2. SYNOPSIS

Name of Company: Gloucester Pharmaceuticals Inc.	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	***(For National Authority Use Only)***
Name of Finished Product: Romidepsin for infusion		
Name of Active Ingredient: Romidepsin (depsipeptide, FK228)		
Title of Study: An Exploratory Phase II, Multicenter, Open-label Trial Evaluating the Activity and Tolerability of Depsipeptide (FK228) in Androgen Independent Metastatic Prostate Cancer Patients With a Rising PSA		
Investigator(s): and		
Study center(s):		
Publication (reference): Molife R, Patterson S, Riggs C, Higano C, Stadler WM, Dearnaley D, Parker C, McCulloch W, Shalaurov A, De Bono J. Phase II study of FK228 in patients with hormone refractory prostate cancer (HRPC). *Journal of Clinical Oncology* 2006 ASCO Annual Meeting Proceedings Part I. Vol 24, No. 18S (June 20 Supplement), 2006:14554.		
Studied period (years): Approximately 3 years	**Phase of development:** Phase 2	
Objectives: The primary objective of the study was to evaluate the activity of romidepsin in patients with metastatic prostate cancer who had developed a rising PSA while undergoing hormonal therapy. Activity was measured as the rate of disease control (CR, PR, or SD for at least 6 months). Secondary objectives were the following: To evaluate the rate of PSA decline by ≥ 50% To evaluate the percentage of PSA decline To evaluate the time to PSA progression To evaluate the duration of objective disease response (including the rate of objective response) To evaluate the time to objective disease progression To assess the tolerability and safety of romidepsin To evaluate the effect of the therapy on disease-related symptoms (Memorial Pain Scale) To evaluate the effect of the therapy on performance status To evaluate the pharmacokinetics of romidepsin.		
Study Design: This was a phase 2, nonrandomized, open-label, single-arm, 2-stage trial that was conducted at 5 sites. Patients received 13 mg/m^2 of romidepsin intravenously over 4 hours on Days 1, 8, and 15 of each 28-day cycle. The planned duration of treatment was 6 cycles or until disease progression. Patients who had SD or an objective response after 6 cycles of therapy had the option of continuing treatment on a separate protocol. Two patients participated in this separate protocol. The 2-stage study was designed on the basis of the rate of disease control (CR or PR, or SD for at least 6 months) as the primary measure of efficacy. The following parameters were used: Futility rate for the study was 10% Rate of interest was 30%		

Name of Company: Gloucester Pharmaceuticals Inc.	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	***(For National Authority Use Only)***

Alpha was set to 10%

Power was set to 90%

In stage 1 of the study, 16 patients were treated with romidepsin for ≥ 1 cycle of treatment. If no objective responses were observed in 16 patients in stage 1, the study was to be terminated because of futility. If objective responses were observed in ≥ 1 of 16 patients in stage 1 of the study, the study design called for an additional 9 patients to be enrolled and treated in stage 2. If objective responses were observed in ≥ 5 of 16 patients in stage 1, there was an option to terminate the study due to adequate evidence that the treatment was successful. One patient experienced objective disease control in stage 1. After 25 patients had completed ≥ 1 cycle of treatment (ie, after completion of stage 2), the treatment was considered successful if objective responses were observed in ≥ 5 of 25 patients who completed ≥ 1 cycle of treatment. Three of 25 patients experienced objective disease control after completion of stage 2 of the study.

Number of patients (planned and analyzed): A total of 16 per-protocol, evaluable patients were planned for stage 1. If 1 to 4 patients experienced disease control, 9 additional per-protocol, evaluable patients were to be recruited and treated. Patients who completed ≥ 2 consecutive cycles of treatment and received ≥ 2 doses per cycle (≥ 4 doses of romidepsin) were included in the evaluable population. The numbers of patients analyzed included 35 patients who received ≥ 1 dose of romidepsin (as-treated population) and 25 patients who received ≥ 4 doses of romidepsin (evaluable population). Four patients completed 6 cycles of therapy.

Diagnosis and main criteria for inclusion: The main criteria for inclusion in the study included the following: patients were males ≥ 18 years of age; provided written informed consent/authorization; had histologically or cytologically confirmed metastatic prostate cancer with documented progression on hormonal therapy; had measurable disease or bone metastasis; had a rising PSA (minimum of 5 ng/mL); had Karnofsky performance status of ≥ 80%; and had a life expectancy of > 12 weeks.

Test product, dose and mode of administration, batch number: Patients received 13 mg/m^2 of romidepsin intravenously over 4 hours on Days 1, 8, and 15 of each 28-day treatment cycle. The batch numbers of romidepsin were 339330 in the US and 485665 in Europe.

Duration of treatment: Patients received romidepsin for up to six 28-day treatment cycles.

Criteria for evaluation:

Primary endpoint:

The primary endpoint was the rate of objective disease control, defined as the proportion of patients with confirmed CR, PR, or SD for at least 6 months, as determined by the Response Evaluation Criteria for Solid Tumors (RECIST).

