2. STUDY SYNOPSIS

Name of Company: Gloucester Pharmaceuticals, Inc.	**Name of Finished Product:** Romidepsin for infusion	**Name of Active Ingredient:** Romidepsin (depsipeptide, FK228, NSC 630176, FR901228)
Title of Study: A Single Agent Phase II Study of Depsipeptide (FK228) in the Treatment of Cutaneous T Cell Lymphoma (CTCL)		
Investigators and/or Study Centers: Patients were treated at a total of 33 study centers in the US (4 study centers), Western Europe (United Kingdom, 5 centers; Germany, 4 centers; France, 1 center) and Eastern Europe (Poland, 8 centers; Russia, 6 centers; Ukraine, 3 centers; Georgia, 2 centers).		
Publications (references): None		
Studied Period: 06 January 2005 to Ongoing (Date of first patient visit to date of last patient visit)		**Phase of development:** Phase 2

Objectives:

The primary objective of the study was to confirm the efficacy of romidepsin, as reported in the Phase 1 and early Phase 2 studies, in patients with CTCL who were no longer controlled on skin-directed therapy and who had received at least 1 prior systemic therapy. The rate of objective disease response, as determined by the protocol-defined Objective Primary Disease Response Evaluation Criteria (OPDREC), was used as the primary endpoint to assess efficacy.

Secondary objectives were the following:

- To evaluate the rate of objective disease control.
- To evaluate duration of objective disease response.
- To evaluate time to objective disease progression.
- To evaluate safety of romidepsin in terms of adverse events (AEs), clinical laboratory data, physical examinations, electrocardiogram (ECG) findings, rate of neutropenic fever and sepsis, blood transfusions, and treatment compliance.
- To evaluate the pharmacokinetics of romidepsin in a cohort of patients with CTCL.
- To evaluate disease status with molecular markers in peripheral blood mononuclear cells and potentially tumors, including acetylation status, apoptosis markers, STAT, AKT, and caspases (subset of patients).

Pruritus relief was assessed and analyzed as a key indicator of clinical benefit.

Methodology:

This was a Phase 2, open-label, single-arm international study designed to assess the efficacy and safety of romidepsin in the treatment of patients with confirmed CTCL. Eligible patients were required to have failed at least 1 prior systemic therapy, e.g., interferon, chemotherapy, Ontak® (denileukin diftitox), or Targretin® (bexarotene).

Patients received romidepsin 14 mg/m^2 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 (SD) had the option of continuing treatment beyond 6 cycles at the discretion of the Investigator and based on local regulations.

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Screening assessments included histologic confirmation of CTCL (both local and central analysis), medical and medication history, physical examination, chest x-ray, vital signs, Eastern Cooperative Oncology Group (ECOG) performance status (PS), safety laboratory assessments, and 12-lead ECG. Evaluation of disease status, including computed tomography (CT)/magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis; assessment of skin involvement, based on either the weighted body surface area/skin weighted assessment tool (WBSA/SWAT) or erythroderma scores; lymph node measurements; peripheral blood examination by flow cytometry immunophenotyping to detect the presence of circulating malignant T-cells (Sézary cells); pruritus assessment using a visual analogue scale (VAS), and standard photographic documentation of skin lesions, was conducted during the screening period.

During treatment, patients attended study visits on all dosing days (i.e., on Days 1, 8, and 15) and on Day 22 of each treatment cycle. Study assessments performed on each dosing day included vital signs, ECOG PS, ECGs, clinical laboratory assessments, and monitoring for adverse events and concomitant medications. Evaluation of response to treatment by OPDREC and assessment of the severity of pruritus were conducted throughout the treatment period; full evaluations were conducted every 2 cycles.

All patients were to attend a final visit 30 days after the end of treatment or at the time of early discontinuation. Assessments conducted during the treatment period were repeated at the final visit. Patients who went off treatment without disease progression were to be followed every 2 months until disease progression or withdrawal from the study.

At the time of this report, the study is ongoing; a limited number of patients remain on treatment or in follow-up. The primary data cut-off for this report was 16 October 07 (designated safety data cut-off). Based on a request by the to capture additional duration of response information, additional efficacy data were captured through 05 May 08 for a total of 11 patients who were ongoing at the time of the original data cut-off (designated efficacy data cut-off).

