# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-991**

# MEDICAL REVIEW(S)

# Interdisciplinary Review Team for QT Studies
# Response to a Request for Consultation: NDA Review

| | |
|---|---|
| **NDA** | 21,991 |
| **Brand Name** | Zolinza |
| **Generic Name** | Vorinostat |
| **Sponsor** | Merck & Co., Inc. |
| **Indication** | Advanced, Refractory, Cutaneous T-Cell Lymphoma |
| **Dosage Form** | 100 mg immediate release hard gelatin capsules |
| **Therapeutic Dose** | 400 mg once daily administered with food |
| **Duration of Therapeutic Use** | Treatment cycle |
| **Maximum Tolerated Dose** | 400 mg once daily administered with food |
| **Application Submission Date** | April 28, 2006 |
| **Review Classification** | Priority |
| **Date Consult Received** | June 29, 2006 |
| **Date Consult Due** | August 11, 2006 |
| **Clinical Division** | Division Drug Oncology Products |
| **PDUFA Date** | October 29, 2006 |

## 1.0 RECOMMENDATION

It is recommended that the Sponsor conduct a clinical trial to evaluate the impact of vorinostat on QT interval. This could be carried out as a Phase 4 commitment.

## 2.0 SUMMARY OF FINDINGS

The Sponsor has not performed a well-designed and well-controlled study to assess the impact of vorinostat on QT interval.

The Sponsor submitted an analysis of pooled data from three Phase 1 and two Phase 2 studies. This report suggests that there may be a forty (40) millisecond increase in QTc from baseline with vorinostat dosing. Additionally, there were several observations of QTc exceeding 550 milliseconds. The Sponsor denied the reviewer's request for data from this analysis.

Based on an exposure-response analysis performed by the reviewer on data from a Phase 1 food effect study, there may be an 11-millisecond (upper 95% predicted value at mean maximum observed concentration) increase in QTc from baseline for vorinostat at 400 mg. But, this result is based on data from a Phase 1 study that has a number of limitations: (1) few subjects were studied, (2) no placebo or positive control was used, (3) ECGs were not taken at Cmax for drug or metabolite, (4) at most, 1-2 ECGs were recorded after steady state dosing, (5) there was no consistent measure of baseline effect in each subject, and (6) results are confounded by different meal instructions provided on different study days.

## 3.0 GOAL OF THE REVIEW

The purpose of this review is to assess the impact of vorinostat on QT interval based on information provided in the submission.

## 4.0 BACKGROUND

### 4.1. Indication

Vorinostat is intended to treat advanced, refractory, cutaneous T-cell lymphoma (CTCL). CTCL is a rare type of malignant non-Hodgkin's lymphoma.

### 4.2. Drug Class

Vorinostat is a potent inhibitor of histone deacetylase (HDAC) activity. A potential mechanism for the anti-tumor action of vorinostat is that inhibition of HDAC activity, and subsequent accumulation of acetylated histones, leads to the activation of genes whose expression causes the observed antiproliferative effects.

### 4.3. Regulatory Classification

This drug has Priority Review classification.

### 4.4. Market approval status

This drug is not approved for use for any indication in the United States, nor is approved for use for any indication in any other country.

## 5.0 DRUG INFORMATION

### 5.1. Preclinical Information

The sponsor evaluated vorinostat for QT effects in 2 nonclinical assays: hERG channels expressed in mammalian cells and QTc in conscious telemeterized dogs. Study reports provided by the sponsor were evaluated.

- Vorinostat at 100 and 300 μM did not affect hERG channels (voltage clamp) expressed in Chinese hamster ovary cells. The highest concentration tested was limited by solubility. A positive control was not utilized to demonstrate assay sensitivity.

- Vorinostat tested negative for QTc effects in conscious, telemeterized dogs (n = 4) given single doses of 20, 60 and 160 mg/kg vorinostat in gelatin capsules. This was an ascending dose study, with ECG, heart rate and blood pressure measured for 24 hrs after dosing. QTc was calculated using Fredericia's methodology. Vorinostat (60 and 160 mg/kg) increased heart rate by approximately 25% (unrelated to dose), decreased PR interval by 9% (unrelated to dose), and decreased QT interval by 5 and 12%, respectively. Vorinostat did not affect QTc. Plasma concentration of vorinostat at 2 hours after administration of 160 mg/kg was similar to the plasma Cmax in humans given the therapeutic dose of 400 mg daily for 22 days ($0.963 \pm 0.349$ μM in animals vs 1.13 μM in humans); whereas the plasma levels of metabolites (L- 000341257 and L-001302381) were less in animals than in humans. The assay sensitivity for QT effects was not provided.

The nonclinical safety factor for QTc effects based on lack of effect at the highest dose tested in conscious dogs was $\geq 1$.

### 5.2. Clinical Pharmacology

The following table summarizes the key features of vorinostat's clinical pharmacology.

| | | |
|---|---|---|
| **Therapeutic dose** | 400 mg once daily administered with food | |
| **Maximum tolerated dose** | 400 mg once daily administered with food | |
| **Principal adverse events** | Thrombocytopenia, dehydration, diarrhea, nausea, vomiting | |
| **Absorption** | Absolute Bioavailability | F = 42.5±16.1% |
| | Tmax | 0.5-14 hours (1st peak of multiple peaks) |
| **Distribution** | $V_z$ | 150±51 L (i.v. dose); extensive distribution |
| | $V_z/F$ | 534±346 L (oral dose) |
| | % bound | 71% (moderate protein binding) |
| **Elimination** | Route | •Primarily metabolism<br>•Renal excretion <1% of dose |
| | Terminal t½ | •Parent: 1.7±1.0 hours<br>•*O*-glucuronide: Range 1.9-2.7 hours<br>•4-anilino-4-oxobutanoic acid: 7-11 hours |
| | CL/F | 4.4±2.7 L/min |
| | Accumulation: $\frac{AUC_{24\ (Day\ 28)}}{AUC_{24\ (Day\ 5)}}$ | •Parent: 1.2<br>•*O*-glucuronide: 0.88<br>•4-anilino-4-oxobutanoic acid: 1.4 |
| **Range of linear PK** | Dose proportional increases in AUC: 200 to 600 mg | |
| **Intrinsic Factors** | Age | No studies conducted |
| | Sex | No studies conducted |
| | Race | No studies conducted |
| **Extrinsic Factors** | Drug interactions | •No *in vivo* drug interaction studies<br>•Induces CYP 1A2 *in vitro*<br>•Weak inhibitor of CYP 3A4 *in vitro* |
| | Food Effects | •Meals increase exposure 38%<br>•Meals delay Tmax 2.5 hrs<br>•Product label: to be taken with food |
| **High Exposure scenario** | •Expected in hepatic impairment<br>•Impact on exposure unknown since study not conducted | |

**Table 1. Highlights of Clinical Pharmacology.**

## 6.0. SPONSOR'S SUBMISSION

### 6.1. Overview

The Sponsor did not conduct a Thorough QT Study to assess the impact of vorinostat on QT interval.

The Sponsor submitted an exploratory analysis of ECGs collected during a Phase 1 safety study entitled, "A Phase I Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Vorinostat in Patients With Advanced Cancer" (Protocol 008).

The Sponsor also submitted a report on an analysis of pooled ECG data available in three Phase 1 studies and two Phase 2 studies. The report is entitled, "Effect of SAHA on QT Interval in Patients with Advanced Solid Tumors and Hematological Malignancies".

**6.2. Study Design(s)**

**6.2.1. Phase 1 Safety Study (Protocol 008)**

**Synopsis**

•An open-label, non-randomized study in patients with relapsed or refractory advanced cancer.

•Primary objectives: (1) assess the safety and tolerability of vorinostat administered at a dose of 400 mg once daily, (2) characterize the pharmacokinetics after single- and multiple-dose administration, and (3) investigate the effect of food on the pharmacokinetics of vorinostat.

**Design**

•Twenty three (23) patients were enrolled.

•ECGs planned to be measured at:

| | |
|---|---|
| Baseline | Performed anytime between screening visit and Day 1 dosing |
| Day 1 | 2, 6 and 24 hours post dose |
| Day 5 | 2 hours post dose |
| Day 28 | 2 hours post dose |

•Blood for serum pharmacokinetic assays were collected at the following time points:

| | |
|---|---|
| Day 1 | predose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 24, and 48 hours |
| Day 5 | predose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, and 24 hours |
| Day 7 | predose |
| Day 15 | predose |
| Day 28 | predose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, and 24 hours |

•Meal instructions with dosing

| | |
|---|---|
| Baseline | No instructions |
| Day 1 | Fasted |
| Day 5 | High fat meal |
| Day 28 | High fat meal |

•Patients received daily doses of vorinostat until: disease progression, intercurrent illness, unacceptable AE(s), withdrawal of patient consent, or discontinuation at the investigator's discretion.

•Not housed during the study, except for 24 hours post dose on days 1,5,28.

**Results**

•The following table highlights available data:

| Study Day(s) | Dosing Regimen | Number of Subjects with data |
|---|---|---|
| 1 | Single Dose | 23 |
| 5 | Single Dose | 20 |
| 28 | After 22 days of daily dosing | 14 |

**Table 2. Data Provided.**

•The Sponsor computed the change in QTc interval by comparing pretreatment baseline QTc values with protocol specified ECG time points after initiation of vorinostat

treatment (see Table 3). According to this analysis, the drug caused anywhere from a 6.5 second *decrease* to a 7.1 millisecond *increase* in QTc. The confidence intervals on these estimates are wide.

•The Sponsor also computed a categorical summary of QTc intervals (see Table 4 and Table 5). According to this analysis, no patient had a QTc value greater than 500 milliseconds (msec). Two (2) patients had a maximum QTc interval between 481 msec and 499 msec.

•Note that the Sponsor did not separate out baseline effects in these categorical analyses.

| | Summary Statistics | | | Change from Baseline | | |
|---|---|---|---|---|---|---|
| Time | N | Mean (SD) | Median (Range) | Mean (StdErr) | 95% CI for Mean | Median (Range) |
| Baseline | 23 | 426.0 (17.9) | 429.0 (403.0, 457.0) | NA | NA | NA |
| Day 1, 2 hr | 23 | 428.2 (19.3) | 424.0 (400.0, 467.0) | 2.2 (4.2) | (-6.5, 10.9) | 8.0 (-56.0, 34.0) |
| Day 1, 6 hr | 23 | 432.0 (25.6) | 431.0 (397.0, 492.0) | 6.0 (3.1) | (-0.3, 12.4) | 4.0 (-36.0, 35.0) |
| Day 1, 24 hr | 22 | 430.1 (19.9) | 429.5 (404.0, 473.0) | 5.5 (2.5) | (0.3, 10.8) | 4.5 (-18.0, 34.0) |
| Day 5, 2 hr | 21 | 430.5 (21.2) | 428.0 (394.0, 477.0) | 7.1 (2.9) | (1.1, 13.2) | 6.0 (-17.0, 32.0) |
| Day 15, predose | 18 | 418.1 (26.1) | 413.5 (387.0, 476.0) | -3.2 (4.6) | (-12.8, 6.5) | -5.5 (-41.0, 42.0) |
| Day 28, 2 hr | 13 | 414.8 (16.1) | 408.0 (394.0, 450.0) | -6.5 (3.2) | (-13.5, 0.5) | -2.0 (-31.0, 6.0) |
| Day 28, 24 hr | 12 | 419.0 (13.8) | 416.0 (403.0, 447.0) | -1.3 (2.6) | (-7.0, 4.3) | -1.0 (-20.0, 13.0) |
| N =Number of patients; SD = Standard Deviation; StdErr = Standard Error; hr = Hour; NA = Not applicable. | | | | | | |

Data Source: [16.4.2.2]

**Table 3. Analysis of QTc Interval (milliseconds) at Standard Times Post-Dose (Protocol 008).** Note that baseline was defined as the predose (time=0 measurement on Day 1) QTc interval. In the event that a predose ECG was not available, the prestudy QTc interval was used.

| | | Maximum QTc Count (%) | | | |
|---|---|---|---|---|---|
| Treatment | N | ≤450 msec | 451 to 480 msec | 481 to 499 msec | ≥500 msec |
| 400 mg | 23 | 15 (65.22%) | 6 (26.09%) | 2 (8.70%) | 0 (0/0%) |
| N= Number of patients. | | | | | |

**Table 4. Categorical Analysis of Absolute Maximum QTc for Patients.**

| | | Number (Percent) of Patients in Each Category | | |
|---|---|---|---|---|
| Treatment | N[†] | ≤30 msec | >30 and ≤60 msec | >60 msec |
| 400 mg qd x 7d/wk | 23 | 18 (78.3%) | 5[‡] (21.7%) | 0 (0.0%) |
| [†] Includes patients with baseline and at least one postdose measurement. | | | | |
| [‡] AN 0001, AN 0005, AN 0007, AN 0009, AN 0014. | | | | |
| N = Number of patients; qd = Once daily; d = Days; wk = Week. | | | | |

**Table 5. Categorical Analysis of Maximum QTc Change From Baseline.**

### 6.2.2. Analysis of pooled ECG data

**Synposis**

This report describes a series of retrospective analyses undertaken on data available from five clinical trials during which ECGs were collected.