Secondary endpoints:

The secondary endpoints were the following:

Rate of PSA decline by ≥50%

Percentage of PSA decline

Time to PSA progression

Rate and duration of objective disease response

Time to objective disease progression

Rate of Grade 3 and Grade 4 nonhematological toxicity, adverse events (AEs), clinical laboratory data, rate

Name of Company: Gloucester Pharmaceuticals Inc.	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	***(For National Authority Use Only)***

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

Change in pain score on the Memorial Pain Scale for symptomatic patients

Change in performance status

Steady-state concentrations of romidepsin

Efficacy assessments: Objective disease response (CR + PR) and SD were defined according to RECIST. Bone lesions were assessed independently but not classified. Objective disease progression was defined according to the RECIST criteria; bone lesions were considered as progressive if new lesions appeared. The RECIST definitions are presented in Appendix F of the study protocol (Appendix 16.1.1 of this study report).

Duration of objective disease response was defined as the time from the first date of a disease response (CR and PR), which was later confirmed, to the first date of an objective diagnosis of progressive disease (PD) (confirmed PD or PD leading to permanent treatment withdrawal) or date of last study assessment if no disease progression was observed. Time to objective disease progression was defined as the time interval from the initiation of study treatment until the first date an objective diagnosis of PD was documented.

Prostate specific antigen progression was defined as a 25% increase over the baseline PSA level (on study), and an absolute increase of ≥ 5 ng/mL. In patients who experienced PSA decreases, PSA progression was defined as a 25% increase above the nadir, provided that the increase was ≥ 5 ng/mL. Confirmation of PSA progression was required by another evaluation at least 1 week after the initial observation. Time to PSA progression was defined as the time interval from the initiation of study treatment until PSA progression was first documented.

Safety assessments: Safety was evaluated using clinical examination, 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 National Cancer Institute Common Toxicity Criteria (NCI-CTC) grading system (version 2.0).

Pharmacokinetic assessments: Blood samples were taken at each administration of romidepsin (3 hours after the start of the infusion and just before the end of each infusion) for the assessment of pharmacokinetic parameters. Plasma concentrations of romidepsin during the course of the study are presented in Appendix 16.1.11.1. These data will be used to determine summary pharmacokinetic parameters for romidepsin over several studies in a combined population pharmacokinetic report, which will be prepared separately from the current study report.

Statistical methods: Results of the study were analyzed by using descriptive statistics. A 2-sided 95% exact confidence interval (CI) was calculated for the primary endpoint of rate of objective disease control (CR + PR + SD for ≥ 6 months).

Patient disposition was summarized for all enrolled patients. Efficacy data were summarized for the evaluable population and limited efficacy endpoints were analyzed using the as-treated population. Demographics and baseline characteristics, the extent of exposure to romidepsin, and safety data were presented in tabular summaries for the as-treated population. Results for individual patients were shown in data listings.

Name of Company: Gloucester Pharmaceuticals Inc.	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	***(For National Authority Use Only)***

Summary and Conclusions

Efficacy Results:

Primary efficacy endpoint

The rate of objective disease control (CR + PR + SD for ≥ 6 months) was 12% (3 of 25 patients) in the evaluable population and 8.6% (3 of 35 patients) in the as-treated population. No patients achieved CR during this study, and 2 patients (8.0% in the evaluable population) experienced best responses of PR.

Secondary efficacy endpoints

Two of 24 patients in the evaluable population had a confirmed PSA decline of ≥ 50%. These 2 patients, and , also experienced best responses of PR as determined by RECIST.

The mean (± standard deviation) best percent change from baseline PSA levels in the evaluable population was 43.7% (67.7%).

The median times to PSA progression were 31 days (range, 28 to 110 days) for the evaluable population and 28 days (range, 14 to 110 days) for the as-treated population.

The median times to objective disease progression were 56 days (range, 42 to 186 days) in the evaluable population and 49.5 days (range, 6 to 186 days) in the as-treated population. Of the 25 patients in the evaluable population, 14 had PD at last assessment. Eleven patients (9 who had SD, and 2 who had PR) did not have evidence of disease progression at last assessment.

Overall, the majority (19 of 25 patients; 76%) of patients with data available experienced no improvement from baseline in pain scores. Improvement from baseline to Cycle 2 Day 1 in pain scores was seen in 4 patients.

Among 35 patients in the as-treated population, 2 patients experienced improvements in Karnofsky performance score (patient from 80 at screening to 100 at the final study visit; patient from 90 at screening to 100 at the Cycle 1 Day 15 visit). Twenty patients experienced no overall change, and 13 patients experienced overall reductions from screening assessment to final study visit.

Pharmacokinetic results: Plasma concentrations of romidepsin from patients in this study are shown in Appendix 16.1.11.1. These data will be used to determine summary pharmacokinetic parameters for romidepsin over several studies in a combined report, which will be prepared separately from the current study report.

Safety Results:

Safety results that are relevant to the determination of romidepsin tolerability include the following:

No patients died during the study

All 35 patients in the as-treated population experienced AEs and treatment-related AEs during the study. The majority of AEs experienced by patients were considered by the investigator to be mild or moderate in intensity.

