CELGENE PROPRIETARY INFORMATION

CLINICAL STUDY SYNOPSIS

A Multicenter, Open-Label Continuation Trial Evaluating the Tolerability and Activity of Depsipeptide (FK228) in Patients That Have Completed a Prior Clinical Study with Depsipeptide

STUDY NUMBER: **FJ-228-0007**

STUDY SPONSORED BY:

Gloucester Pharmaceuticals, Inc
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REPORT PRODUCED BY:

21 April 2008

CLINICAL STUDY SYNOPSIS

Name of Company: Gloucester Pharmaceuticals, Inc	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	***(For National Authority Use Only)***
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Name of Active Ingredient: Romidepsin (Depsipeptide, FK228)		

Title of study: A Multicenter, Open-Label Continuation Trial Evaluating the Tolerability and Activity of Depsipeptide (FK228) in Patients That Have Completed a Prior Clinical Study with Depsipeptide

Investigator(s):
(investigator curriculum vitae are included in Appendix D)

Study center(s):

Publication (reference): None

Studied period (years): Approximately 2.5 years; 03 May 2004 (first patient signed informed consent) to 22 September 2006 (last patient last evaluation)	**Phase of development:** Phase 2

Objectives:

The primary objective of the study was to evaluate the safety and tolerability of extended treatment with romidepsin (depsipeptide, FK228) in patients who had demonstrated at least stable disease on a prior Gloucester-sponsored romidepsin clinical study, and in the opinion of their physician/investigator might benefit from continued treatment with romidepsin.

The secondary objectives were to evaluate the effect of romidepsin therapy on performance status and to evaluate the time to objective disease progression.

Study design: This was a Phase 2, nonrandomized, open-label, single-arm, continuation study. This study was designed to provide continuing access to romidepsin in patients who had demonstrated at least stable disease on a prior Gloucester-sponsored romidepsin study. Patients were continued at the same dose of romidepsin as in the previous study, which could have been 13 mg/m^2 or a reduced dose of 10 mg/m^2, administered intravenously over 4 hours on Days 1, 8, and 15 of each 28-day cycle. Any toxicity from a prior cycle must have improved to at least Grade 1 (based on the Common Toxicity Criteria for Adverse Events [CTCAE]) or baseline value prior to beginning each new cycle, unless otherwise indicated. Patients could remain on treatment until there was intolerance to continued therapy, objective evidence of disease progression, or upon meeting a criterion for withdrawal. The main objective of the study was to evaluate the long-term safety and tolerability of romidepsin, so patients only underwent periodic assessments of the extent of their disease.

Number of patients (planned and analyzed): Up to 40 patients from 9 sites were planned for enrollment in this continuation study. Actual enrollment was 2 patients from 2 sites.

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Diagnosis and main criteria for inclusion: The main criteria for inclusion in the study included the following: had immediate past participation in, and had completed 6 cycles of therapy in, a prior Gloucester-sponsored romidepsin clinical study; had demonstrated stable disease, partial response, or complete response as best overall response during a prior Gloucester-sponsored romidepsin clinical study, and such a response was ongoing at the time of enrollment; had serum potassium levels >4.0 mEq/L and serum magnesium levels >2.0 mg/dL; and had provided written informed consent. The complete list of exclusion criteria are in the protocol (Appendix B).

Test product, dose and mode of administration, batch number: Patients received 13 mg/m^2 or 10 mg/m^2 of romidepsin intravenously (via a central or peripheral line) over 4 hours on Days 1, 8, and 15 of each 28-day treatment cycle. Detailed guidelines for dose modifications and treatment delays were provided in the protocol. Romidepsin was provided in a dual pack containing 1 vial of romidepsin for injection and 1 vial of diluent. The drug vial contained a lyophilized powder of 10 mg lyophilized romidepsin and 20 mg povidone. The diluent vial contained 2 mL of a 4:1 mixture of propylene glycol and ethanol. The batch number of romidepsin used in the United States (Patient) was 339330 and the batch number used in the United Kingdom (Patient) was 485665.

Duration of treatment: Patients could remain on treatment until there was intolerance to continued therapy, objective evidence of disease progression, or upon meeting a criterion for withdrawal.

Criteria for evaluation: The primary endpoints of safety and tolerability were assessed as the rate of Grade 3 and Grade 4 nonhematological toxicity, adverse events (AEs), clinical laboratory data, rate of Grade 4 hematological toxicity, rate of neutropenic fever/sepsis, number of blood transfusions, electrocardiogram (ECG) findings, frequency of cycles and administrations delayed as result of toxicity, and the frequency of cycles and administrations requiring dose modification because of toxicity.

The secondary endpoints were the change in performance status and the time to objective disease progression.