**Design**

•The studies included in the analysis are listed below:

| | |
|---|---|
| CL-01-0101 | A Phase I Clinical Trial of Oral Suberoylanilide Hydroxamic Acid SAHA (MSK 390) in patients with Advanced Solid Tumor and Hematologic Malignancies [MRL PN 006] |
| CL-01-9901 | Phase I Clinical and Pharmacological study of Suberoylanilide Hydroxamic Acid - SAHA (MSK390) in Patients with advanced solid tumors and hematological Malignancies Therapeutic Protocol [MRL PN 010] |
| CL-01-0201 | Phase II clinical Trial of Oral Suberoylanilide Hydroxamic Acid (SAHA) in Patients with —— —— MRL PN 002] |
| CL-01-0202 | Phase II clinical trial of Oral Suberoylanilide Hydroxamic Acid (SAHA) in Patients with Cutaneous T-Cell Lymphoma and Peripheral T-Cell Lymphomas Unresponsive to Conventional Treatment [MRL PN 005] |
| CL-01-0301 | A Phase I clinical Trial of Oral Suberoylanilide Hydroxamic Acid (SAHA) in Patients with Advanced leukemia or Myelodysplastic Syndrome [MRL PN 003] |

**Analysis**

•The Sponsor performed an unpaired analysis of the pre-dose and post-dose data.

•In addition, the Sponsor performed a concentration-response analysis.

•The Bazetts correction for heart rate was used in the analyses.

**Results**

•The report notes that there is no information on dose timing.

•The report notes that ECGs are not available at the same time as concentration data.

•The report further notes the following with respect to evaluating the ECGs:

A total of 627 ECGs were examined. Of these, 131 were judged by the cardiologist to be unsuitable for QT analysis, commonly because the T-waves were too flat or right bundle branch block or atrial fibrillation was present. Of the 496 suitable ECGs, 117 were "baseline" (taken prior to the first SAHA dose) and 379 were "treatment". The QT values in 25 of the ECGs were adjusted by amounts ranging from an 80 msec decrease to a 150 msec increase).

**Unpaired Analysis**

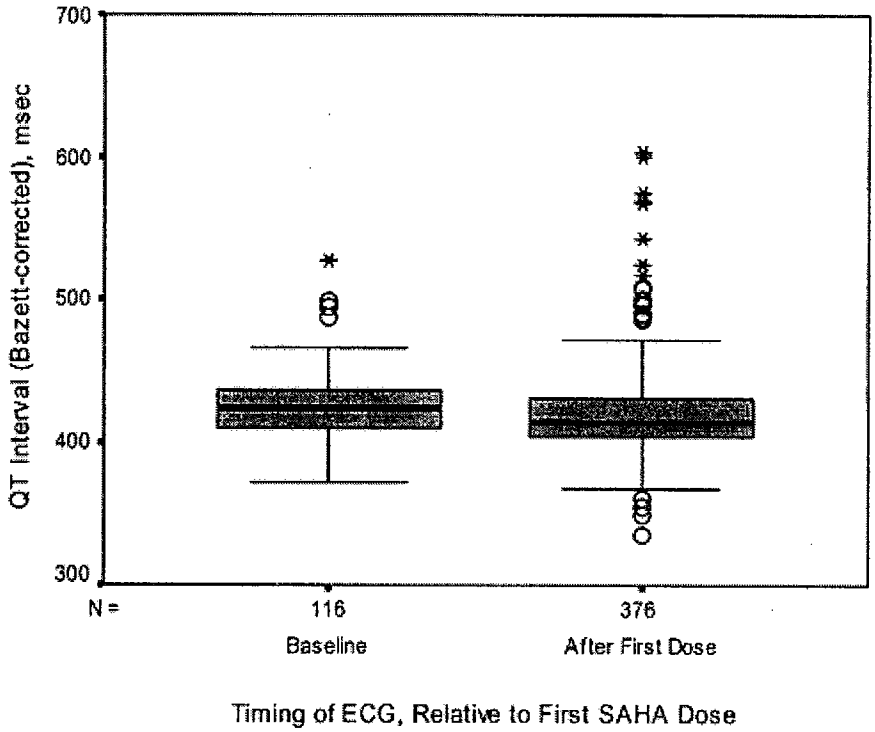


**Figure 1. Distribution of QTcB in ECGs taken at baseline and following first dose.** By ANOVA: QTcB not significantly different after first dose compared to baseline (p=0.153). Although insignificant, the report indicates that QTcB is 4.6 ms lower after first dose.

Reviewer's Comments:
There are more measures of QTcB above 500 milliseconds after the first dose compared to at baseline. Values above 550 ms are of great concern. It would be useful if all of these ECGs could be examined.

**Concentration-Response Analysis**

- In this analysis, the first ECG was taken as the baseline measure.
- Since no dose-timing information were available, the Sponsor used the following approach to determine exposure:

> To obtain the average concentration-vs.-time curve, all IV PK data from both studies were utilized. Because nine different dosing levels were used in the five studies, and since concentrations are assumed to be proportional to dosage, the concentrations from each PK curve were divided by the total dose of SAHA administered. The total dose (in mg) was calculated by multiplying the dosing level (in $mg/m^2$) by the patient's body surface area (in $m^2$). The following graphs show the individual concentration-vs.-time curves, with separate plotting symbols used to distinguish between dose level and between protocols

The scaled concentrations were combined and fit to a model that assumed an initial increase with first-order (exponential) approach to a plateau during the infusion, followed by first-order (exponential) decline after the infusion. The resulting fitted model was:

```
C = 4.2 * Total Dose * ( 1 - Exp(- t / 12.3 ) ) for t≤120 minutes
C = 4.2 * Total Dose * Exp(- (t - 120) / 12.3 ) for t>120 minutes
```

It is recognized that concentrations estimated from a general model such as this are not as reliable as those obtained by direct interpolation of a subject's actual SAHA concentrations observed immediately before and after an ECG collection. This process produces only a rough approximation to the SAHA concentration at any particular time, and may under- or over-estimate the subject's actual concentration at the time of ECG collection.

Despite pooling data from five studies, the following note from the Sponsor indicates that few data were available for this analysis.

The 37 usable data points (16 from the PK-interpolation approach, and 21 from the Chemo-and-Pooled-PK-Model approach) were combined, and are displayed (with the two protocols indicated by separate plotting symbols) in the following graph:

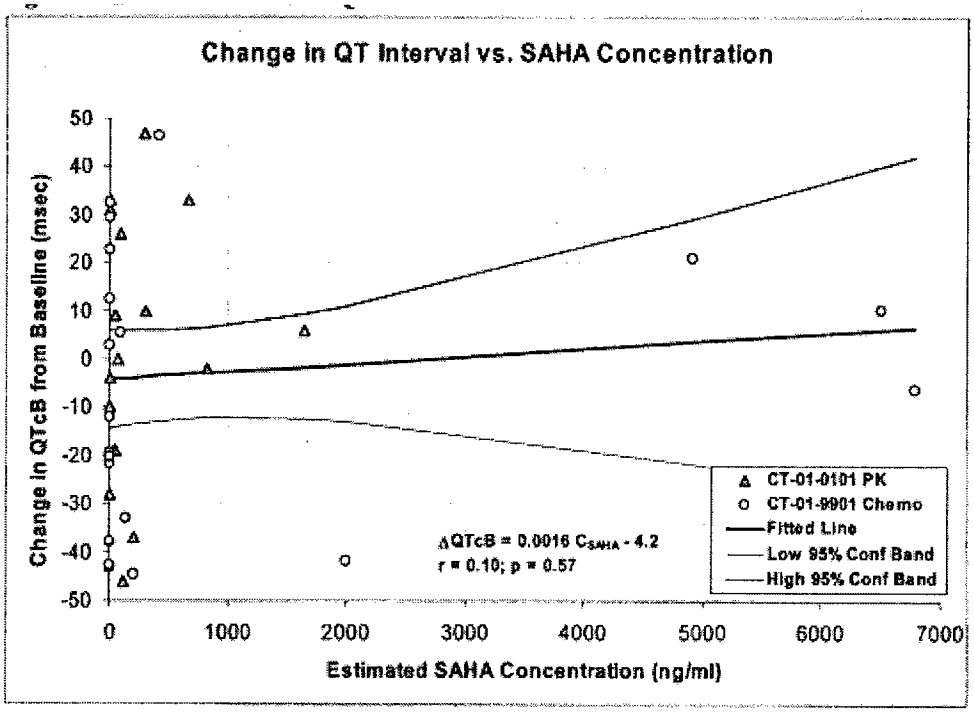


**Figure 2. Result of the Sponsor's Concentration-Response Analysis.**

The Sponsor notes that the impact on QTc could be up to 40 milliseconds:

From the upper confidence band, we may infer an upper limit to the likely magnitude of the effect: the prolongation of QTcB above baseline at a SAHA concentration of 7,000 ng/ml probably does not exceed 40 msec.

## 7.0. REVIEWERS' ASSESSMENT OF DATA

### 7.1. Protocol 008

**Reviewer's analysis**

A linear, mixed effects concentration-response model was fit to the Phase 1 data. The upper 95% confidence value of slope was used to predict effect on QTc at mean Cmax.

According to this analysis, vorinostat is associated with up to an 11 millisecond increase in QTc interval from baseline at the mean maximum concentration for subjects receiving the maximum tolerated dose when the upper 95% confidence value of slope is used to calculate drug effect (Figure 3 and Figure 4).

By the same method of analysis, vorinostat's two metabolites each are associated with less than a 5 millisecond increase in QTc from baseline (Figure 5 and Figure 6).

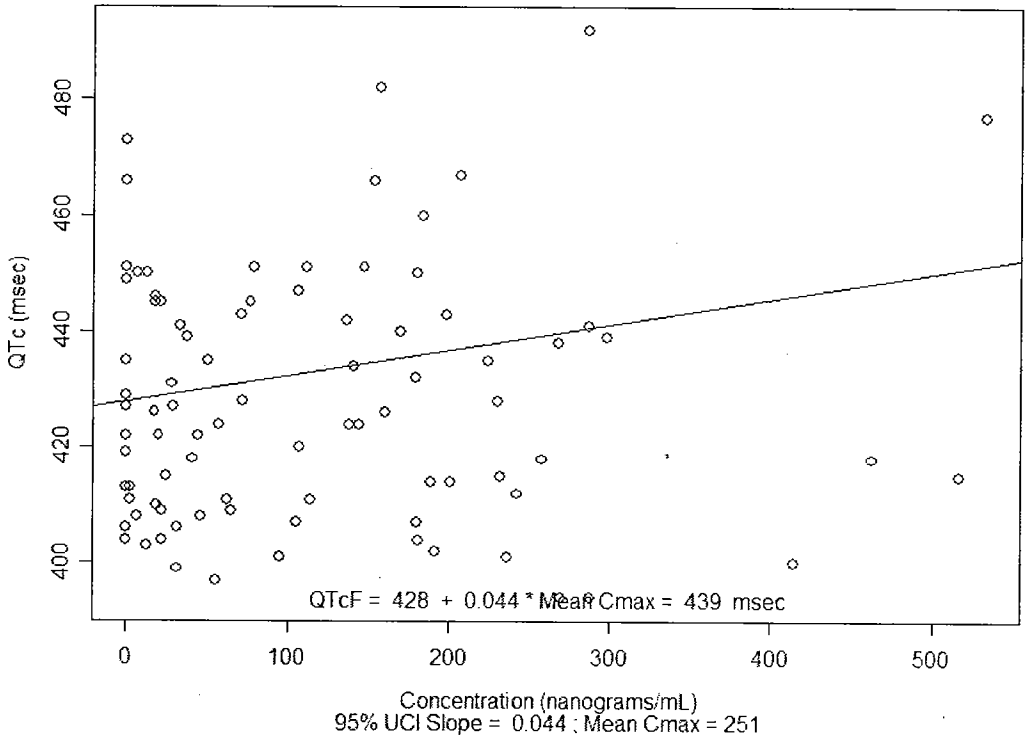


**Figure 3. Linear Mixed Effects Model of Concentration-QTc Data for Parent Drug.** Model suggests that there is an 11 millisecond increase from baseline in Fridericia corrected QT interval at mean Cmax when the upper 95% confidence interval value of slope is used to predict response.

