## 2. SYNOPSIS

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**Title of Study:**

An Open-Label, Single-Arm Rollover Study for Subjects Who Participated in Other Romidepsin Protocols.

**Principal Investigator:**

**Investigators:**

**Study center(s):**

**Publications (reference):** None

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| **Studied period (years):**<br>Date first patient enrolled: 23 May 2011<br>Date last patient completed: 05 Sep 2012 | Phase of development: N/A |

**Objectives:**

Primary: The primary objective of the study was to allow access to romidepsin for subjects who received romidepsin in other studies and for subjects whom the investigator felt could benefit from continued treatment with romidepsin.

Secondary: The secondary objective of the study was to evaluate the safety of intravenous (IV) infusion of romidepsin in subjects who received romidepsin in other studies.

**Methodology:**

This rollover study was intended to provide access to romidepsin for subjects who participated in and then discontinued from other studies of romidepsin monotherapy sponsored by Celgene Corporation or Gloucester Pharmaceuticals (hereafter referred to as the "preceding romidepsin study") and who in the opinion of the investigator could have benefited from continued treatment with romidepsin. Subjects from preceding romidepsin studies ROMI-ADVM-001, ROMI-ADVM-002, and GPI-06-0002 were eligible for this study; however, subjects from the ROMI-ADVM-001 and ROMI-ADVM-002 studies finally rolled over. Subjects from the GPI-06-0002 study did not rollover as this study did not close. The primary study

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endpoint was safety (type, frequency, severity and relationship of adverse events [AE] to study drug) as efficacy could not be assessed due to the absence of subjects from study GPI-06-0002.

This study was an open-label, single-arm study divided into a Screening Period, Treatment Period, and Follow-up Period.

Each subject was required not to have had anti-cancer treatment other than romidepsin from the time of discontinuation from the preceding romidepsin study to participation in this rollover study. Use of steroids for purposes other than cancer treatment (eg, as an antiemetic) was permitted.

Screening Period

Subjects commenced screening procedures within 7 days of last dose from their previous study. Within 3 weeks prior to dosing on this study, subjects signed an informed consent document (ICD) and underwent screening procedures and assessments. Assessments conducted in the preceding romidepsin study could be used if they were the same assessments specified in this rollover study and fell within the required time frame. Screening assessments included assessment for inclusion/exclusion criteria, baseline medical history and details of prior therapies. Safety assessments included recording of AEs, physical examination, measurement of vital signs assessment, hematological/serum chemistry laboratory screening, recording of concomitant medications/procedures, baseline electrocardiogram (ECG) assessments, pregnancy testing for females of child bearing potential (FCBP), and assessment of the Eastern Cooperative Oncology Group (ECOG) performance status.

Treatment Period

Once eligibility criteria were met in the Screening Period, subjects entered the Treatment Period. Subjects were evaluated at the clinic on Day 1 (ie, predose) for baseline assessments and reconfirmation of eligibility. Prior to romidepsin infusion, antiemetic drugs could be given prophylactically to mitigate nausea and vomiting. In addition, serum potassium (K) and magnesium (Mg) levels were to be determined prior to romidepsin infusion. Supplements were to be administered to subjects if their K was $< 3.8$ mmol/L or Mg was $< 0.85$ mmol/L. These tests were repeated to ensure K was $\geq 3.8$ mmol/L and Mg was $\geq 0.85$ mmol/L prior to dosing, if the original values were outside the normal range.

The dose of romidepsin was dictated by the preceding romidepsin study in which a subject had previously participated, taking into account any dose-limiting toxicities (DLT) that occurred during their last dose of romidepsin. For some subjects, a switch to a 1-hour infusion was permitted under certain stipulations.

Safety was monitored throughout the study from the time informed consent was obtained to 28 days after the last dose of romidepsin. For this reason, the same data or event were reported in two studies (this study and the preceding study) due to overlap. If a subject had a DLT, then the dose of romidepsin was adjusted.

Efficacy assessments were initially planned for any subjects who were previously enrolled in the GPI-06-0002 study, however, none of these subjects rolled over into the present study as the GPI-06-0002 study did not close. Subjects had to remain in this study until disease progression or until a withdrawal criterion was met.

Follow-up Period

Follow-up visit assessments were performed up to 28 days after the last dose of study drug. Subjects who

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discontinued due to an AE were followed until resolution of the AE or return to baseline.