Number of Patients (Planned and Analyzed):

A total of 90 patients were to be enrolled to provide data from a total of 64 evaluable patients.

Ninety-six patients were enrolled and treated in this study; these 96 patients comprise the As-Treated Patients Analysis Set (TP Analysis Set). Data from 72 patients were considered evaluable for efficacy analysis (Evaluable Patients [EP] Analysis Set) according to predefined criteria.

Diagnosis and Main Criteria for Inclusion:

Males or nonpregnant females ≥18 years of age with histologically confirmed Stage IIA, IIB, III or IVA CTCL at study entry, including mycosis fungoides and Sézary syndrome, who were no longer controlled on standard skin-directed therapy and had received at least 1 course of prior systemic therapy, were candidates for the study. Patients with Stage IB CTCL also were eligible provided they had relapsed following previous therapy and in the Investigator's opinion the potential benefit of treatment with romidepsin outweighed the possible risks. Patients also were required to have a life expectancy of >6 months, ECOG PS ≤1, and no known cardiac abnormalities (e.g., congenital long QT syndrome, QTc >480 msec, cardiac arrhythmia requiring anti-arrhythmic medication, myocardial infarction within the previous 12 months).

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Test Product, Dose and Mode of Administration, Batch Number(s):
Patients received 14 mg/m^2 of romidepsin IV over 4 hours on Days 1, 8, and 15 of each 28-day treatment cycle.

The lot numbers of romidepsin used in this study were 485665 (with diluent lot 499450) and 909090 (with diluent lot 909093).

Reference Therapy, Dose and Mode of Administration, Batch Number(s):
No reference therapy was employed in this study.

Duration of Treatment:
Treatment was planned for 6 months. Patients could continue to receive treatment until disease progression or other withdrawal criteria were met at the discretion of the investigator and based on local regulations.

Criteria for Evaluation:
Analysis Sets:
Three analysis sets, the As-Treated Patients (TP), the Evaluable Patients (EP), and the Modified Evaluable Patients (MEP), were used in summary tabulations.

- TP: all patients who received at least 1 dose of romidepsin (96 patients). This population was used to summarize patient characteristics, treatment administration, safety endpoints, and supportive analyses of efficacy.
- EP: all patients who received 2 consecutive cycles of study treatment, with at least 2 of the 3 doses received in each cycle, and had disease assessments performed at Baseline and after the last of the 2 consecutive cycles; and who did not receive concomitant steroid therapy or other therapy for CTCL (whether systemic or topical) that may have biased the assessment of disease response (72 patients). The EP was used to assess the primary analyses of efficacy.
- MEP: all patients who received 2 consecutive cycles of study treatment, with at least 2 of the 3 doses received in each cycle, and had disease assessments performed at Baseline and after the last of the 2 consecutive cycles (76 patients). The MEP was used for supportive summaries of response to treatment.

Efficacy:
The efficacy of romidepsin therapy was evaluated by the rate of confirmed objective disease response (confirmed best responses of complete response [CR], clinical complete response [CCR], or partial response [PR]). Responses were evaluated according to a composite assessment (OPDREC) that included cutaneous manifestations of disease, lymph node involvement, and circulating malignant T-cells (Sézary cells). Disease response was assessed by both the Investigators and an Independent Response Review Committee (IRRC) comprised of 3 CTCL experts, with the IRRC assessment considered supportive of the Investigator's evaluations. The date of response and dates of progression were recorded and used to assess duration of response, time to response, and time to progression.

Pharmacokinetics:
In a cohort of patients, blood samples were obtained at specified times during the study for measurement of plasma romidepsin concentrations; results are to be included in a population pharmacokinetic analysis.

Safety:
The safety and tolerability of romidepsin were evaluated by monitoring AEs, concomitant medication

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use, laboratory test results, physical examination findings, vital signs, and ECG findings.

Statistical Methods:

Efficacy Analyses:

The primary efficacy endpoint was the confirmed objective response rate (ORR), defined as the proportion of patients with confirmed CR, CCR, or PR, based on OPDREC. A 2-sided 95% confidence interval (CI) was constructed about the ORR. The primary population for analysis of ORR was the EP Analysis Set and the primary data were based on the Investigators' evaluations of ORR. The primary efficacy endpoint was considered to have been met if the 95% CI for ORR by the Investigators' assessment lay entirely above 15% (i.e., the lower bound of the 95% CI was >15%). ORR based on the IRRC's evaluations were assessed as a secondary endpoint.