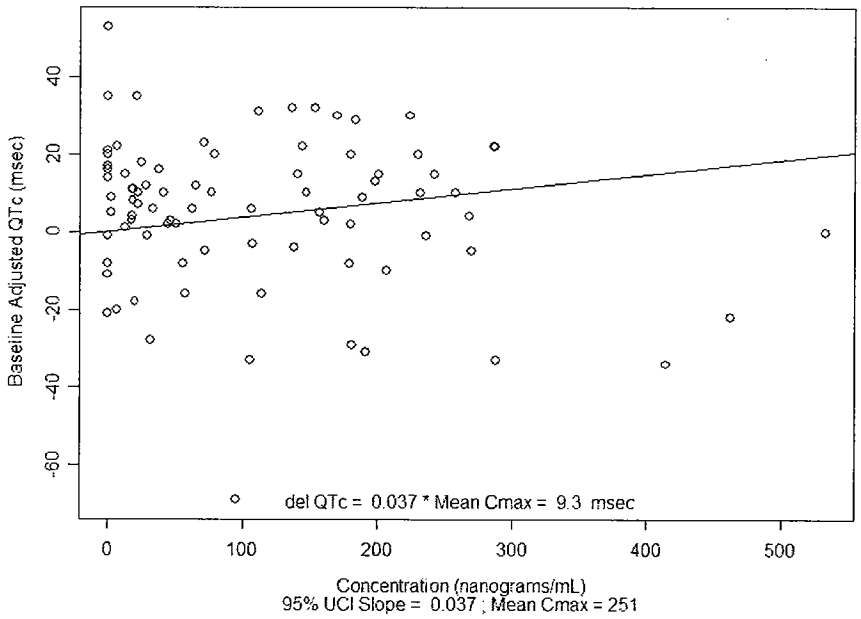


**Figure 4. Linear Mixed Effects Model of Concentration-Baseline Adjusted QTc (ΔQTc) Data for Parent Drug.** Model suggests that there is an 9.3 millisecond increase from baseline in Fridericia corrected QT interval at mean Cmax when the upper 95% confidence interval value of slope is used to predict response.

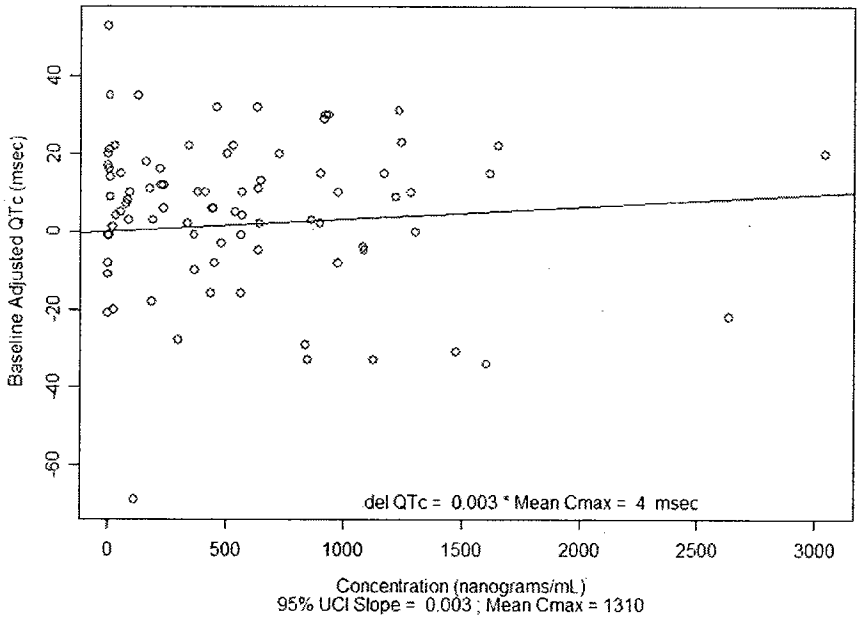


**Figure 5. Linear Mixed Effects Model of Concentration-Baseline Adjusted QTc Data for Metabolite #1.** Model suggests that there is a 4 millisecond increase from baseline in Fridericia corrected QT interval at mean Cmax when the upper 95% confidence interval value of slope is used to predict response.

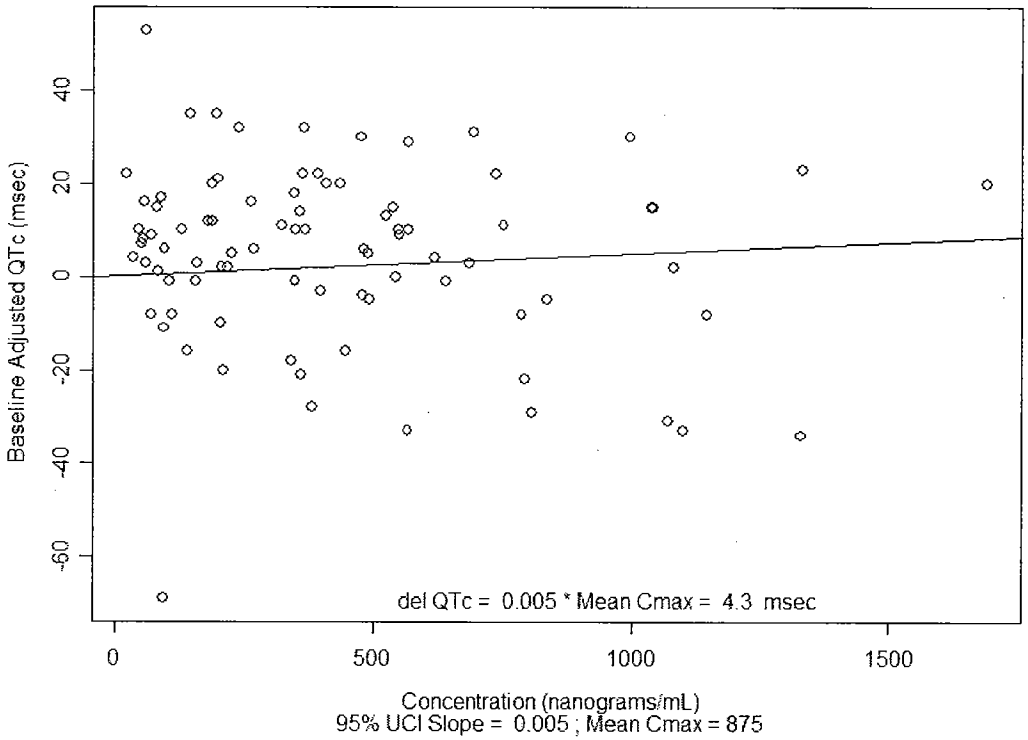


**Figure 6. Linear Mixed Effects Model of Concentration-Baseline Adjusted QTc Data for Metabolite #2.** Model suggests that there is a 4.3 millisecond increase from baseline in Fridericia corrected QT interval at mean Cmax when the upper 95% confidence interval value of slope is used to predict response.

### 8.2. Pooled data analysis

**Reviewer's Analysis**

There were several new observations of QTc exceeding 550 milliseconds after drug administration. The data could not be explored in any greater detail than by reviewing the Sponsor's report since the Sponsor denied the reviewer's request for data.

### 8.3. Summary

The Sponsor's exposure-response analysis of the pooled Phase 1 and Phase 2 suggests that there may be a 40 millisecond increase in QTc from baseline with vorinostat dosing. Additionally, the report shows that there were several new observations of QTc exceeding 550 milliseconds. We consider these ominous.

It is possible that the QT prolongation findings are spurious and would not be replicated in a subsequent, more careful study. If real, the effects of vorinostat on QT are, in some individuals, of a magnitude that, at the least, some risk management strategy is indicated.

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Division Director Summary Review of a New Drug Application

NDA: 21-991
Drug: Zolinza™ (vorinostat) Capsules
Applicant: Merck
Date: October 2, 2006

This new drug application seeks approval of vorinostat for the treatment of patients with cutaneous T-cell lymphoma (CTCL) who have progressive, persistent, or recurrent disease [redacted] The clinical studies supporting the application and the safety and efficacy data are summarized in the following information from the FDA version of the proposed labeling.

> In two open-label clinical studies, patients with refractory CTCL have been evaluated to determine their response rate to oral ZOLINZA. One study was a single-arm clinical study and the other assessed several dosing regimens. In both studies, patients were treated until disease progression or intolerable toxicity.
>
> **Study 1**
> In an open-label, single-arm, multicenter, non-randomized study, 74 patients with advanced CTCL were treated with ZOLINZA at a dose of 400 mg once daily. The primary endpoint was response rate to oral ZOLINZA in the treatment of skin disease in patients with advanced CTCL (Stage IIB and higher) who have progressive, persistent, or recurrent disease on or following two systemic therapies. Enrolled patients should have received, been intolerant to or not a candidate for bexarotene. Extent of skin disease was quantitatively assessed by investigators using a modified Severity Weighted Assessment Tool (SWAT). The investigator measured the percentage total body surface area (%TBSA) involvement separately for patches, plaques, and tumors within 12 body regions using the patient's palm as a "ruler". The total %TBSA for each lesion type was multiplied by a severity weighting factor (1=patch, 2=plaque and 4=tumor) and summed to derive the SWAT score. Efficacy was measured as either a Complete Clinical Response (CCR) defined as no evidence of disease, or Partial Response (PR) defined as a ≥50% decrease in SWAT skin assessment score compared to baseline. Both CCR and PR had to be maintained for at least 4 weeks. Secondary efficacy endpoints included response duration, time to progression, and time to objective response.
>
> Table 2 summarizes the demographic and disease characteristics of the Study 1 population.

Table 2
Baseline Patient Characteristics
(All Patients As Treated)

| Characteristics | Vorinostat (N=74) |
|---|---|
| **Age (year)** | |
| Mean (SD) | 61.2 (11.3) |
| Median (Range) | 60.0 (39.0, 83.0) |
| **Gender, n (%)** | |
| Male | 38 (51.4%) |
| Female | 36 (48.6%) |
| **CTCL stage, n (%)** | |
| IB | 11 (14.9%) |
| IIA | 2 (2.7%) |
| IIB | 19 (25.7%) |
| III | 22 (29.7%) |
| IVA | 16 (21.6%) |
| IVB | 4 (5.4%) |
| **Racial Origin, n (%)** | |
| Asian | 1 (1.4%) |
| Black | 11 (14.9%) |
| Other | 1 (1.4%) |
| White | 61 (82.4%) |
| **Time from Initial CTCL Diagnosis (year)** | |
| Median (Range) | 2.6 (0.0, 27.3) |
| **Clinical Characteristics** | |
| Number of prior systemic treatments, median (range) | 3.0 (1.0, 12.0) |

The overall objective response rate was 29.7% (22/74, 95% C.I. [19.7 to41.5%]) in all patients treated with ZOLINZA. In patients with Stage IIB and higher CTCL, the overall objective response rate was 29.5% (18/61). One patient with Stage IIB CTCL achieved a CCR. Median times to response were 55 and 56 days (range 28 to 171 days), respectively in the overall population and in patients with Stage IIB and higher CTCL. However, in rare cases it took up to 6 months for patients to achieve an objective response to ZOLINZA.

The median response duration was not reached since the majority of responses continued at the time of analysis, but was estimated to exceed 6 months for both the overall population and in patients with Stage IIB and higher CTCL. When end of response was defined as a 50% increase in SWAT score from the nadir, the estimated median response duration was 168 days and the median time to tumor progression was 202 days.

Using a criterion for tumor progression of a 25% increase in SWAT score from the nadir, the estimated median time-to-progression was 148 days for the overall population and 169 days in the 61 patients with Stage IIB and higher CTCL, both ranging from 1+ to 380 days. Response to any previous systemic therapy does not appear to be predictive of response to ZOLINZA.

**Study 2**
In an open-label, non-randomized study, ZOLINZA was evaluated to determine the response rate for patients with CTCL who were refractory or intolerant to at

least one treatment. In this study, 33 patients were assigned to one of 3 cohorts: Cohort 1, 400 mg once daily; Cohort 2, 300 mg twice daily 3 days/week; or Cohort 3, 300 mg twice daily for 14 days followed by a 7-day rest (induction). In Cohort 3, if at least a partial response was not observed then patients were dosed with a maintenance regimen of 200 mg twice daily. The primary efficacy endpoint, objective response, was measured by the 7-point Physician's Global Assessment (PGA) scale. The investigator assessed improvement or worsening in overall disease compared to baseline based on overall clinical impression. Index and non-index cutaneous lesions as well as cutaneous tumors, lymph nodes and all other disease manifestations were also assessed and included in the overall clinical impression. CCR required 100% clearing of all findings, and PR required at least 50% improvement in disease findings.

In all patients treated, the objective response was 24.2% (8/33) in the overall population, 25% (7/28) in patients with Stage IIB or higher disease and 36.4% (4/11) in patients with Sezary syndrome. The overall response rates were 30.8%, 9.1% and 33.3% in Cohort 1, Cohort 2 and Cohort 3, respectively. The 300 mg twice daily regimen had higher toxicity with no additional clinical benefit over the 400 mg once daily regimen. No CCR was observed.

Among the 8 patients who responded to study treatment, the median time to response was 83.5 days (range 25 to 153 days). The median response duration was 106 days (range 66 to 136 days). Median time to progression was 211.5 days (range 94 to 255 days).

The safety of ZOLINZA was evaluated in 107 CTCL patients in the two single arm clinical studies in which 86 patients received 400 mg once daily. Table 1 summarizes the specific adverse events, regardless of causality, by frequency and National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE, version 3.0) Grade in the 86 CTCL patients who received 400 mg once daily.

