac ischemia/infarction) 1 day after his 26th study drug dose on C10D8. The patient was confirmed at post-mortem to have significant cardiomegaly (810 gram heart), biventricular dilatation, and valvular pathology, without evidence of cardiac infarction.

With the exception of Patient No. 900-00-4757, study drug was not discontinued for any other patient because of a cardiac event. However, 1 patient [Patient No. 37-72-13-5] had study drug discontinued because of elevated troponin I and T, events within the Investigations SOC.

Overall, at least 1 cardiac event was reported as serious for 8 (11%) patients. Serious cardiac events included supraventricular arrhythmia NOS (4 patients; 6%), ventricular arrhythmia NOS (3 patients; 4%), and myocardial ischemia, nodal arrhythmia, and sinus bradycardia (1 patient each; 1%). The serious cardiac event was considered to be study drug-related for 7 of these 8 patients.

One patient (Patient No. 36-00-75-0) had hypomagnesemia concurrent with ventricular arrhythmia (described as Grade 1 asymptomatic ventricular trigemini) reported as a serious adverse event.

Patient No. 900-00-4853 was a 70-year-old white male with (MF) died due to an Escherichia coli infection 10 days after his 7th study drug dose on C3D8. On C1D15, the patient's study drug dose was held because of fatigue, and, it was reported, shortness of breath. On C1D28, the patient presented to the study center for C2 with episodes of palpitations. ECG findings revealed atrial fibrillation, with rapid ventricular response, but no evidence of myocardial infarction (MI). He was hospitalized, treated with IV amiodarone, and converted to sinus rhythm. Thereafter, IV amiodarone was replaced by oral amiodarone. Supraventricular arrhythmia was considered resolved on C1D29.

Patient 38-55-93-4 was a 69-year-old white male with Mycosis Fungoides (MF), diagnosed in _____ On C1D1, the patient received his first dose of study drug. It was reported that the patient underwent telemetry monitoring after the first study drug dose and was found to have premature supraventricular and ventricular beats, as well as episodes of supraventricular tachycardia, accelerated idioventricular rhythm, and ventricular tachycardia. Holter monitoring also captured ventricular tachycardia, with runs of 3 beats, 9 beats and 28 beats in the 48 hours of monitoring after C1D1. It is of note that screening 24-hour Holter monitoring had revealed supraventricular tachycardia in runs of up to 13 beats. Confirmation that the study drug was not

b(6)

exacerbating the SVT and idioventricular rhythms was obtained through electrophysiologic testing, revealing an absence of inducible sustained ventricular rhythms.

Reviewers Comments: there were no episodes of TdP. One patient experienced a syncopal episode that was not reported to be associated with QT prolongation and coded as vasovagal. Patient was noted to have junctional rhythm.

In summary Cardiac AEs in both studies are confounded due to co-morbidities. However relationship to study drug cannot be excluded. Moreover, stringent exclusion criteria were in place to exclude subjects with coronary artery disease.

3.5.3.3 Changes in troponin and LVEF

This was only done in NCI study 1312. 3 (4%) of 71 patients had a treatment-emergent abnormal LVEF. In this study, LVEF was to be measured via ECHO, MUGA scan, or cardiac MRI within 4 weeks before Baseline for intramural patients. During treatment, LVEF was to be measured after completion of C2 and every 3 cycles thereafter. Review of individual patient data revealed no clinically significant changes from Baseline in LVEF attributable to romidepsin.

In this study, troponin was to be measured within 48 hours before study drug administration on Day 1 and before and 1 day after each romidepsin dose (i.e. on Days 1, 2, 8, 9, 15, and 16) of each treatment cycle. Troponin I was measured at least once in most (55 of 71 patients; 77%) of these patients. Among these 55 patients, all troponin I measurements were within normal limits at all time points for 49 (89%) patients. Six (11%) patients had at least 1 abnormal troponin I measurement. Of these 6 patients, 2 had abnormal values >ULN but ≤ 2 x ULN, and 4 had abnormal troponin I measurements >2 x ULN.

Reviewers Comments: LVEF data are limited.

Patient No. 37-72-13-5 had study drug discontinued because of elevated troponin I and T, events within the Investigations SOC, but had a mass in the left ventricle. Of the remaining 5 patients, none had a concurrent condition that would typically be associated with troponin I elevations (e.g., sepsis, renal failure or pulmonary embolism). One patient (Patient No. 35-54-80-6) was receiving concomitant anticoagulant treatment with heparin, which has been reported to contribute to false elevations in troponin I. In 2 of 6 cases there were concurrent ECGs; 1 patient had an abnormal ECG finding that was a non-specific ST segment depression. There were no repeat ECGs or troponin I values taken in either patient with concurrent ECGs. Clearly there was a possible association to study drug in 5/6 cases.