Other secondary efficacy endpoints included duration of objective disease response; time to objective disease response; rate of objective disease control (CR+CCR+PR+SD_{90}; the latter representing stable disease for at least 90 days); time to disease progression, and change in pruritus VAS scores. The secondary endpoints of duration of objective disease response and time to disease progression were analyzed by Kaplan-Meier product limit estimates. Change from Baseline over time on study in the pruritus VAS score and time to response were assessed using descriptive statistics.

Safety Analyses:

The number and percentage of patients in each group who reported any treatment-emergent AE (TEAE) were tabulated by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term. Summaries were provided for all TEAEs; TEAEs judged by the Investigator as possibly, probably or definitely related to study drug; TEAEs of Grade 3, 4 and 5 intensity; serious TEAEs; and TEAEs leading to termination of treatment.

Clinical laboratory, vital signs, and ECG interval data were summarized using descriptive statistics. A shift analysis of laboratory data from Baseline to worst on-study value, based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), was produced.

Summary and Conclusions:

Patient Disposition and Analysis Sets:

A total of 96 patients received at least 1 dose of romidepsin and had data included in the TP Analysis Set. Among the 96 patients enrolled in this study, 24 (25%) were enrolled at study centers in Poland, 20 (21%) in the UK, 18 (19%) in the US, 15 (16%) in Russia, 7 (7%) in the Ukraine, 6 (6%) in Germany, and 3 (3%) each in France and Georgia.

At the time of the efficacy data cut-off, 35 of the 96 patients had either completed 6 cycles of treatment and elected not to continue or were ongoing on treatment. Ten patients received treatment beyond Cycle 6; 4 were ongoing on treatment at the time of the efficacy data cut-off. A total of 61 patients had discontinued treatment during Cycles 1 to 6. The primary reasons for discontinuation from the study were disease progression (21 patients), withdrawal of consent (21 patients), and adverse event (17 patients).

The EP Analysis Set includes 72 (75.0%) of the 96 treated patients and the MEP Analysis Set includes 76 (79.2%) of the 96 treated patients.

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Patient Characteristics at Study Entry:

A total of 90 (94%) of the 96 patients in the TP Analysis Set were Caucasian and the majority were male (59 patients, 61%). Mean age of all patients was 56.9 years, with a range of 21 to 89 years. All patients had ECOG PS of 0 (49 patients, 51%) or 1 (47 patients, 49%).

Mean duration of disease since diagnosis of CTCL was 4.1 years. At study entry, 28 (29%) of the 96 patients had Stage IB or IIA disease and 68 (71%) had Stage IIB, III or IVA disease.

All 96 patients had received prior systemic therapy for CTCL. In general, patients had been exposed to multiple prior regimens, with a median number of prior systemic regimens of 2 (range 1 to 8).

Similar patient characteristics were noted in the EP and MEP Analysis Sets.

Summary of Efficacy:

The ORR (CR+CCR+PR) following treatment with romidepsin, based on the Investigators' evaluations, was 41.7% (30 of 72 patients) for the EP Analysis Set with a CCR rate of 8.3% (6 of 72 patients) and a PR rate of 33.3% (24 of 72 patients). The lower bound of the 95% CI for ORR was 30.1%, therefore the study met the primary efficacy endpoint as the lower bound was >15%.

ORR for the MEP Analysis Set based on the Investigators' evaluations was 42.1% (32 of 76 patients) with the lower bound of the 95% CI at 30.9%. In the TP Analysis Set, the ORR based on the Investigators' evaluations was 34.4% (33 of 96 patients) with the lower bound of the 95% CI at 25.0%.

Results based on the IRRC's evaluations support those observed based on the Investigators' evaluations. The ORR based on the IRRC's evaluations was 36.1% (26 of 72 patients) with the lower bound of the 95% CI at 25.1% in the EP Analysis Set, 36.8% (28 of 76 patients) with the lower bound of the 95% CI at 26.0% in the MEP Analysis Set, and 29.2% (28 of 96 patients) with the lower bound of the 95% CI at 20.3% in the TP Analysis Set. In the EP Analysis Set, the CCR rate was 9.7% (7 of 72 patients) and the PR rate was 26.4% (19 of 72 patients) based on the IRRC's evaluations.