Table 1
Clinical or Laboratory Adverse Events Occurring in CTCL Patients
(Incidence ≥10%)

| | ZOLINZA 400 mg once daily (N=86) | | | |
|---|---|---|---|---|
| **Adverse Experience** | **All Grades** | | **Grades 3-5*** | |
| | **n** | **%** | **n** | **%** |
| Fatigue | 45 | 52.3 | 3 | 3.5 |
| Diarrhea | 45 | 52.3 | 0 | 0.0 |
| Nausea | 35 | 40.7 | 3 | 3.5 |
| Dysgeusia | 24 | 27.9 | 0 | 0.0 |
| Thrombocytopenia | 22 | 25.6 | 5 | 5.8 |
| Anorexia | 21 | 24.4 | 2 | 2.3 |
| Weight Decreased | 18 | 20.9 | 1 | 1.2 |
| Muscle Spasms | 17 | 19.8 | 2 | 2.3 |
| Alopecia | 16 | 18.6 | 0 | 0.0 |
| Dry Mouth | 14 | 16.3 | 0 | 0.0 |
| Blood Creatinine Increased | 14 | 16.3 | 0 | 0.0 |
| Chills | 14 | 16.3 | 1 | 1.2 |
| Vomiting | 13 | 15.1 | 1 | 1.2 |
| Constipation | 13 | 15.1 | 0 | 0.0 |
| Dizziness | 13 | 15.1 | 1 | 1.2 |
| Anemia | 12 | 14.0 | 2 | 2.3 |
| Decreased Appetite | 12 | 14.0 | 1 | 1.2 |
| Peripheral Edema | 11 | 12.8 | 0 | 0.0 |
| Headache | 10 | 11.6 | 0 | 0.0 |
| Pruritus | 10 | 11.6 | 1 | 1.2 |
| Cough | 9 | 10.5 | 0 | 0.0 |
| Upper Respiratory Infection | 9 | 10.5 | 0 | 0.0 |
| Pyrexia | 9 | 10.5 | 1 | 1.2 |

* No Grade 5 events were reported.

The most common drug-related adverse reactions could be classified into four symptom complexes: gastrointestinal symptoms (diarrhea, nausea, anorexia, weight decreased, vomiting, constipation, decreased appetite), constitutional symptoms (fatigue, chills), hematologic abnormalities (thrombocytopenia, anemia), and taste disorders (dysgeusia, dry mouth).

The most common serious adverse events, regardless of causality, in the 107 CTCL patients in two clinical studies (including all doses) were pulmonary embolism reported in 5.6% (6/107) of patients, dehydration and T-cell lymphoma each reported in 4.7% (5/107) of patients and thrombocytopenia reported in 3.7% (4/107) of patients. Anemia, sepsis, squamous cell carcinoma and vomiting were reported in 2.8% (3/107) of patients. Deep vein thrombosis, hypotension, infection and nausea were reported in 1.9% (2/107) of patients. There were single events of chest pain, death (of unknown cause), diarrhea, gastrointestinal hemorrhage, hepatic ischemia, herpes zoster, ischemic stroke, lung neoplasm, oral intake reduced, orthostatic hypotension, pyrexia, streptococcal bacteremia, subdural hematoma, syncope, urinary tract infection or wound infection.

Of the CTCL patients who received the 400-mg once daily dose, 9.3% (8/86) of patients discontinued ZOLINZA due to adverse events, regardless of causality. These adverse events included anemia, angioneurotic edema, asthenia, chest pain, exfoliative dermatitis, death, deep vein thrombosis, ischemic stroke, lethargy, pulmonary embolism, and spinal cord injury.

Of the CTCL patients who received the 400-mg once daily dose, 10.5% (9/86) of patients required a dose modification of ZOLINZA due to adverse events. These adverse experiences included increased serum creatinine, decreased appetite, hypokalemia, leukopenia, nausea, neutropenia, thrombocytopenia and vomiting. The median time to the first adverse experience resulting in dose reduction was 42 days (range 17 to 263 days).

Increased serum glucose was reported as a laboratory abnormality in 69% (60/87) of CTCL patients; only 5 of these abnormalities were severe (Grade 3). Increased serum glucose was reported as an adverse event in 8.1% (7/86) of CTCL patients who received the 400-mg once daily dose. Transient, NCI CTCAE Grade 1 or 2 increases in serum creatinine were detected in 47.1% (41/87) of CTCL patients. Proteinuria was detected as a laboratory abnormality (51.4%) in 38 of 74 patients tested.

Clinical and Statistical Review

A combined clinical and statistical review by Drs. Mann, Johnson, He, and Sridhara was completed on 9/6/06. The review made the following recommendations.

### 1.1 Recommendation on Regulatory Action

Vorinostat (Zolinza ™) 400 mg orally once daily with food is recommended for approval for the treatment of cutaneous manifestations of cutaneous T-cell lymphoma (CTCL) in patients with progressive, persistent, or recurrent disease on or following two systemic therapies, —

—

#### 1.2.1 Risk Management Activity

The safety issues with Vorinostat are consistent with those of other cancer therapies and the Sponsor's proposal for routine risk management measures including labeling and routine pharmacovigilance are sufficient at this time.

- The risks associated with Zolinza will be conveyed to the prescribers and other healthcare professionals using the Professional Labeling.
- A separate Patient Package Insert (PPI) will be used to convey the risks associated with Zolinza use to the patients.
- The Sponsor proposes routine post-marketing surveillance for Vorinostat and plans to conduct "enhanced surveillance" by soliciting details of adverse

events in the postmarketing arena and clinical trials via a questionnaire to the providers who report a thromboembolic event.

The Office of Surveillance and Epidemiology (OSE) reviewed the proposed Risk Management Plan (RMP) for Zolinza and also consulted with DDOP. It was concluded that the risk management plan was adequate.

### 1.2.2 Required Phase 4 Commitments

- None

### 1.2.3 Other Phase 4 Requests

1. The applicant should make a Phase 4 commitment to follow all the patients in the pivotal trial (Protocol 001) and the continuation trial (Protocol 007) who remain on treatment and submit annual reports and a final study report.
2. The applicant should make a Phase 4 commitment to study Vorinostat in patients with hepatic impairment.
4. The applicant should make a Phase 4 commitment to provide adequate data on the effect of Vorinostat on ECG QT interval prolongation.
5. The applicant should make a Phase 4 commitment to collect and submit data on Vorinostat and coumadin interaction as these data become available.
6. The applicant should make a Phase 4 commitment to collect and submit data on Vorinostat-other drug interactions as these data become available.

Clinical Team Leader Review

The clinical team leader review by John R. Johnson was completed on September 18, 2006. The reviewer's conclusion is quoted below.

> Efficacy based on a 30 % tumor response rate has been demonstrated. This is similar to tumor response rates seen with FDA approved Targretin and Ontak in similar populations of CTCL patients. There are no good treatments for these patients. A minority of patients respond to any of these drugs and all relapse. Thus more treatment options are needed. No tumor response at sites other than cutaneous was demonstrated. Thus the proposed indication should be modified to "cutaneous manifestations" of CTCL. Safety is acceptable for this patient population, considering the efficacy and lack of good treatment alternatives.

The review made the following recommendation.

> Regular approval is recommended for the following indication. Zolinza is indicated for treatment of cutaneous manifestations of cutaneous T-cell lymphoma (CTCL) in patients with progressive, persistent, or recurrent disease on or following two systemic therapies.

The applicant should agree to the following Phase 4 requests.

1. The applicant should make a Phase 4 commitment to follow all the patients in the pivotal trial (Protocol 001) and the continuation trial (Protocol 007) who remain on treatment and submit annual reports and a final study report.
2. The applicant should make a Phase 4 commitment to study Vorinostat in patients with hepatic impairment.
4. The applicant should make a Phase 4 commitment to provide adequate data on the effect of Vorinostat on ECG QT interval prolongation.
5. The applicant should make a Phase 4 commitment to collect and submit data on Vorinostat and coumadin interaction as these data become available.
6. The applicant should make a Phase 4 commitment to collect and submit data on Vorinostat-other drug interactions as these data become available.

Clinical Inspection Summary

The clinical inspection summary by J. Lloyd Johnson, Pharm.D., was completed on August 28, 2006. The overall assessment of findings and general recommendations are provided below.

In general, based on the inspection of the two clinical study sites combined with the sponsor/monitor audit for this NDA, it appears that sufficient documentation to assure that study subjects audited at the three sites did exist, study eligibility criteria were fulfilled, participants received assigned study medications, and adverse events were adequately reported. Primary endpoints and secondary endpoints were captured in accordance with protocol requirements.

Clinical Pharmacology Review

The clinical pharmacology review by Sophia Abraham, Ph.D. was completed on September 15, 2006. The review recommended the following.

**1.1 RECOMMENDATION**

NDA 21-991 filed for ZONLIZA (Vorisnotat) Capsules is acceptable from the Clinical Pharmacology perspectives. The Applicant should incorporate the OCP Labeling Recommendations in the proposed package insert for ZOLINZA and address the following Phase 4 Commitments and General Comments:

**1.2 PHASE 4 COMMITMENTS**

1. As vorinostat is predominantly eliminated through metabolism, we recommend that you conduct a pharmacokinetic study in cancer patients with hepatic impairment to provide proper dosing recommendations. We refer you to the FDA published Guidance for Industry, Pharmacokinetics in Patients with Impaired

Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling http://www.fda-.gov/cder/guidance/3625fnl.pdf).

2. We recommend that you conduct a clinical study to evaluate the impact of vorinostat on QT interval in cancer patients.

3. We recommend that you conduct in vitro efflux studies to determine whether vorinostat is a substrate and/or inhibitor of P-glycoprotein.

**GENERAL COMMENTS (To be sent to the Applicant)**

1. You have collected blood samples in Studies 005, 006, and 008 to evaluate the levels of the pharmacodynamic marker, histone acetylation, in peripheral blood mononuclear cells. Please submit these data to the Agency.

2. As vorinostat is glucuronidated by several UGTs including UGT1A1, UGT1A3, UGT1A7, UGT1A8, UGT1A9, UGT2B7, and UGT2B17, we recommend that you collect blood samples that could be used in the future to determine if UGT polymorphisms are correlated with individual variation of PK parameters or adverse events. It would be prudent to collect the samples during the clinical studies as vorinostat was glucuronidated by multiple UGTs that are known to have polymorphisms that can lead to large inter-individual variability in drug concentrations.

Consultation by the Interdisciplinary Review Team for QT Studies

The IRT consultation by Leslie Kenna was completed on August 10, 2006. The consultation's recommendation and summary of findings are quoted below.

**1.0 RECOMMENDATION**

It is recommended that the Sponsor conduct a clinical trial to evaluate the impact of vorinostat on QT interval. This could be carried out as a Phase 4 commitment.

**2.0 SUMMARY OF FINDINGS**

The Sponsor has not performed a well-designed and well-controlled study to assess the impact of vorinostat on QT interval.

The Sponsor submitted an analysis of pooled data from three Phase 1 and two Phase 2 studies. This report suggests that there may be a forty (40) millisecond increase in QTc from baseline with vorinostat dosing. Additionally, there were several observations of QTc exceeding 550 milliseconds. The Sponsor denied the reviewer's request for data from this analysis.

Based on an exposure-response analysis performed by the reviewer on data from a Phase 1 food effect study, there may be an 11-millisecond (upper 95% predicted value at mean maximum observed concentration) increase in QTc from baseline

for vorinostat at 400 mg. But, this result is based on data from a Phase 1 study that has a number of limitations: (1) few subjects were studied, (2) no placebo or positive control was used, (3) ECGs were not taken at Cmax for drug or metabolite, (4) at most, 1-2 ECGs were recorded after steady state dosing, (5) there was no consistent measure of baseline effect in each subject, and (6) results are confounded by different meal instructions provided on different study days.

Pharmacology/Toxicology Review and Evaluation

The pharmacology/toxicology review by S. Leigh Verbois, Ph.D., was completed on September 13, 2006. The reviewer's recommendation was that "The nonclinical studies submitted to this NDA provide sufficient information to support the use of vorinostat (ZOLINZA®) for the treatment of patients with cutaneous T-cell lymphoma who have progressive persistent or recurrent disease — No additional nonclinical studies were recommended.

Chemistry Review

The chemistry review by Josephine M. Jee was completed on September 29, 2006. The review had the following recommendations.

**A. Recommendation and Conclusion on Approvability**
From the standpoint of Product quality CMC, NDA 21-991 is recommended for approval. An expiration period of 24 months may be granted based on the assessment of — real time stability data. Comments on carton labels, listed at the end of the review should be communicated to the firm and should be included in the final printed labels.

**B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable**
There are no Phase 4 CMC commitments.

**CMC Agreement:** Provide justification and summary data for the selection of 2% Tween 80 and 100 rpm in the regulatory method for dissolution testing and comment on its discriminatory power. To this end, provide supporting data using lower concentrations of Tween 80 and lower paddle speeds.

Chemistry Division Director Memo

The chemistry Division Director Memo is pending.

DDMAC Consultation

The DDMAC consultation by Joseph Grillo was completed on September 1, 2006. The consultation provided comments on the draft labeling which were considered during the labeling discussions.

DSRCS PPI Review

The DSRCS review of the patient package insert by Sharon R. Mills, BSN, RN, CCRP, was completed on September 5, 2006. The review recommended revisions to the PPI and had the following comments and recommendations.