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/s/

Suchitra Balakrishnan

7/1/2009 10:29:25 AM

MEDICAL OFFICER

Christine Garnett was the Clinical Pharmacology Reviewer

Joanne Zhang

7/1/2009 11:09:02 AM

BIOMETRICS

Norman Stockbridge

7/1/2009 12:55:28 PM

MEDICAL OFFICER

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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HUA ZHANG
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BRIAN P BOOTH
09/08/2009

NAM ATIQRUR RAHMAN
09/10/2009

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

Office of Clinical Pharmacology				
<i>New Drug Application Filing and Review Form</i>				
<u>General Information About the Submission</u>				
	Information		Information	
NDA/BLA Number	22-393		Brand Name	ISODAX
OCP Division (I, II, III, IV, V)	V		Generic Name	Romidepsin
Medical Division	Oncology		Drug Class	Histone deacetylase (HDAC) inhibitor
OCP Reviewer	Hua Lillian Zhang, Ph.D.		Indication(s)	Treatment of cutaneous T-cell lymphoma (CTCL), including relief of pruritus, in patients who have received at least one prior systemic therapy
OCP Deputy Director	Brian Booth, Ph.D.		Dosage Form	Lyophilized powder for solution: 10 mg per vial, copackaged with 1 diluent vial
Pharmacometrics Reviewer	Nitin Mehrotra		Dosing Regimen	14 mg/m ² administered intravenously (IV) over a 4-hour period on days 1, 8 and 15 of a 28-day cycle.
Date of Submission	12 January 2009		Route of Administration	IV infusion
Estimated Due Date of OCP Review	12 September 2009		Sponsor	Gloucester Pharmaceuticals, Inc
Medical Division Due Date			Priority Classification	Standard Review
PDUFA Due Date	12 November 2009			
<i>Clin. Pharm. and Biopharm. Information</i>				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				

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Table of Contents present and sufficient to locate reports, tables, data, etc.	x			Data submitted for studies: <ul style="list-style-type: none"> • T-95-0077 (Phase 1) • AN10018a (Reanalysis of T-95-0077 PK data- NCA, dose proportionality finding) • AN10019 (QT data, ECG and PK data obtained from GPI-06-0005 and NCI 1312) • AN10022 (Pop PK dataset, pulled out from six studies) • GPI-04-0001 (Phase 2 pivotal efficacy) • NCI1312 (Phase 2 supportive efficacy) • ISE (integrated summary of efficacy, GPI-04-001 and NCI1312) • ISS (integrated summary of safety, GPI-04-001 and NCI1312) • CAR (cardiac assessment report, GPI-04-0001, NCI1312, GPI-06-0005)
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x	1		JCL026011
I. Clinical Pharmacology				
Mass balance:		1 in rat		CRD040009
Isozyme characterization:				
Blood/plasma ratio:	x	1		CRD040012
Plasma protein binding:	x	1		CRD040011
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:	x	1		T-95-0077 (Phase 1)
multiple dose:	x	3		<ul style="list-style-type: none"> • T-95-0077 (Phase 1) • GPI-04-0001 (Phase 2) • NCI1312 (Phase 2)
Dose proportionality -				
fasting / non-fasting single dose:	x	1		T-95-0077 (Phase 1)
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:	x	2		<ul style="list-style-type: none"> • CRD030201 (CYPs identification+ ketoconazole) • CRD030209
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:	x	2		GPI-04-0001, NCI1312
Phase 3:				

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PK/PD -				
Phase 1 and/or 2, proof of concept:	x			PPK AN10019 (GPI-06-0005 and NCI 1312)
Phase 3 clinical trial:				
Population Analyses -				
Data rich:	x	3		AN10022 (Pop PK, 6 studies evaluated): NCI 1312, GPI-06-0005 T-95-0077
Data sparse:	x	3		FJ-228-0001 FJ-228-0002 GPI-04-0001
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		12		

On initial review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	
2	Has the applicant provided metabolism and drug-drug interaction information?	x			only in vitro info available
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			x	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have	x			

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	appropriate hyperlinks and do the hyperlinks work?				
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	x			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?		x		No exposure-response analysis for efficacy.
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	x			There was an attempt but it was not sufficient due to lack of in vivo human data.
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?		x		No exposure-response info about efficacy
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?		x		<ul style="list-style-type: none"> • No human DDI info • No human ADME info • No hepatic/ renal impairment studies done in human
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

Yes

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

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
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Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

- Please resubmit dataset (pkdata) in SAS transport file (*.xpt) for AN10018a

Hua Lillian Zhang	02/27/09
Reviewing Clinical Pharmacologist	Date
Brian Booth	03/02/09
Team Leader/Supervisor	Date

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

/s/

Hua Zhang
3/2/2009 10:20:44 AM
PHARMACIST

Filing Checklist

Brian Booth
3/3/2009 10:39:51 AM
BIOPHARMACEUTICS