Median time to OR was 57 days (1.9 months), based on both the Investigators' and IRRC's evaluations, for both the EP and TP Analysis Sets and ranged from 27 to 145 days (0.9 to 4.8 months) with 8 of the 30 responses noted at Cycle 3 or later. Median time to CCR was longer at 134 days (4.4 months) based on the Investigator's evaluations; 4 of the 6 patients who achieved CCR based on the Investigators' evaluations initially had achieved PR in Cycles 2 through 4 and remained on treatment achieving CCR in Cycles 5 through 8.

At the time of the analysis with a median duration of follow-up of 162 days (5.3 months), median duration of response for the EP Analysis Set had not been reached based on either the Investigators' or IRRC's evaluations. Twenty-four (80.0%) of the 30 patients who achieved OR based on the Investigators' evaluations had not progressed as of the last evaluation and therefore were censored in the analysis. As of the data cut-off, 16 of the 30 responders based on the Investigators' evaluations had durations of response ≥153 days (≥5.0 months), with 10 patients having durations ≥246 days (≥8.1 months). Maximum duration of response was 603+ days (19.8+ months). Review of study completion status for those patients who were censored in the duration of response analysis reveals that data from only 5 patients could potentially be updated; thus it is not likely that a median duration of response will be reached for the EP Analysis Set. In the TP Analysis Set, median duration of response based on the Investigators' evaluations was 454 days (14.9 months).

Median TTP for all 72 patients in the EP Analysis Set, based on the Investigators' evaluations, was 538 days (17.7 months) with 61% of the data censored. In the TP Analysis Set, median TTP was

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252 days (8.3 months) with 60% of the data censored.

The ORR (CCR+PR) based on the Investigators' evaluations for the EP Analysis Set was consistent across patient subgroups including patients with tumor stage disease (≥Stage IIB; 48%, 23 of 48 patients), erythroderma (43%; 12 of 28 patients), Sézary syndrome (50%; 4 of 8 patients), and lymphadenopathy at study entry (34%; 13 of 38 patients). In addition, response rates were consistent with the overall results for patients who had received 2 or more prior systemic therapies (43%, 19 of 44 patients) and for patients who had received prior therapy with bexarotene and/or denileukin diftitox (44%, 12 of 27).

Romidepsin was active at all sites of disease. In 46% of patients (33 of 72), ≥50% reductions (improvements) were noted in WBSA/SWAT or erythroderma scores. Among patients with lymphadenopathy at study entry and post-baseline data available, 35% (13 of 37 patients) experienced a ≥30% reduction in the sum of the longest diameter of lymph nodes, including 10 patients (27%) with a ≥50% reduction.

Nearly all patients (48 of 52, 92%) with moderate to severe pruritus at Baseline (VAS score of ≥30 mm) included in the EP Analysis Set who did not receive confounding treatment for pruritus had a decrease in VAS scores during the study. Relief of pruritus symptoms, defined as a decrease in VAS score of at least 30 mm or a score of 0 for at least 2 consecutive cycles, was observed in 25 (48%) of the 52 patients with moderate to severe pruritus at Baseline. Importantly, the majority of patients (16 of 29, 55%) with severe pruritus (VAS score of 70 to 100 mm) at Baseline experienced relief during the study, including 7 patients with VAS scores between 72 to 100 at Baseline who had complete relief of pruritus (i.e., VAS scores decreased to 0 for at least 2 consecutive cycles). Pruritus relief was not limited to patients who achieved a response to treatment; 10 (34%) of 29 patients who did not achieve OR during the study experienced pruritus relief as did 15 (65%) of 23 patients who achieved OR.

Summary of Safety:

A total of 93 (97%) of the 96 patients experienced at least 1 TEAE during the study. The principal features of the adverse event profile of romidepsin in this study were gastrointestinal (GI) disturbances and asthenic conditions.

Overall, the common categories of AEs included GI disorders (66 patients, 69%), most commonly mild to moderate nausea with or without vomiting (61%), and diarrhea (18%); asthenic conditions (52%), including reports of fatigue, asthenia, and lethargy; anorexia (23%); taste disorders (22%), including ageusia and dysgeusia; hypomagnesemia (21%); pyrexia (20%); anemia (18%); headache (15%); and thrombocytopenia (14%). All other events were reported in <10% of patients.