If a subject discontinued from the study for any reason, the subject underwent the required assessments in the closeout period prior to discontinuation.

**Number of Subjects (planned and analyzed):**

Planned: 32 evaluable subjects.

Analyzed: 19 subjects were enrolled at three investigational sites (two sites in the USA and one site in the UK). All 19 subjects received at least one dose of study drug and were included in the intent-to-treat (ITT) population. As the ITT population was identical to the safety population, the same 19 subjects also formed the safety population.

**Diagnosis and main criteria for inclusion:**

- Subjects who participated in and fulfilled the inclusion and exclusion criteria of one of the previous romidepsin clinical studies (ROMI-ADVM-001 and ROMI-ADVM-002)
- Investigator believed continued romidepsin treatment would benefit subject
- Subjects understood and voluntarily signed an ICD prior to any study-related assessments/procedures
- Subjects were able to adhere to the study visit schedule and other study requirements
- Subjects were required to have a negative urine or serum pregnancy test for FCBP.

**Test product, dose and mode of administration, batch number:**

Identity of the Product:

Romidepsin was provided as dual packs containing one vial of romidepsin for injection and one vial of diluent. Each drug vial contained a lyophilized powder of 10 mg of romidepsin and 20 mg of povidone, United States Pharmacopeial Convention (USP) (used as a bulking agent). The diluent vial contained 2 mL of a 4:1 mixture of propylene glycol and ethanol. Following reconstitution, the final drug concentration was 5 mg/mL. The stock solution was diluted using aseptic technique in 500 mL 0.9% sodium chloride injection USP (0.9% saline) for subjects with a body surface area (BSA) ranging from 1.35 $m^2$ to 2.79 $m^2$, and in 1000 mL 0.9% saline for subjects with a BSA of $\geq$ 2.80 $m^2$.

Dose and Mode of Administration:

The dose of romidepsin was dictated by the preceding romidepsin study in which the subject had previously participated, taking into account any DLTs that occurred during their last dose of romidepsin in the preceding romidepsin study, as follows:

- Subjects from ROMI-ADVM-001: 8 mg/$m^2$ over 4 hours on Days 1, 8 and 15 of a 28-day cycle. A 1-hour infusion at 10 mg/$m^2$ was permitted.
- Subjects from ROMI-ADVM-002: 14 mg/$m^2$ over 4 hours on Days 1, 8 and 15 of a 28-day cycle. A 1-hour infusion at 10 mg/$m^2$ was permitted.

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**Duration of treatment:**

The overall study duration was estimated at 5 years with approximately 24 weeks participation for each subject anticipated.

**Reference therapy, dose and mode of administration, batch number:**

Not applicable.

**Criteria for evaluation:**

Safety: physical examination (included height, weight, spleen, liver, lymph node involvement, and ECOG status); vital signs (included blood pressure, pulse, temperature); 12-lead ECGs; concomitant medications/procedures; hematology/chemistry laboratory evaluations; pregnancy testing (FCBP only); and AEs.

**Statistical methods:**

Study Populations: The safety population included all enrolled subjects who received at least one dose of study drug. The ITT population was identical to the safety population.

Presentation of Data: Baseline characteristics/demographics, subject disposition, drug exposure, and protocol deviations were summarized using descriptive statistics or frequency tabulations as appropriate.

Safety Analysis: The primary endpoint was the safety profile of romidepsin as defined by the type, frequency, severity and relationship of treatment-emergent adverse events (TEAE) to study drug, vital sign measurements, physical exam findings, clinical laboratory information, ECG interpretations, and concomitant medications.

**SUMMARY – CONCLUSIONS**

Subject Disposition

Twenty one subjects were screened. Two subjects were considered as screen failures. Although both subjects signed informed consent, neither took study drug. A total of 19 subjects were therefore included in the analysis set at the three study sites. The first subject entered the study on 23 May 2011. All 19 subjects discontinued from treatment. The primary reasons for treatment (and follow-up) discontinuation for the 19 subjects were as follows: 16 subjects withdrew due to disease progression while three subjects withdrew for other reasons. The last subject withdrew from the study on 05 Sep 2012.