1. The draft PPI submitted by the sponsor has a Flesch Kincaid grade level of 69.7, and a Flesch Reading Ease score of 6.2. These reading scores as submitted by the sponsor are acceptable; we have made only minor changes where indicated. To enhance comprehension, patient materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60% (60% corresponds to an 8th grade reading level.
2. A PPI for ZOLINZA is voluntary. The sponsor proposes to supply ZOLINZA in "unit of use bottles of 120." The sponsor should clarify how they intend to distribute the PPI to patients and whether it will be enclosed with the drug product in the packaging.
3. All serious side effects listed in the Warnings and Precautions section of the PI should be listed in the PPI. The pertinent signs and symptoms of these serious side effects as well as any actions that the patient should take should be listed in the PPI. We have revised the PPI to reflect this.
4. In the "Patient Counseling" section of the PI (section 17.1), the sponsor should clarify what is meant by "excessive" vomiting and diarrhea as well as under "Tell your doctor if you develop" in the proposed PPI. This will not be intuitive to patients.

Study Endpoint and Label Development Consultation

The Study Endpoint and Label Development consultation by Jeanne M. Delasko, RN, MS was completed on August 23, 2006 and provided a list of revisions for the proposed labeling to be communicated to the applicant. A member of the SEALD team participated in labeling discussions.

Risk Management Team Consultation

The Office of Surveillance and Epidemiology Risk Management Team reviewed the proposed Risk Management Plan and concluded that "it does not appear to differ substantially from routine risk management measures, such as FDA-approved professional labeling and routine post-marketing surveillance." OSE concluded "that the Sponsor's proposal for routine risk management measures including labeling and routine pharmacovigilance are sufficient at this time."

Recommended Regulatory Action

I concur with the recommendations for approval of the application once agreement has been reached with the applicant on the labeling and on the phase 4 commitments. Two

major outstanding issues relate to the potential for QTc prolongation as described in the IRT review. The applicant has not conducted a well-designed and well-conducted study to evaluate the potential for QTc prolongation. Given the potential signal identified in the IRT review, the applicant's proposed phase 4 commitment to start a QT study in 2007 and submit the study report in is not acceptable. The study should be conducted as expeditiously as possible. In addition, the package insert should include information on the potential for QTc prolongation and on monitoring electrolytes (including potassium, magnesium, and calcium) and ECG's. The applicant's agreement on these two issues is pending at the time of this review.

Robert L. Justice, M.D., M.S.
Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Office of New Drugs
Center for Drug Evaluation and Research

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

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/s/
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Robert Justice
10/2/2006 06:19:36 PM
MEDICAL OFFICER

## CLINICAL & STATISTICAL REVIEW

| | |
|---|---|
| **Application Type** | NDA |
| **Submission Number** | 021991 |
| **Submission Code** | 000 |
| **Letter Date** | 4-5-06 |
| **Stamp Date** | 4-7-06 |
| **PDUFA Goal Date** | 10-7-06 |
| **Reviewer Name** | Bhupinder S Mann, MO<br>John R Johnson, TL<br>Kun He, Statistics Reviewer<br>Rajeshwari Sridhara, TL |
| **Review Completion Date** | 9-6-06 |
| **Established Name** | Vorinostat |
| **(Proposed) Trade Name** | Zolinza™ |
| **Therapeutic Class** | Histone deacetylase inhibitor |
| **Applicant** | Merck |
| **Priority Designation** | P |
| **Formulation** | Capsules for oral administration |
| **Dosing Regimen** | 400 mg orally once daily with food |

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# 1 EXECUTIVE SUMMARY

## 1.1 Recommendation on Regulatory Action

Vorinostat (Zolinza ™) 400 mg orally once daily with food is recommended for approval for the treatment of cutaneous manifestations of cutaneous T-cell lymphoma (CTCL) in patients with progressive, persistent, or recurrent disease on or following two systemic therapies,

## 1.2 Recommendation on Postmarketing Actions

### 1.2.1 Risk Management Activity

The safety issues with Vorinostat are consistent with those of other cancer therapies and the Sponsor's proposal for routine risk management measures including labeling and routine pharmacovigilance are sufficient at this time.

- The risks associated with Zolinza will be conveyed to the prescribers and other healthcare professionals using the Professional Labeling.
- A separate Patient Package Insert (PPI) will be used to convey the risks associated with Zolinza use to the patients.
- The Sponsor proposes routine post-marketing surveillance for Vorinostat and plans to conduct "enhanced surveillance" by soliciting details of adverse events in the postmarketing arena and clinical trials via a questionnaire to the providers who report a thromboembolic event.

The Office of Surveillance and Epidemiology (OSE) reviewed the proposed Risk Management Plan (RMP) for Zolinza and also consulted with DDOP. It was concluded that the risk management plan was adequate.

### 1.2.2 Required Phase 4 Commitments

- None

### 1.2.3 Other Phase 4 Requests

1. The applicant should make a Phase 4 commitment to follow all the patients in the pivotal trial (Protocol 001) and the continuation trial (Protocol 007) who remain on treatment and submit annual reports and a final study report.
2. The applicant should make a Phase 4 commitment to study Vorinostat in patients with hepatic impairment.

## 1.3.2 Efficacy

Data from the pivotal trial (Protocol 001) and the supporting trial (Protocol 005) demonstrating the efficacy and safety of Vorinostat for the proposed indication—treatment of patients with cutaneous T-cell lymphoma (CTCL) who have progressive, persistent, or recurrent disease were reviewed.

The pivotal trial is an open-label, single-arm, multicenter, Phase 2, non-randomized study of 74 patients with stage IB or higher stage cutaneous T-cell lymphoma (61 patients had stage IIB or higher stage disease) who were treated with Vorinostat 400 mg orally once daily.

- In the pivotal trial, the extent of the skin disease at the baseline and response to treatment were measured using a Severity Weighted Assessment Tool (SWAT). In the responding patients a confirmation of the response was required four weeks later.

The primary endpoint was the objective tumor response rate based on assessment of the overall skin disease measured by the Severity Weighted Assessment Tool (SWAT) in patients with Stage IIB or higher CTCL. Responses were classified as complete, partial, stable, or progressive disease.

- Submission of a standard set of photographs for each patient in the trial was required as supporting evidence to demonstrate responses measured by the SWAT methodology. Adequate photographs were provided by the applicant and were reviewed.

A positive study required an observed response rate of $\geq 20\%$ and that the lower bound of the 95% Confidence Interval (CI) excluded 5%.

The secondary endpoints were time to response, duration of overall response, pruritis relief, and time to tumor progression.

- Intensity of pruritis was evaluated at baseline and during each visit using a two-part, patient-completed and self-administered pruritis questionnaire. It assessed the skin itch over the past week using a 10-point scale (0 = no itching, 10 = itching as bad as it can be) and the patient also provided the amount of medication taken to relieve symptoms of itching in the past week compared to the amount taken in the previous week (response categories for medication use: (a) did not use, (b) used less, (c) no change in use, or (d) used more). A 3-point decrease in pruritis intensity, confirmed by a second assessment at least 4 weeks later, and without an increase in the use of anti-pruritic medications, was considered clinically significant in those patients whose pruritis score was > 3 on the 0-10 point scale at the baseline.

From the 17th of March 2004 to the 23rd of November 2005, eighteen (18) sites the United States and Canada enrolled 74 CTCL patients who received at least one dose of Vorinostat; 61/74 patients (82.4%) had advanced stage disease (clinical stage $\geq$ IIB).

- Median duration of protocol treatment was 118 days.
- Ten (10) patients required dose modification and 9 patients discontinued treatment due to adverse events (AEs).
- At the time of study completion: 15 patients were still on treatment, one had completed treatment, and 58 patients had discontinued treatment (49, the majority, due to lack of efficacy or progressive disease, and 9 due to adverse events).

- All responses except one were partial

The observed response rates (95% CI) in the pivotal trial (All Patients as Treated Analysis):

- Overall study population (22 responses in 74 patients) 29.7% (19.7 to 41.5)
- Stage IIB or higher disease (18 responses in 61 patients) 29.5% (18.5 to 42.6)
- Sezary syndrome (10 responses in 30 patients) 33.3% (17.3 to 52.8)
- T3 tumor disease (5 responses in 22 patients) 22.7% (7.8 to 45.4)

The observed response rates in the pivotal trial (Per Protocol Analysis: excluding 8 protocol violators):

- Overall study population (21 responses in 65 patients) 32.3% (21.2 to 45.1)
- Stage IIB or higher disease (17 responses in 54 patients) 31.5% (19.5 to 45.6)
- Sezary syndrome (9 responses in 27 patients) 33.3% (16.5 to 54.0)
- T3 tumor disease (5 responses in 20 patients) 22.7% (8.7 to 49.1)

- For the responders: the overall median time to objective response was 55 days; the overall median duration of response was not reached but exceeded 168 days (range 34+ to 322+ days); and the overall median time to progression was not reached but exceeded 202 days (range 78+ to 365+ days).
    - Use of FDA revised definitions of endpoints changed these results slightly. Time to objective response remained 55 days; the overall median duration of response was 168 days (range 34 to 280+); and the overall median time to progression was 202 days ( range 78 to 323)
- Of the patients evaluable of relief of pruritis, overall 23/72 patients (32%) had clinically significant pruritis relief and 8/72 (11%) had complete resolution of pruritis.
- Responses to Vorinostat were seen irrespective of the responses to the last treatment that the patient was receiving prior to Vorinostat. Five (5) of 16 (31%) non-responders and 2 of 7 (29%) responders to *bexarotene as last therapy* had a response and 10 of 36 (28%) non-responders and 5 of 15(33%) responders to *non-bexarotene as last therapy* had a response.

- The observed response rates and durations of response are robust and demonstrate the efficacy of Vorinostat.
- These results compare favorably to the approved and available systemic therapies. Vorinostat meets the need for a new treatment in the CTCL patients who have progressive, persistent, or recurrent disease on or following two systemic therapies.

**Reviewer Comments:**

- *The observed modest, approximately 30%, objective response rate in the skin disease (evaluated using SWAT, supported by patient photographs) in a heavily pre-treated advanced CTCL patient population demonstrates the clinical benefit and efficacy of Vorinostat. Currently, no good therapeutic alternatives are available to these patients. Therefore Vorinostat is recommended for approval.*
  - *Details of the supportive study (Protocol 005) are presented under Integrated Review of Efficacy*
- *Applicant attempted to evaluate relief of pruritis (a common symptom in CTCL) using a patient administered questionnaire; however in a single arm trial with no control arm the observed results of a patient reported outcome are not reliable.*
- *FDA approved Ontak (denileukin diftitox) in February 1999 and Targretin (bexarotene) in December 1999 based on response rates and durations of response.*
  - *Efficacy of Targretin was evaluated by Physician's Global Assessment of the skin disease and Composite Assessment of Index Lesions.*
  - *Efficacy of Ontak was evaluated by using Severity Weighted Assessment Tool (when ≥ 10% body surface area was involved, or by weighted score and measurements of 5 target lesions (when ≤ 10% body surface area was involved)*

## 1.3.3 Safety

Safety of Vorinostat was evaluated primarily using the clinical and laboratory adverse events (AEs) data from the 74 patients in the pivotal trial (protocol 001). Data from the supportive study (Protocol 005) that enrolled CTCL patients and 10 other studies that enrolled diverse other tumor types were evaluated for additional supportive evidence.

For each adverse experience in the pivotal trial (Protocol 001), its onset and end dates, severity, and relationship to Vorinostat were recorded.

- Severity was graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events Version 3.0 published December 12, 2003 (CTCAE V3). In the CTCAE the grades refer to the severity of AEs: Grade 1 = Mild AE, Grade 2 = Moderate AE, Grade 3 = Severe AE, Grade 4 = Life-threatening or disabling AE, and Grade 5 = Death related to AE.
- Relationship of the AE to Vorinostat was categorized, by the investigator, as definitely related, probably related, possibly related, probably not related, or definitely not related to the test drug.

In the pivotal trial, all patients started Vorinostat at the recommended dose of 400 mg once daily; 10 patients required one or more dose modifications; and 9 patients required discontinuation of Vorinostat due to clinical AEs, 7 of these were considered drug related. Other patients discontinued Vorinostat due to lack of efficacy or eventual disease progression after an initial response or stable disease. Fifteen (15) patients were still receiving Vorinostat at the time of study closure in November 2005.

- The median duration of exposure to Vorinostat was 118 days (range 2 to 365 days).

- Clinical adverse experiences (AEs) were reported by the majority of the patients: 70/74 (94.6%); however, serious clinical adverse experiences were reported by 16/74 (22%) patients and 8 were considered drug related AEs.
- Laboratory AEs were reported by 22/74 patients (29.7%) and 20 were considered drug related. However, only 1 laboratory AE (increased creatinine) was serious. This was considered drug related.

Specific clinical or laboratory AEs of all grades with incidence of $\geq$ 10% were:

- Diarrhea (51%), fatigue (51%), nausea (43%), anorexia (27%), dysgeusia (27%), thrombocytopenia (20%), weight loss (20%), alopecia (19%), chills (18%), increased creatinine (16%), constipation (16%), muscle spasms (16%), anemia (15%), dizziness (15%), vomiting (15%), pruritus (14%), headache (12%), peripheral edema (12%), upper respiratory tract infection (12%), and dry mouth (11%).
- Of the above, the AEs of grades 3 to 5 were fatigue (7%), nausea (4%), anorexia (3%), thrombocytopenia (4%), weight loss (1%), chills (1%), increased creatinine (1%), muscle spasms (3%), anemia (1%), dizziness (1%), vomiting (1%), and pruritus (1%).