Safety assessments: All patients who received at least one dose of romidepsin were assessed for safety and tolerability. Safety was evaluated using clinical examination including ECGs, laboratory screens, and documentation of all AEs and serious adverse events (SAEs). Toxicities were classified according to the Medical Dictionary for Regulatory Activities (MedDRA) and assessed according to the CTCAE grading system.

Efficacy assessments: Performance status was assessed using the Karnofsky scale at the time of each romidepsin administration after Day 1, at the final assessment, and at any follow-up visits for toxicities.

Objective disease progression was defined as at least a 20% increase in the sum of the longest diameters of target lesions, or unequivocal progression of existing nontarget lesions, or appearance of new lesions. Time to objective disease progression was defined as the time interval from the initiation of study treatment in a prior Gloucester-sponsored clinical study until the first date an objective diagnosis of disease progression was documented in the current study.

The schedule of study procedures is presented in Table 1.

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Table 1 Schedule of Study Procedures

Evaluations	Prior to Treatment [1]	Treatment Period				Final Assessment [3]	Follow-Up [4]
		Day 1 Cycle 7 [2]	Day 1 Cycles 8-12	Day 8 All Cycles	Day 15 All Cycles		
Physical examination	X					X	X
Concomitant medications	X	X	X	X	X	X	X
Body weight	X		X	X	X	X	X
Vital signs [5]	X	X	X	X	X	X	X
Body surface area	X		X				
Performance status	X		X	X	X	X	X
Complete blood count/ differentials/platelets [6,7]	X	X	X	X	X	X	X
Biochemistry [7,8]	X	X	X			X	X
Serum electrolytes [7,9]	X	X	X			X	X
Electrocardiogram [10]	X	X	X	X	X	X	X
Disease assessment [11]	X					X	
Study drug dosing		X	X	X	X		
Adverse events		X	X	X	X	X	X

[1] Pretreatment items were performed as part of the final assessment on the prior romidepsin clinical study.
[2] Patients completed 6 cycles of romidepsin in their prior study; therefore, the first cycle of treatment in the continuation study is Cycle 7 of romidepsin treatment.
[3] 30 days (± 3 days) after the last dose of romidepsin.
[4] Performed only in the case of drug-related toxicity.
[5] Vital signs included pulse, blood pressure, and temperature.
[6] In case of Grade 4 neutropenia or thrombocytopenia.
[7] Repeated if clinically indicated.
[8] Panel included creatinine, blood urea nitrogen, alanine aminotransferase, alkaline phosphatase, total bilirubin, magnesium, aspartate aminotransferase, total protein, albumin, and lactate dehydrogenase.
[9] Panel included sodium, calcium, bicarbonate, potassium, and magnesium.
[10] See cardiac monitoring Section 7.1 of the protocol (Appendix B) for specific timing and identification of cardiac alerts.
[11] Computed tomography or magnetic resonance imaging, bone scan, and prostate-specific antigen, if applicable, were required prior to treatment, at the final evaluation visit, and whenever needed to confirm disease progression.

Statistical methods: Results of the study were to be analyzed by using descriptive statistics. Continuous variables were to be summarized by N, mean, standard deviation, minimum, and maximum. Categorical variables were to be summarized by N and percentage. Since only 2 patients were enrolled in the study, results are presented by patient number and parameter of interest.

Results

Disposition: Two patients (and) enrolled in this continuation study (patient case report forms are provided in Appendix C). Patient discontinued from this study following 4 cycles of romidepsin (total of 10 cycles across both studies) due to objective disease progression (new brain metastases) and AEs. Patient discontinued from this study following 6 cycles of romidepsin (total of 12 cycles across both studies) due to prostate-specific antigen (PSA) progression.

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Demographics: Both patients were [redacted] with adenocarcinoma of the prostate who had previously completed 6 cycles of romidepsin on protocol FJ-228-0002. [redacted]

Extent of exposure: Both patients received romidepsin at a dose of 13 mg/m^2. Patient [redacted] received 8 doses of romidepsin during 4 treatment cycles for a total of 187 mg. Patient [redacted] received 18 doses of romidepsin during 6 treatment cycles for a total of 491.4 mg.

Safety results:

No patients experienced an SAE during the study. There were no incidences of neutropenic fever or sepsis. No patients experienced a Grade 4 hematological or nonhematological AE. No patients required a blood transfusion during the study.

Both patients experienced treatment-related AEs during the study. The majority of AEs were considered by the investigator to be mild or moderate in intensity. The only Grade 3 AEs were nausea and vomiting in Patient [redacted], which occurred during Cycle 8 Days 13 to 15 and were considered by the investigator to be probably related to study drug.

Patient [redacted] missed 4 doses of romidepsin during the study due to toxicity, and the occurrence of AEs contributed to [redacted] discontinuation from the study. The specific doses missed and the associated toxicity were as follows: Cycle 8 Day 15 severe nausea and vomiting; Cycle 9 Day 8 and Cycle 10 Day 1 moderate neutropenia; and Cycle 10 Day 15 moderate fatigue. The AEs that contributed to discontinuation from the study were mild loss of equilibrium and slurred speech on Cycle 11 Day 1 that were considered unlikely related to study drug.