Subject Demographics/Characteristics

The median age of subjects was 64.2 years with approximately a 50% split in female and male subjects. The majority of subjects were Caucasian (78.9%) with an ECOG performance status score of 0 or 1. All subjects had at least one medical history and the most common disorders were gastrointestinal disorders (63.2%), mainly nausea. All 19 subjects in the Safety Population were taking at least one concomitant medication during the study and those medications were consistent with the underlying medical conditions that the subjects had at baseline or with medications that are used to maintain good health. The most frequently used concomitant medications in the Safety Population were the serotonin (5-HT3) antagonists (94.7%): ondansetron (Zofran®) (47.4%); generic granisetron (42.1%); granisetran;

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granisetron (Kytril®), ondansetron (generic), and palonosetron (Aloxi®) (each in 5.3% of subjects). Fifteen (78.9%) subjects were receiving concomitant corticosteroid therapy: dexamethasone (68.4%); prednisone (10.5%); dexamethasone (Decadron®), generic dexamethasone prophylaxis, and methylprednisolone (Medrol dose pak) (each in 5.3% of subjects).

**SAFETY RESULTS:**

Extent of Exposure

All 19 subjects in the ITT/Safety Population underwent dosing schedule modifications per protocol. The mean duration of exposure was 80.7 days (standard deviation [SD] of 76.3) with a mean average daily dose of 3.6 mg/day and cumulative dose of 138.2 mg, respectively. The mean actual dose intensity over the reported duration of exposure was 9.9 mg/m$^2$/dose.

Treatment-Emergent Adverse Events by Frequency

Eighteen (94.7%) subjects experienced at least one TEAE. The most frequently reported TEAEs in the Safety Population included fatigue (57.9%); and constipation, decreased appetite, and nausea (26.3% in each).

Treatment-Emergent Adverse Events by Severity

Overall, there were 11 (57.9%) subjects who had at least one National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 TEAE in the Safety Population (N = 19). None of the subjects in the Safety Population experienced a Grade 4 TEAE. The most frequently reported Grade 3 TEAEs were fatigue (15.8%); dehydration, and dyspnea (10.5% in each).

Treatment-Emergent Adverse Events by Causality

Overall, there were 14 (73.7%) subjects who experienced at least one TEAE that was considered related to romidepsin therapy. The most common related TEAEs were fatigue (57.9%), nausea (26.3%), decreased appetite (21.1%); diarrhea, asthenia, and vomiting (15.8% in each).

Deaths

There were no deaths reported within 28 days after the last study drug dose. However, four off-treatment deaths were noted during follow-up; the causes of which were attributed to progression of underlying disease. There were no TEAEs that led to death during this study.

Other Serious Adverse Events

At least one serious TEAE was reported in six (31.6%) subjects. The reported serious TEAEs (by preferred term [PT] within [SOC]) were as follows:

- Gastrointestinal disorders (two subjects): constipation, diarrhea, nausea, vomiting (each in one subject)
- Infections and infestations (two subjects): pneumonia and sepsis (each in one subject)

All these serious TEAEs had a severity rating of Grade 3.

One (Subject ) of the six subjects who experienced serious TEAEs had at least one serious treatment-related TEAE. Romidepsin-related treatment-emergent SAEs experienced by this subject were in the gastrointestinal disorders SOC and were as follows: diarrhea, nausea, and vomiting.

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Other Significant Adverse Events

There was one subject (Subject ) who experienced a TEAE of metastatic carcinoma of the bladder that led to study drug discontinuation. None of the 19 subjects in the Safety Population experienced study drug-related TEAEs that led to discontinuation of study drug.

At least one TEAE that led to dose reduction/interruption was reported in 7 (36.8%) subjects. The most frequently reported TEAEs that led to dose reduction/interruption (by PT within SOC) were as follows:

- Blood and lymphatic disorders (three subjects [15.8%]): anemia (two subjects [10.5%]) and thrombocytopenia (one subject [5.3%])
- General disorders and administration site conditions (three subjects [15.8%]): fatigue (two subjects [10.5%]) and pyrexia (one subject [5.3%])

Four (21.1%) subjects experienced at least one study drug-related TEAE that led to dose reduction/interruption. The most frequently reported study drug-related TEAEs that led to dose reduction/interruption (by PT within SOC) were as follows:

- Blood and lymphatic disorders (two subjects [10.5%]): anemia and thrombocytopenia (one subject each [5.3%])
- General disorders and administration site conditions (two subjects [10.5%]): fatigue (two subjects [10.5%])