Specific grade 3, 4, or 5 clinical adverse experiences with incidence $\geq$ 0%, irrespective of the causation, seen in the overall population were:

- Fatigue (7%), pulmonary embolism (5.4%), squamous cell carcinoma (4.1%), T-Cell lymphoma (2.7%), and 1 (1.4%) case each of anemia, death, deep vein thrombosis, dehydration, dermatitis exfoliative, enterococcal infection, gastrointestinal hemorrhage, ischaemic stroke, lung neoplasm, myocardial infarction, pelvi-ureteric obstruction, sepsis, spinal cord injury, streptococcal bacteremia, syncope, thrombocytopenia, and ureteric obstruction.
- Of these, the clinical adverse experiences considered possibly related to Vorinostat were pulmonary embolism (5.4%), and 1 (1.4%) case each of anemia, death, deep vein thrombosis, dehydration, gastrointestinal hemorrhage, ischaemic stroke, streptococcal bacteremia, syncope, and thrombocytopenia.

**Reviewer Comments:**

- *The duration of exposure to Vorinostat is relatively short. A large number of patients discontinue therapy due to lack of benefit. Accordingly data on the long-term safety of Vorinostat is not available at present. Post-marketing surveillance is required to collect emerging safety data on longer drug exposure.*
- *The observed high incidence of AEs of all grades with a smaller number of these assessed as serious and related to the study drug can be expected in a heavily pre-treated population. This is comparable to that seen with the available systemic therapies for advanced CTCL.*

- *Vorinostat has not been studied in patients with compromised renal and liver functions; the sponsor needs to study Vorinostat in these patient populations.*
- *Median age of the study population in the pivotal trial is 60 years. No dose adjustments are recommended at the beginning of treatment with Vorinostat in the elderly.*

## 1.3.4 Dosing Regimen and Administration

Vorinostat (Zolinza ™) will be available as 100 mg capsules. The recommended dose for Vorinostat is 400 mg orally once daily with food.

- 400 mg orally once daily was the starting dose used in the pivotal trial.
- Ten (10) patients required one or more dose modifications due to AEs and 9 patients discontinued Vorinostat due to AEs (7 of these were considered drug related).
- The first dose modification in the study was lowering the dose to 300 mg once daily and the second dose modification was lowering the dose to 300 mg five days a week.
- Many patients discontinued Vorinostat due to lack of efficacy.

## 1.3.5 Drug-Drug Interactions

Coumarin-Derivative Anticoagulants

- Prolongation of prothrombin time (PT) and International Normalized Ratio (INR) has been observed in patients receiving Vorinostat and coumarin-derivative anticoagulants.

Other histone deacetylase inhibitors (eg valproic acid)

- Vorinostat should not be administered concomitantly with other histone deacetylase inhibitors. Severe thrombocytopenia, gastrointestinal hemorrhage, and anemia have been reported with the concomitant use of Vorinostat and valproic acid.

## 1.3.6 Special Populations

**Pregnant Women**

- Data from adequate and well-controlled studies in pregnant women using Vorinostat are not available.
- Women of childbearing potential should be advised to avoid pregnancy while on Vorinostat.

**Nursing Mothers**

- It is not known whether Vorinostat is excreted in human milk.

- Because many drugs are excreted in human milk and because of the possibility for serious adverse reactions in nursing infants from Vorinostat, women should be advised against breast-feeding while taking Vorinostat.

**Pediatric Use**

- The safety and efficacy of Vorinostat has not been studied in pediatric patients
- CTCL is not reported in pediatric patients

**Geriatric Use**

- The median age of patients in the pivotal trial was 60 years
- The efficacy and safety of Vorinostat in the elderly (age $\geq$ 65 years) were comparable to those in the younger (age $\leq$ 65 years) patients
- Adjustment of starting dose due to age is not recommended

**Hepatic Insufficiency**

- Vorinostat has not been evaluated in patients with hepatic impairment

**Renal Insufficiency**

- Vorinostat has not been evaluated in patients with renal impairment
- Renal excretion does not play a role in the elimination of Vorinostat

# 6 INTEGRATED REVIEW OF EFFICACY

## 6.1 Indication

**Proposed indication:**

- Zolinza is indicated for the treatment of patients with cutaneous T-cell lymphoma who have progressive, persistent, or recurrent disease —

### 6.1.1 Methods

Data from two Phase II studies of Vorinostat in patients with CTCL were submitted to support the proposed indication and reviewed for evaluation of efficacy:

- Protocol 001 (Pivotal study)
- Protocol 005 (Supportive study)

- Supportive study (Protocol 005) was conducted first. It was an open-label, non-randomized trial that explored several Vorinostat dosing regimens for the treatment of CTCL unresponsive to conventional treatment
  - 400 mg orally daily continuously (13 patients)
  - 300 mg orally BID for 3 days each week (12 patients)
  - 300 mg orally BID for induction, followed by 200 mg orally BID for maintenance (12 patients)
- Based on the results of protocol 005, the pivotal phase II trial (Protocol 001) was conducted.
  - Dose of Vorinostat in this trial was 400 mg orally daily continuously
- In this study (protocol 001) a total of 74 patients were enrolled and 61 of these had CTCL stage IIB or higher. Data from this study is used for the evaluation of efficacy.
  - Thus Protocol 001 is the pivotal trial supporting the efficacy claim.

***Reviewer Comments:***
*The applicant commented that a comparative Phase 3 study was not performed as no standard therapy is available for the studied population (patients who had failed two systemic therapies and one of which must have been bexarotene), and an adequate size population of eligible patients does not exist.*
*Reviewer noted that the above issues were prospectively discussed with the FDA and agreement on the design of Protocol 001 was reached with the Agency as part of the SPA.*

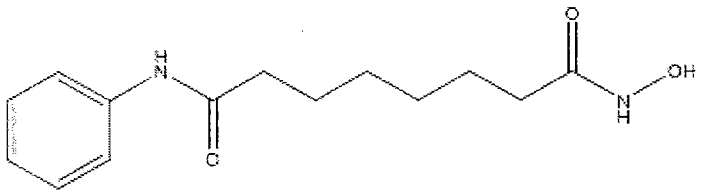
# 2 INTRODUCTION AND BACKGROUND

## 2.1 Product Information

Vorinostat (Zolinza ™) is available as 100 mg capsules for oral administration. Each 100 mg Zolinza capsule contains 100 mg Vorinostat and the following inactive ingredients: microcrystalline cellulose, sodium croscarmellose, and magnesium stearate.

Vorinostat is also known as suberoylanilide hydroxamic acid (SAHA), MK-0683, and L-001079038. The chemical name of the drug substance is *N*-hydroxy-*N*'-phenyloctanediamide.

The USAN Council adopted name is Vorinostat. Vorinostat has an empirical formula of $C_{14}H_{20}N_2O_3$. The structure of Vorinostat:



**Chemical Class:** Vorinostat, a new molecular entity, is an orally active inhibitor of histone deacetylase (HDAC) activity. Histone deacetylase inhibitors are a new therapeutic class of medications being studied for cancer treatment.

**Applicant's proposed indication:** Zolinza™ is indicated —

**Dosing regimen:** the recommended dose of Vorinostat is 400 mg orally daily with food. If patients are intolerant to therapy, subsequent doses may be reduced to 300 mg orally once daily with food. The dose schedule may be further reduced to 300 mg once daily with food for 5 consecutive days each week, as necessary. Treatment may be continued as long as there is no evidence of progressive disease or unacceptable toxicity. No dosage adjustment is necessary for the elderly.

## 2.2 Currently Available Treatment for Indications

Treatment of CTCL is determined by the clinical history and the stage of the disease. None of the available treatments is curable—the goal of treatment of CTCL is palliation of symptoms while keeping the treatment related toxicities at minimum. With passage of time, responses to treatments become less frequent and shorter in duration.

- Initial therapies are skin directed and may consist of topical chemotherapy (nitrogen mustard), retinoids (Targretin™ gel), electron beam therapy, and Psoralen plus ultraviolet light (PUVA).
- Subsequent therapies may be systemic and may consist of interferon, single and multi-agent chemotherapeutic agents (eg, cyclophosphamide, methotrexate, vinca alkaloids, and CHOP), Ontak™ (denileukin diftitox), and oral Targretin™ (bexarotene). Only the latter two are approved by the FDA for this indication.
- Available therapies for CTCL in the patients who have failed two systemic treatments remain unsatisfactory due to modest responses and significant toxicities.

## 2.3 Availability of Proposed Active Ingredient in the United States

- Zolinza™ (active ingredient: suberoylanilide hydroxamic acid or SAHA) is manufactured by Merck & Co., Inc., Whitehouse Station, New Jersey 08889 USA.
- Merck & Co., Inc. is the applicant for this NDA

## 2.4 Important Issues with Pharmacologically Related Products

- Vorinostat is the first agent in a new class of drugs—histone deacetylase inhibitors. Issues with pharmacologically related products, outside the data submitted in support of this NDA, are currently unknown.
- Anticonvulsant valproic acid has been found to have histone deacetylase inhibitory activity and concomitant use leads to clinically significant thrombocytopenia and GI hemorrhage.

## 2.5 Pre-submission Regulatory Activity

**End of Phase II meeting (September 9, 2003)**

Vorinostat clinical development program was reviewed and discussed with the FDA at an End of Phase II meeting on 09-Sep-2003.

- The Agency concurred that a well-conducted single arm study might support registration in CTCL patients who had failed two prior systemic therapies.
- It was agreed at this meeting that the proposed single arm pivotal study would be submitted for Special Protocol Assessment (SPA).

**Special Protocol Assessment (December 19, 2003)**

Discussions regarding the SPA and follow-up comments regarding the End of Phase II meeting were summarized in meeting minutes from the Agency on 19-Dec-2003 and were reviewed.

The Agency concurred with the proposed study design and analysis plan for the proposed pivotal study:

- Patients eligible for the pivotal trial (Protocol 001) must have advanced disease documented at study entry as Stage IB or higher, including Sezary syndrome, with

progressive, persistent, or recurrent disease on or following 2 systemic therapies, one of which must contain bexarotene unless the patient was intolerant of or not a candidate for bexarotene therapy. *It was recommended that the applicant enrolled enough patients with stage IIB and higher disease and analyzed them separately.*

- A pre-specified subgroup analysis would be performed in those patients with T3 disease and response rate in the overall skin disease would be calculated along with its 95% confidence interval.
- The inclusion criteria would not specify a minimum amount of time on prior therapy.
- The primary endpoint of the study would be overall skin response based on Severity-Weighted Assessment Tool (SWAT) scores with tumor volume as a secondary endpoint.
- Digital photographs and worksheets incorporating body diagrams would serve as supportive information for the primary endpoint.
- Radiation, PUVA, photopheresis and/or interferon would not be allowed during the study and patients who required these therapies would be withdrawn from the study.
- Additional safety data from other studies in the safety database should be included.

**Fast Track Designation (December 3, 2003)**

**Orphan Drug Designation (March 16, 2004)**

**Pre-NDA Meeting (November 30, 2005)**

### 2.6 Other Relevant Background Information

- Vorinostat is not approved in other countries at present.

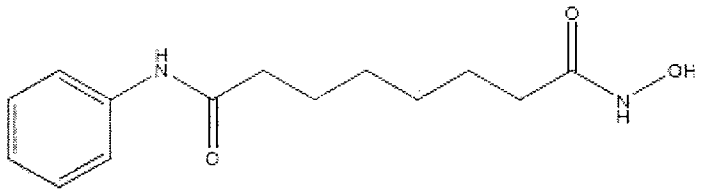
## 3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

### 3.1 CMC (and Product Microbiology, if Applicable)

Vorinostat (Zolinza ™) is available as 100 mg capsules for oral administration. Each 100 mg Zolinza capsule contains 100 mg Vorinostat and the following inactive ingredients: microcrystalline cellulose, sodium croscarmellose, and magnesium stearate.

Vorinostat is also known as suberoylanilide hydroxamic acid (SAHA), MK-0683, and L-001079038. The chemical name of the drug substance is *N*-hydroxy-*N*'-phenyloctanediamide.

The USAN Council adopted name is Vorinostat. Vorinostat has an empirical formula of $C_{14}H_{20}N_2O_3$. The structure of Vorinostat:



For further CMC details please see the CMC Review

## 3.2 Animal Pharmacology/Toxicology

### Summary of Significant Findings from Pharmacology Toxicology Review

Pivotal nonclinical toxicity studies of Vorinostat in support of this NDA were conducted in rats and dogs—these mimicked the clinical route of administration. These studies included single- and repeat-dose toxicity, reproductive toxicity, genotoxicity, and local tolerance studies and were conducted in compliance with Good Laboratory Practice regulations.