Two AEs of neutropenia were reported, each event was considered moderate in intensity and definitely related to study drug. Patient [redacted] had an absolute neutrophil count (ANC) of 2070.6/mL on Cycle 7 Day 1. The level fluctuated during Cycles 7 and 8, and reached a low of 1280.4/mL on Cycle 9 Day 8, causing an interruption in dosing. The ANC rebounded slightly then decreased to 1466.4/mL on Cycle 10 Day 1, again causing an interruption in dosing.

Patient [redacted] did not experience any AEs leading to delayed, reduced, or missed doses and [redacted] received all 18 doses of romidepsin on schedule.

The most frequently experienced AE was vomiting. Patient [redacted] had 2 AEs of vomiting accompanied by nausea; 1 episode was severe in intensity and probably related, and 1 episode was mild in intensity and possibly related. Patient [redacted] had 1 AE of mild-moderate vomiting accompanied by nausea and 3 AEs of mild vomiting; all were considered by the investigator to be possibly related to study drug.

Patient [redacted] also experienced altered taste (mild to moderate in intensity; possibly to probably related) throughout most of the study and experienced 4 AEs of constipation (mild in intensity; possibly related). Additional AEs of mild intensity experienced on a single occasion by at least 1 of the patients during the study were nose bleed, numbness and tingling of left cheek, weakness, head pressure and sinus drainage, anorexia, loose stools, and upper respiratory tract infection. Additional AEs of moderate

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intensity experienced on a single occasion by at least 1 of the patients during the study were head pain and chest pain. The chest pain accompanied the nausea and vomiting of Patient during Cycle 10 Day 9, was considered possibly related to study drug, and resolved after 1 day.

Patient had normal ECG recordings prior to dosing and less than 1 hour after completion of the romidepsin infusion during Cycles 7 and 8. During Cycle 9, the Day 1 pre- and postdose and Day 15 predose ECGs were normal, but the Day 15 postdose ECG was abnormal (nonalert). The finding was described as sinus rhythm with premature atrial complexes (otherwise normal). During Cycle 10, the Day 8 predose ECG was abnormal (nonalert). The finding was described as sinus rhythm with premature supraventricular complexes (otherwise normal). However, the Cycle 10 Day 8 postdose ECG was normal. Patient had normal ECG recordings prior to each dose of romidepsin. Postdose ECGs were not performed.

There were no trends in vital sign changes during the study. Blood pressure readings for Patient ranged from a low of 137/71 mmHg (Cycle 7 Day 15) to a high of 161/76 mmHg (Cycle 10 Day 1). Blood pressure readings for Patient ranged from a low of 116/76 mmHg (Cycle 10 Day 1) to a high of 169/106 mmHg (final evaluation visit).

Efficacy results:

Both patients had Karnofsky performance status scores of 100 (normal, no evidence of disease) at the start of the continuation study. Patient had a score of 100 on Days 1 and 8 of Cycles 7 and 8, but a score of 90 (minor signs or symptoms of disease) on Day 15 of both cycles. again had a score of 100 on Cycle 9 Day 1, but performance status decreased to 90 on Cycle 9 Day 8 and remained there throughout Cycle 10 and at the final evaluation visit. Patient only had 1 performance status evaluation less than 100 (a score of 90 on Cycle 9 Day 1), although there were 3 days that performance status was not evaluated or not recorded. had a score of 100 at the final evaluation visit.

Patient had documented objective disease progression after 317 days of romidepsin treatment (total days across both studies). An MRI on documented new brain metastases.

Patient had PSA progression documented on , after 299 days of romidepsin treatment, but continued to receive romidepsin and was on the study for a total of 358 days (total days across both studies). Cycle 7 Day 1 PSA level was 14.1 ng/mL, by Cycle 11 Day 8 PSA had increased to 19.1 ng/mL, and at the final evaluation PSA level was 37.2 ng/mL.

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Conclusions:

As only 2 patients were enrolled in this extended-treatment continuation study, no conclusions can be drawn regarding the long-term use of romidepsin.

There were no deaths, SAEs, or Grade 4 AEs during the continuation study. One patient missed 4 doses of romidepsin due to toxicity and discontinued treatment after Cycle 10, in part due to AEs. The most common AE was vomiting, which was severe in 1 patient and caused an interruption in treatment.

There were no appreciable changes in performance status during the study.

One patient demonstrated objective disease progression after Cycle 10 (317 days total of romidepsin treatment). The second patient had PSA progression during Cycle 11 (299 days total of romidepsin treatment), but remained on the study through Cycle 12.