The most frequently experienced AEs were nausea in 30 of 35 patients (85.7%), fatigue in 28 patients (80.0%), vomiting NOS in 23 patients (65.7%), and anorexia in 20 patients (57.1%).

Adverse events occurred most frequently in the following system organ classes (SOCs): gastrointestinal disorders in 34 of 35 patients (97.1%); general disorders and administration site conditions in 31 patients (88.6%), metabolism and nutrition disorders in 25 patients (71.4%); blood and lymphatic system disorders in 21 patients (60.0%); investigations in 20 patients (57.1%); and nervous system disorders in 19 patients (54.3%).

Name of Company: Gloucester Pharmaceuticals Inc.	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	***(For National Authority Use Only)***

Ten of 35 patients (28.6%) experienced AEs of Grade 3 toxicity according to the NCI CTC, Version 2. No patient experienced a Grade 4 AE. The most frequently occurring Grade 3 AEs were fatigue, nausea, and vomiting NOS each in 2 of 35 patients (5.7%). The Grade 3 events of fatigue, nausea, and vomiting NOS were considered related to treatment with romidepsin.

Eight of 35 patients (22.9%) experienced SAEs. Six patients experienced SAEs that were considered treatment-related (ie, definitely, probably, or possibly related). Treatment-related SAEs included ECG T wave inversion in patient ; pain in extremity in patient ; vomiting NOS and nausea in patient ; vomiting NOS in patient ; constipation in patient ; and ventricular arrhythmia NOS in patient .

Eleven of 35 patients (31.4%) experienced AEs leading to discontinuation of romidepsin treatments. Eight patients had treatment-related AEs that resulted in discontinuation; for 3 of these 8 patients; the AE also was considered to be serious. Treatment-related AEs that led to discontinuation included the following: abnormal ECG ST segment in patient ; ECG ST segment depression and ECG T wave inversion in patient ; thrombocytopenia, nausea, leukopenia NOS, neutropenia, vomiting NOS, and ECG change NOS in patient . Additional treatment-related AEs that led to discontinuation were constipation, nausea, fatigue, and weight decrease in patient ; fatigue and anorexia in patient ; ventricular arrhythmia NOS in patient ; fatigue, anorexia, and nausea in patient ; and nausea and vomiting NOS in patient .

Dose modifications, delays, or missed doses due to AEs were required for 20 of 35 patients (57.1%). Eight of 35 patients (22.9%) experienced cardiac AEs, 7 of 35 patients (20.0%) experienced constitutional AEs, and 3 of 35 patients (8.6%) experienced hematological AEs that resulted in dose modifications or delays. Gastrointestinal AEs caused dose modifications in 2 of 35 patients (5.7%). The dosing modifications included missed doses in 13 patients, dose reductions in 9 patients, and delay in dosing in 3 patients.

Thirteen of 35 patients (37.1%) experienced Grade 3/4 nonhematological toxicities. These toxicities were predominantly at the Grade 3 severity level. Three of 35 patients (8.6%) had Grade 4 hematological toxicities, and no patients had neutropenic fever or sepsis.

No patients had abnormal multiple-gated acquisition (MUGA) scan results during this study.

Conclusions:

Evidence of romidepsin antitumor activity was seen in patients with androgen-independent, metastatic prostate cancer, as determined by the rates of objective disease control and PSA declines of ≥ 50%. Two patients experienced best overall responses of PR and achieved PSA declines of ≥ 50% in this study. Nine patients experienced best responses of SD and 14 patients experienced best responses of PD in the evaluable analysis set. In order to determine the effectiveness of romidepsin therapy in comparison to other available therapies for prostate cancer, additional studies, including combinations, would be needed that should include survival time to event assessments and a larger patient population when compared with the current study.

Most patients experienced mild or moderate AEs of nausea, fatigue, vomiting, or anorexia. Severe AEs (grade 3) were experienced by 10 patients, and 6 of these patients experienced Grade 3 AEs that were considered related to romidepsin therapy. The most frequently occurring Grade 3 AEs were fatigue, nausea, and vomiting NOS. The Grade 3 fatigue, nausea, and vomiting NOS events were each experienced by 2 patients, and these events were considered to be treatment related.

Eleven patients discontinued study drug because of AEs. Overall, the most common AEs leading to romidepsin discontinuation were nausea in 4 patients, fatigue in 3 patients, and vomiting and anorexia each

Name of Company: Gloucester Pharmaceuticals Inc.	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	***(For National Authority Use Only)***

in 2 patients. For most patients (7 of 11 patients), times of onset were early (ie, during the first 2 weeks of therapy) for AEs that led to discontinuation of romidepsin therapy.

No patient died during the study. Other SAEs were reported by 8 patients and most were reports of in-patient hospitalization. Six patients experienced at least 1 SAE that was considered by the investigator to be treatment-related, including nausea and vomiting (2 patients each) and single reports of ECG T-wave inversion, pain in extremity, constipation, and ventricular arrhythmia. Study drug was permanently discontinued because of a treatment-related SAE for 2 of these 6 patients. All treatment-related SAEs were reported to be resolved by last follow-up.

Date of the report: 29 February 2008