### Pharmacologic activity

Vorinostat is an inhibitor of histone deacetylase 1, 2, 3 (Class I), and 6 (Class 2) with nanomolar affinity. It results in hyper-acetylation of histones *in vivo* and *in vitro*. Induction of apoptosis and inhibition of proliferation has been shown to occur at concentrations which induce accumulation of hyper-acetylated histones (~μM). Studies demonstrated a dose and time dependant accumulation of histones, cell cycle arrest, and apoptosis in some transformed cell lines and xenograft models. Inhibition of proliferation was evident i*n vitro* in the NCI cell line screen, and *in vivo* in various xenograft models.

Additionally, *in vitro,* Vorinostat has been show to result in acetylation of HSP90, and tubulin when incubated with transformed cell lines. This acetylation of HSP90 and tubulin is associated with reductions of pro-survival proteins HER2, BCL-$X_L$, BCL2, XIAP and Survivin. The sponsor has asserted that antineoplastic effects of Vorinostat are due to hyper-acetylation of histones due to the antagonisms of histone deacetylases; however, hyper-acetylation of histones could also result from agonism of histone acetyltransferase. The activity of Vorinostat on histone acetyltransferase has not been investigated; therefore, the mechanism of the antineoplastic activity of Vorinostat is not fully characterized.

### Nonclinical safety issues relevant to clinical use

*Safety Pharmacology*

The safety profile of orally administered and locally applied Vorinostat was evaluated *in vitro* and *in vivo* in rats and dogs.

- Evaluation of CNS and pulmonary effects did not identify Vorinostat induced CNS or pulmonary toxicity at the highest doses evaluated (900 mg/m2) when administered to rats.
- Evaluation of cardiovascular toxicity was performed *in vitro* in transgenic CHO-K1 cells and *in vivo* in dogs. Evidence of potential cardiotoxicity was limited to 7 to 8% increase in hERG currents at 300μM and a ~25% increase in maximal heart rate following administration of ≥1800 mg/m2.

*Toxicology*

Toxicities in rats and dogs after oral administration of Vorinostat were predictive of adverse effects in humans (anorexia, weight loss, fatigue, hematologic, and gastrointestinal effects).

In the 26-week GLP repeat-dose oral toxicity study of Vorinostat in Sprague-Dawley rats, a significant, dose-dependent reduction in food consumption and body weight gain was observed in both females and males at doses of 50 mg/kg/day (300 mg/m2/day) or 150 mg/kg/day (900 mg/m2/day). Lower white blood cell counts (WBC; ↑20-70%) (primarily due to the lower lymphocyte counts, but also including monocytes, eosinophils, and neutrophils), decreased globulin (up to 40%)and increased absolute reticulocyte counts (↑ 162%) were observed at all doses in at least one sex at more than one interval. The magnitudes of changes were dose dependent. Decreased thymus weight, and splenic and thymic lymphoid depletion along with bone marrow erythroid hyperplasia/myeloid hypoplasia were treatment-related findings. These treatment-related findings are likely related to the mechanisms by which Vorinostat induces cell differentiation and cell death. All these effects were partially or completely reversible by 4 weeks of recovery. Based on the findings at the lowest dose, a no-observable-adverse-effect level (NOAEL) could not be established in this study.

In the 26–week GLP repeat-dose oral toxicity study in beagle dogs with a 4-week recovery period, no adverse effects were found at doses of 20 mg/kg/day (400 mg/m2/day) and 60 mg/kg/day (1200 mg/m2/day); the doses administered via capsule were 20, 60, 80, 100, 125, or 160 mg/kg/day. Reversible GI toxicity (characterized by non-formed or liquid feces, and macroscopic: red foci, or microscopic findings: villous blunting with crypt epithelium regeneration, inflammation and necrosis in the large and small intestine) caused by Vorinostat was associated with the high-dose regimen (at the 160-mg/kg/day [3200 mg/m2/day]). Histologically, no evidence of serious, irreversible damage to any organ was observed. No treatment-related findings at any dose were noted for the endpoints of mean body weight, mean food consumption, ophthalmologic abnormalities, electrocardiographic parameters, or blood pressure. The NOAEL of Vorinostat was 60 mg/kg/day (1200 mg/m2/day) in this study.

*Genetic Toxicology*

Positive genotoxicity effects were obtained for Vorinostat in the *in vitro* assays (AMES Assay) for mutagenicity in the presence and absence of metabolic activation. SAHA was positive for clastogenicity in an *in vitro* CHO cell assay in the presence and absence of metabolic activation and an *in vivo* mouse micronucleus assay. Additional testing was conducted in human peripheral

lymphocytes. SAHA was not found to be clastogenic in this assay; however, a confirmatory assay was not conducted.

*Reproductive and Developmental Toxicology*

Assessment of reproductive toxicity of SAHA showed early embryonic development (Segment I) impairments in female rats treated with 300 mg/m2. This was manifested by treatment-related increases in the peri-implantation loss, a treatment-related increase in post-implantation loss secondary to increases in the percentage of resorptions and dead fetuses per implants. Decreases in the mean number of live fetuses/pregnant female (900 mg/m2/day) were also observed. The NOEL for embryonic development is 300 mg/m2. Based on a dose dependent increase in corpora lutea, the NOEL for female fertility is 15 mg/m2.

In male rats, there were no treatment related effects of Vorinostat on reproductive parameters at doses up to 900 mg/m$^2$ (the highest dose administered in this study).

Developmental toxicity was observed with SAHA, 50 mg/kg/day, when administered to GD6-20 rats and rabbits at 300 mg/m2 and 600 mg/m2, respectively. In rats, findings consisted of marked decreases in weight and increases in fetuses with skeletal variations (cervical ribs, supernumerary ribs and vertebral count, and sacral arch variations) and sites of incomplete ossifications (the skull, thoracic vertebra, and sternebra). In the rabbit, findings consisted of decreased fetal weight, incomplete ossification of the metacarpals, and increased incidence in 13$^{th}$ rib)

*Toxicokinetics studies*

Toxicokinetics studies were not conducted concurrent with fertility and reproductive toxicology studies. Additional studies in the rat and rabbit to assess placental transfer of SAHA were conducted. SAHA, SAHA Glucoronide, and N-phenyl-succinamic acid were found to cross the placenta and the fetus in both rats and rabbits. Fetal serum concentrations were found to be ≤50% of maternal serum concentrations and to have a delay in the $t_{max}$ of metabolites, indicative of slow transplacental transfer of SAHA metabolites.

*Carcinogenicity*

Carcinogenicity studies were not conducted and are generally not required to support the safety of the product for the proposed cancer indication.

# 4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

## 4.1 Sources of Clinical Data

- Clinical data reviewed to assess the efficacy of Vorinostat came from the pivotal trial (Protocol 001) and the supportive trial (Protocol 005)
- Clinical data reviewed to assess the safety of Vorinostat came from the pivotal and the supportive trials and 10 other trials (Protocols 002, 003, 004, 006, 008, 011, 012, 013, 015, and 016) which are included and detailed in the tables in section 4.2.
- Tables 2 to 6 include other ongoing trials for completeness
- All of these trials were sponsored by the applicant

- Findings of the review of digital photographs of the patients in the pivotal trial conducted by external consultant, Dr. Mark Pittelkow, Professor of Dermatology, Mayo Clinic College of Medicine, Rochester, MN, USA were also considered in evaluation of the efficacy claim

## 4.2 Tables of Clinical Studies

The following table defines different patient populations and the clinical studies by protocol numbers, and the number of total patients in each population and total patient exposures per population. Data from these trials were used for Vorinostat safety evaluation.

**Table 1. Patient Populations: Definitions, Protocols, Number of Patients, and Number of Patient Exposures (Applicant's Table)**

| Population Definition | Protocols | Total Patients Per Population | Total Patient Exposure Per Population |
|---|---|---|---|
| Vorinostat Monotherapy-CTCL | 001, 005 | 107 | 111[*] |
| Vorinostat Monotherapy-CTCL Stage IIB and Higher | 001, 005 – only Stage IIB and higher | 89[‡] | 93[‡] |
| Vorinostat Monotherapy – Solid Tumors | 002, 008 (Part I), 011, 006 (solid tumor patients) | 101 | 101 |
| Vorinostat Monotherapy – Hematologic Malignancies | 003, 004, 013, 006 (hematologic malignancy patients) | 87 | 87 |
| Vorinostat Combination Therapies | 012, 015, 016 | 10 | 10 |
| Total Patients | | 305 | 309 |

[*] In Protocol 005, 4 patients were exposed to 2 different dose cohorts.
[‡] These patients are a subset of the those in the Vorinostat Monotherapy – CTCL population.
Protocol 014, an on-going double-blind monotherapy study, provided summarized serious adverse experience data only.

[Ref. 5.3.5.2: P008] [Ref. 5.3.5.2: P001, P005] [Ref. 5.3.5.4: P002, P003V1, P004V1, P006, P011V1, P012V1, P013V1, P014V1, P015V1, P016V1, P029V1, P030V1]

The following tables detail the Vorinostat studies by their titles and objectives. The studies are grouped as:

- Completed Vorinostat Monotherapy Studies with full Clinical Study Reports
- Ongoing Open-Label Monotherapy Studies of Vorinostat
- Ongoing Open-Label Combination Therapy Studies
- Ongoing Blinded Monotherapy Studies
- Ongoing Monotherapy Studies (Banyu/Japan) with Interim Safety Reports

## Table 2. Completed Vorinostat Monotherapy Studies with full Clinical Study Reports (Applicant's Table)

| Protocol | Phase | Study Title | Dose | Study Objectives | n |
|---|---|---|---|---|---|
| 001 | IIb | Phase IIb Study in Advanced Cutaneous T-Cell Lymphoma (CTCL) | 400 mg once daily | Primary:<br>To determine the response rate of oral Vorinostat in the treatment of skin disease in patients with advanced CTCL.<br>Secondary:<br>1) to assess response duration<br>2) to evaluate relief of pruritis<br>3) to assess time to progression<br>4) to assess time to objective response<br>5) to assess safety and tolerability of oral Vorinostat | 74 |
| 002 | | | 400 mg once daily | Primary:<br>Secondary:<br>1) to determine the safety and tolerability of oral Vorinostat administered continuously | 12 |
| 005 | IIa | Phase IIa Study in Cutaneous T-Cell Lymphomas and Peripheral T-Cell Lymphomas Unresponsive to Conventional Therapy | 1) 400 mg once daily<br>2) 300 mg twice daily 3 out of 7 days<br>3) 300 mg twice daily 14 out of 21 days | Primary:<br>To determine the response rate for oral Vorinostat administered to patients with Cutaneous T-cell Lymphomas or Peripheral T-Cell Lymphomas.<br>Secondary:<br>1) to determine safety and tolerability<br>2) to determine duration of response | 33† |
| 006 | I | Phase I Study in Advanced Solid Tumors and Hematological Malignancies | 1) 200, 400, or 600 mg once daily<br>2) 200, 300, or 400 mg every 12 hours<br>3) 300, or 400 mg every 12 hours daily<br>for 3 out of 7 days | Primary:<br>To define a safe daily oral regimen of Vorinostat for phase II studies.<br>Secondary:<br>1) to evaluate the pharmacokinetic profile of the oral formulation of Vorinostat<br>2) to determine the oral bioavailability<br>3) to document any anti-tumor effects.<br>Additional: to assess the biological effects of Vorinostat on normal tissues and tumor cells and correlate outcomes of response with histone acetylation levels. | 73 |
| 008 | I | Phase I Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Vorinostat in Patients With Advanced Cancer | Part 1: A single 400 mg dose of Vorinostat administered on Day 1 in the fasted state and on Day 5 following a standard high fat meal with pharmacokinetic sampling for 48 hours post-dose. Continuous dosing with 400 mg once daily on Days 7 to 28. Dosing on Day 28 followed a standard high fat meal with pharmacokinetic sampling for 24 hours post-dose.<br>Part 2: Continuous dosing with 300 mg twice daily Vorinostat for 14 out of 21 days. The a.m. dose on Days 1 and 14 administered following a standard high fat breakfast with pharmacokinetic sampling for 12 hours post-dose. | Primary:<br>1) to evaluate the safety and tolerability<br>2) to obtain serum pharmacokinetics after single and multiple-dose administration<br>3) to obtain single-dose serum pharmacokinetics in the fed versus fasted state<br>Secondary:<br>To evaluate the urinary excretion of Vorinostat. | 23 |