For most patients who experienced these common adverse events, at least 1 occurrence was considered by the Investigator to be study drug-related. Overall, 88 (92%) of the 96 patients experienced at least 1 study drug-related TEAE. The most commonly reported drug-related events were GI disturbances (68%), including nausea (56%), vomiting (26%), and diarrhea (14%); asthenic conditions (44%); taste disorders (21%); anorexia (20%); headache (14%); thrombocytopenia (11%); and anemia (10%).

A total of 32 (33%) of the 96 patients experienced at least 1 TEAE that was assessed as ≥Grade 3 in intensity. The most commonly reported ≥Grade 3 events were fatigue (7%), neoplasm progression NOS and pyrexia (4% each), and anemia and hypotension NOS (3% each).

Overall, 6 (6%) patients died within 30 days after the last study drug dose. The adverse events leading to death were progression of disease for 4 patients (MedDRA preferred terms neoplasm progression

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NOS and disease progression NOS), cardiac disorder (MedDRA preferred term cardiopulmonary failure) for 1 patient, and a renal event (MedDRA preferred term acute renal failure) for 1 patient. For 1 of these 6 patients, the cause of death was considered by the Investigator to be at least possibly related to study drug. This patient (Patient No.), who received 3 cycles of romidepsin, developed pyrexia, hypotension, hepatomegaly, hyperbilirubinemia, left lobar pneumonia, and pleuritis post-treatment. The patient was admitted to the intensive care unit with signs of acute cardiovascular insufficiency 10 days after last study drug dose. Life-saving measures were unsuccessful, and the patient died that day. Upon independent review of this case, carried out by a senior Investigator at the request of Institutional Review Board, progressive disease with cardiopulmonary insufficiency as the terminal event was considered to be the likely cause of death.

Overall, 21 (22%) patients experienced at least 1 serious adverse event (SAE) during the study. Infections were the most common type of SAE reported, with 7 (7%) patients experiencing a serious infection during the study. Serious infections reported in these 7 patients included sepsis NOS and oral candidiasis in 1 patient; oropharyngeal candidiasis, urinary tract infection, and bacterial skin infection in 1 patient; and sepsis NOS, staphylococcal bacteremia, perineal abscess, pharyngitis, and tonsillitis in 1 patient each. Based on review of ANC and ALC data obtained within ±4 days of the onset of these infections, none of the patients had Grade 3 or 4 ANC concurrent with the infection.

Adverse events leading to discontinuation were reported in 20 (21%) of the 96 patients and primarily included reports of fatigue (4 patients, 4%), pyrexia (2 patients, 2%), electrocardiogram QT prolonged (2 patients, 2%), and neoplasm progression NOS (2 patients, 2%). All other events leading to discontinuation were reported in 1 patient each.

No clinically meaningful changes in hematologic, clinical chemistry, or vital sign parameters were noted. Mean platelet count decreased during the treatment period of each cycle, and rapidly recovered between cycles.

Mean QTcF change from baseline was 4.6±14.1 ms (90% CI upper bound of 7.4 ms) observed 2 hours post romidepsin infusion. This finding was in relation to the pre-comedication (prior to anti-emetics) baseline. When examining the post-comedication baseline, the observed change was smaller; a mean QTcF change of 1.3±14.9 ms (90% CI upper bound of 4.2 ms) was observed, which provides evidence that the comedications likely account for a portion of the QTc effect. There were no patients with an absolute QTcF >500 msec.

Conclusions:

The results of this study demonstrate that romidepsin at a dose of 14 mg/m^2 administered on Days 1, 8 and 15 of a 28-day cycle is an effective agent in the treatment of patients with CTCL, including those with pruritus, whose disease has relapsed following, or become refractory to at least 1 other systemic therapy. The ORR based on Investigators' evaluations in the EP Analysis Set was 42% and the primary efficacy criterion of the study was met as the lower bound of the 95% CI for the ORR was 30.1%. With a median duration of follow-up of >5 months, the median duration of response has not been reached for the EP Analysis Set. Approximately 50% of responders had durations of response ≥5.0 months and 30% had durations of response >8 months. Pruritus relief was observed in the majority of patients with this symptom at Baseline including both responders and non-responders. Importantly, no anti-pruritic treatments were permitted during the study.

Romidepsin at this dose and schedule was generally well tolerated and exhibited a manageable safety profile in patients with CTCL in this study.

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