Clinical Laboratory Evaluations, Vital Signs, and Electrocardiogram Assessments

Laboratory Values Over Time

The mean platelet count at baseline was $218.6 \times 10^9$/L ($\pm$ $105.91 \times 10^9$/L). The most notable change in mean platelet count, pre- and post visit, was observed at Cycle 1 Day 8 with a value of $-173.3 \times 10^9$/L ($\pm$ $127.68 \times 10^9$/L). During the first four cycles, the mean values for platelets remained higher than $175 \times 10^9$/L, after which the number of subjects was too small to draw any conclusions. The mean platelet count at treatment discontinuation was $191.6 \times 10^9$/L ($\pm$ $88.0 \times 10^9$/L). There were no important trends over time noted in any of the serum chemistry parameters.

Individual Subject Changes

Analysis of individual subject shifts from baseline to Grade 3/4 levels post baseline in hematologic parameters revealed one subject (5.3%) (Subject ), who had shifts in platelet count from normal to Grade 3 post baseline. One subject (5.3%) had shifts in white blood cell (WBC) count from normal to Grade 4 post baseline. However, no important changes from baseline in mean WBC counts was noted. Analysis of individual subject shifts from baseline to Grade 3/4 levels post baseline in chemistry parameters revealed one subject (5.3%) (Subject ), who had shifts in glucose levels from Grade 2 at baseline to Grade 3 post baseline. However, this did not lead to a change in mean glucose level. One subject (5.3%) had shifts in magnesium levels from Grade 1 to Grade 3 levels post baseline. This did not lead to a change in mean magnesium level. One subject (5.3%) had shifts in sodium levels from Grade 1 to Grade 3 levels post baseline. This did not lead to a change in mean sodium level.

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Individual Clinically Significant Abnormalities

Hematology abnormalities were most frequently observed at Cycle 3 Day 15 visit. Overall, there was one (5.3%) subject (Subject ) with at least one post baseline clinically significant abnormal laboratory value in hematology. This subject had a clinically significant drop in platelets to NCI CTCAE Grade 3 with a platelet count of $32.0 \times 10^9$/L (normal range: $140 \times 10^9$/L to $440 \times 10^9$/L). This abnormality appears to have been only transient as platelet count increased to $499 \times 10^9$/L following the Cycle 4 Day 1 visit. No clinically significant NCI CTCAE Grade 4 laboratory abnormalities in hematology were observed in this study. Chemistry abnormalities were most frequently observed at the Cycle 2 visit. Overall, there were two subjects (10.5%) with at least one post baseline clinically significant abnormal laboratory value in serum chemistry: Subject with clinically significant increases in glucose levels (NCI CTCAE Grade 3: 14.64 mmol/L on Cycle 2 Day 1 and 13.98 mmol/L on Cycle 2 Day 8; normal range: 3.58 to 6 mmol/L). However, this subject had elevated glucose levels (Grade 2) at baseline. Subject was noted with clinically significant decreases in sodium levels (NCI CTCAE Grade 3: 129 mmol/L; normal range: 135 to 145 mmol/L) on Cycle 1 Day 8 of romidepsin therapy. No clinically significant NCI CTCAE Grade 4 laboratory abnormalities in serum chemistry were observed in this study.

Vital Signs

A mean change in systolic blood pressure from baseline was observed at Cycle 3 Day 1 and treatment discontinuation of -8.2 mmHg (± 16.59) and -2.8 mmHg (± 21.84), respectively. A mean change in pulse rate from baseline was observed at Cycle 3 Day 1 and treatment discontinuation: 10.3 bpm (± 10.31) and 7.5 bpm (± 13.98), respectively.

Electrocardiograms

Abnormal clinically significant ECG findings from baseline to the end of treatment were not observed in this study. A mean change in QTcF data from baseline was observed at Cycle 3 Day 1 of 19.6 msec (± 20.84). Overall, the worst mean post baseline change was 28.9 msec (± 15.63). None of the 19 subjects in the Safety Population had abnormal/clinically significant ECG changes.

**CONCLUSION:**

In conclusion, romidepsin, administered at a dose of 8 mg/m$^2$ and 14 mg/m$^2$ on Days 1, 8, and 15 of a 28-day cycle, was well tolerated in subjects with a variety of advanced cancers. The safety profile was comparable to those observed in previous clinical studies.

Date of the report: 23 Aug 2013