## Table 3. Ongoing Open-Label Monotherapy Studies of Vorinostat (Applicant's Table)

| Protocol | Phase | Study Title | Dose | Study Objectives | n |
|---|---|---|---|---|---|
| 003 | I | Phase I Study in Advanced Leukemias or Myelodysplastic Syndromes | Starting dose at 100 mg three times daily, then escalation in the increments of 50 mg three times daily or 100 mg twice daily for 14 days out of 21 days<br>Second schedule tested 300 mg twice daily for 14 out of 21 days deescalated to 200 mg twice daily. | Primary:<br>To determine Maximum Tolerated Dose (MTD) of Vorinostat administered every 8 hours or every 12 hours for 14 out of 21 days.<br>Secondary: | 41 |
| 004 | I | Phase I/II Study in Advanced Multiple Myeloma | Original Dosing Regimen:<br>Starting dose at 200 mg administered every 12 hours for 5 out of 7 days. Escalation in the increments of 50 mg every 12 hours (total daily dose of 100 mg).<br>Amended Dosing Regimen:<br>Starting dose at 200 mg administered every 12 hours for 14 out of 21 days. Escalation in the increments of 100 mg every 12 hours (total daily dose of 200 mg). | Old Primary for Phase I:<br>To determine the MTD of Vorinostat administered every 12 hours for 5 out of 7 days during the first cycle (i.e., first 4 weeks).<br>New Primary for Phase I:<br>To determine the MTD of Vorinostat administered every 12 hours for 14 out of 21 days during the first 2 cycles (i.e., first 6 weeks).<br>Primary for Phase II:<br>To assess the safety and overall response rate to Vorinostat.<br>Secondary: | 13 |
| 011 | II | Phase II Study in Patients with Relapsed or Refractory Breast, Colorectal, and Non-Small Cell Lung Cancer | Original Dosing Regimen:<br>400 mg twice daily for 14 out of 21 days.<br>Amended Dosing Regimen:<br>300 mg twice daily for 14 out of 21 days.<br>Amended Dosing Regimen:<br>200 mg twice daily for 14 out of 21 days. | Primary:<br>3) To evaluate the safety and tolerability.<br>Exploratory: | 16 |
| 013 | II | Phase II Study in Relapsed Diffuse Large B-Cell Lymphoma | Original Dosing Regimen:<br>300 mg twice daily x 14 days every 21 days.<br>Amended Dosing Regimen:<br>300 mg twice daily x 3 days every 7 days. | 2) To assess the safety or oral Vorinostat in this patient population. | 10 |

## Table 4. Ongoing Open-Label Combination Therapy Studies (Applicant's Table)

| Protocol | Phase | Study Title | Dose | Study Objectives | n |
|---|---|---|---|---|---|
| 012 | I | A Phase I Clinical Trial of Oral Suberoylanilide Hydroxamic Acid in Combination with Pemetrexed and Cisplatin in Patients with Advanced Cancer | Initial Dose Level:<br>Vorinostat 200 mg twice daily for 14 out of 21 days + pemetrexed and cisplatin<br>Amended Design:<br>Cohort A (Vorinostat twice daily + pemetrexed and cisplatin):<br>Dose Level 1 - 300 mg twice daily for 3 out of 7 days for first week, then 2 weeks off<br>Dose Level 2 - 300 mg twice daily for 3 out of 7 days for first 2 weeks, then 1 week off<br>Dose Level 3 - 300 mg twice daily for 3 out of 7 days repeated weekly for 3 weeks<br>Cohort B (Vorinostat once daily + pemetrexed and cisplatin):<br>Dose Level 1 - 400 mg daily for 7 days<br>Dose Level 2 - 500 mg daily for 7 days<br>Dose Level 3 - 600 mg daily for 7 days | Primary:<br>1) To determine the (MTD) of Vorinostat when administered in repeated 21-day cycles in combination with standard doses of pemetrexed and cisplatin in patients with advanced solid tumors<br>2) To determine the MTD of Vorinostat when administered in repeated 21-day cycles in combination with standard doses of pemetrexed in patients with advanced solid tumors<br>3) To assess at the MTD the pharmacokinetics of Vorinostat, pemetrexed, and cisplatin when administered in combination.<br>Secondary:<br>To assess the safety and tolerability of these combination regimens. | 6 |
| 015 | I | Phase I Clinical Trial of Oral Suberoylanilide Hydroxamic Acid (L-001079038) in Combination With Bortezomib in Patients With Advanced Multiple Myeloma | Combination of Vorinostat + increasing doses of bortezomib<br>Dose Level 1 –<br>200 mg twice daily for 14 days<br>Dose Level 2 –<br>200 mg twice daily for 14 out of 21 days<br>Dose Level 3 –<br>300 mg twice daily for 14 out of 21 days<br>Dose Level 4 –<br>300 mg twice daily for 14 out of 21 days<br>Dose Level 5 –<br>300 mg twice daily for 14 out of 21 days. | Primary:<br>To determine the MTD for the combination of oral Vorinostat and standard doses of bortezomib in patients with advanced multiple myeloma.<br>Secondary:<br>To assess the safety and tolerability of the combination regimen of Vorinostat and bortezomib.<br>Exploratory:<br>1) To assess the pharmacokinetics of Vorinostat alone and when administered in combination with bortezomib | 1 |
| 016 | I | Phase I Study in Combination with Bexarotene in Patients with Advanced CTCL | Starting dose at 200 mg once daily Vorinostat + 150 mg/m2 bexarotene once daily then escalating to 400 mg once daily Vorinostat in 100 mg increments followed by escalating to 300 mg/m2 bexarotene in 75 mg increments. No intra-patient dose escalation. | Primary:<br>To determine MTD of Vorinostat administered once daily x 28 days in repeated cycles in combination with escalating doses of up to 300 mg/m2 bexarotene.<br>Secondary:<br>(1) To assess the safety and tolerability this regimen | 6 |

## Table 5. Ongoing Blinded Monotherapy Studies (Applicant's Table)

| Protocol | Phase | Study Title | Dose | Study Objectives | n |
|---|---|---|---|---|---|
| 014 | III | A Phase III, Randomized, Double-Blind Placebo-controlled Trial of Oral Suberoylanilide Hydroxamic Acid in Patients With Advanced Malignant Pleural Mesothelioma Previously Treated With Systemic Chemotherapy | Original Dose: 300 mg twice daily for 14 out of 21 days. Amended Dose: 300 mg twice daily for 3 out of 7 days. | Primary: patients with advanced malignant pleural mesothelioma who have failed prior chemotherapy that had included pemetrexed in combination with either cisplatin or carboplatin and to determine the overall safety and toxicity of Vorinostat in this population. | 10 |

## Table 6. Ongoing Monotherapy Studies ( ) with Interim Safety Reports (Applicant's Table)

| Protocol | Phase | Study Title | Dose | Study Objectives | n |
|---|---|---|---|---|---|
| 029 | I | A Phase I Clinical Trial of Vorinostat (MK-0683) in Patients With Solid Tumors | Vorinostat will be administered orally once daily on Days 1 (fasted), 3 (fed) and 19 (fed) as well as twice daily on Days 5-18. The dose escalation on each patient is prohibited during this period. Cohorts are as follows:<br>1 – 100 mg twice daily<br>2 – 200 mg twice daily<br>3 – 300 mg twice daily<br>4 – 400 mg twice daily<br>In addition, the following dose level will be conducted in concurrence with dose level 3 above:<br>3 – 400 mg once daily | Primary:<br>1) To determine the MTD, or the maximum acceptable dose (MAD) and evaluate the dose limiting toxicity (DLT) of Vorinostat in patients with solid tumors<br>2) To evaluate the overall safety profile of Vorinostat in the first cycle<br>Secondary:<br>1) To obtain pharmacokinetics of Vorinostat after 14 days administration with once daily or twice daily regimen<br>2) To obtain pharmacokinetics of Vorinostat in the fasted and fed state<br>3) To evaluate the overall safety profile of Vorinostat in subsequent cycles | 15 |
| 030 | I | A Phase I Clinical Trial of Vorinostat | Vorinostat will be administered orally once daily on Days 1 and 17 as well as twice daily on Days 3-16. The dose escalation on each patient is prohibited during this period.<br>Cohorts are as follows:<br>1 – 100 mg twice daily<br>2 – 200 mg twice daily<br>3 – 300 mg twice daily<br>4 – 400 mg twice daily | Primary:<br>1) To determine the MTD, or the MAD, and evaluate the DLT of Vorinostat in the first cycle;<br>2) To evaluate the overall safety profile of Vorinostat in the first cycle.<br>Secondary:<br>1) To obtain pharmacokinetics of Vorinostat<br>2) To evaluate the overall safety profile of Vorinostat in subsequent cycles | 12 |

## 4.3 Review Strategy

- Data from the pivotal trial (Protocol 001) and the supportive trial (Protocol 005) were reviewed in detail using the submitted electronic database. (This was a joint Clinical and Statistical review and the Clinical Reviewer had the primary responsibility for writing the review)
- Applicant's original efficacy analysis and its update were reviewed and confirmed independently by the medical reviewer
- Applicant was also asked to recalculate the secondary endpoints of time to progression and duration of response using FDA provided definitions of these endpoints and the results were reviewed and confirmed
- Digital photographs of all the responding patients in the pivotal trial (Protocol 001) were reviewed by the clinical reviewers (Dr. Bhupinder S Mann, Medical Officer and Dr. John Johnson, Team Leader) along with the external consultant (Dr. Mark Pittelkow, Professor of Dermatology, Mayo Clinic College of Medicine, Rochester, MN, USA)
- For evaluation of safety, in addition to the pivotal and supportive trials, data from 10 other trials was reviewed (these have been tabulated above)
- Material used in the applicant's presentation to the FDA after the NDA submission (Vorinostat Briefing Meeting on May 8, 2006) was reviewed and necessary clarifications were obtained verbally

## 4.4 Data Quality and Integrity

A number of methods were used to evaluate the quality and integrity of the data from the pivotal trial and other trials. Any discrepancies in the results obtained by the reviewer and the applicant are discussed in the relevant sections of the review.

- The medical reviewer conducted independent efficacy and safety analyses based on the primary data submitted in SAS transporter files after conversion to JMP format.
- Copies of the case report forms, body diagrams, and the supporting digital photographs from selected patients were reviewed by the medical reviewer
- Digital photographs and body diagrams of all the responding patients from the pivotal trial (Protocol 001) were reviewed by the medical reviewer in detail after the NDA submission.
    - Digital photographs and body diagrams of all the responding patients from the pivotal trial (Protocol 001) were also reviewed at a later date (The 21$^{st}$ of August 2006) by the clinical reviewers (Dr. Bhupinder S Mann, Medical Officer and Dr. John Johnson, Team Leader) and external consultant (Dr. Mark Pittelkow, Professor of Dermatology, Mayo Clinic College of Medicine, Rochester, MN, USA).
    - Multi-panel (eight panels) computerized display equipment (courtesy DMIHP) was used to serially display patients' photographs from up to six visits at-a-time to allow an efficient review.

- Reports of all the serious adverse events submitted in this NDA were reviewed by the clinical reviewer

Division of Scientific Investigations (DSI) of the FDA conducted two on-site audits of the pivotal trial (Protocol 001). These sites were selected based on the number of patients enrolled into the trial.

**Table 7. Division of Scientific Investigations (DSI) Audit**

| **Clinical Investigators** | **District Office** | **Protocols** | **Total No. Enrolled** | Date Inspection Completed | ***"Preliminary Results*** |
|---|---|---|---|---|---|
| (Site 0009)<br>Timothy M. Kuzel, MD<br>Northwestern University Medical School<br>Suite 850<br>676 North Saint Clair<br>Chicago, IL 60611 | CHI-DO | Protocol P001 (CL-01-0303) | 6 Subjects with 2 responses | 7/21/06 | No deviation from regulations |
| (Site 0011)<br>Theresa R. Pacheco, MD<br>University of Colorado Health Sciences Center<br>Room CP-3245<br>1665 North Ursula Street<br>Aurora, CO 80010 | DEN-DO | Protocol P001 (CL-01-0303) | 5 Subjects with 4 responses | 7/20/06 | No deviation from regulations |
| **SPONSOR INSPECTION**<br><br>Merck and Co., Inc.,<br>World Wide Regulatory Affairs Blue Bell, PA | PHIL-DO | Protocol P001 (CL-01-0303 | | 8/10/06 | No deviation from regulations |

## 4.5 Compliance with Good Clinical Practices

The studies submitted to support this NDA were conducted in accordance with acceptable ethical standards and good clinical practices.

- The trial protocols and amendments were reviewed by the Institutional Review Boards (IRBs)

- The studies were conducted in conformance with Good Clinical Practice (GCP) standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.
- IRB approval letters were received and verified before the shipment of study therapy.
- Prior to initiation of the study, an informed consent agreement explaining the procedures of the study, together with the potential risks, was read by and explained to all the patients or their legally authorized representatives. Each patient (or representative) signed and received a dated copy of such an informed consent form and was assured of freedom to withdraw from participation in the study, without prejudice, at any time. The same process was followed for each patient continuing in the study prior to the initiation of each new amendment using updated informed consent forms.

## 4.6 Financial Disclosures

- In compliance with the U.S. Food and Drug Administration's regulation, *Financial Disclosure by Clinical Investigators,* published 02-Feb-1998 and revised 31-Dec-1998, the applicant provided the requested information concerning the financial interests of and compensation to the investigators participating in the covered clinical studies presented in this application.
- Integrity of the data in this single-arm open-label Phase-2 study is preserved.

**Financial Disclosure Forms**

- Form FDA 3454 – Certification: Financial Interest and Arrangements of Clinical Investigators
- Form FDA 3455 – Disclosure: Financial Interests and Arrangements of Clinical Investigators

**Presentation of Financial Disclosure Information**

- The applicant Merck & Co., Inc. (hereinafter referred to as "Merck") acquired the initial developer of Vorinostat, Aton Pharma, Inc. (hereinafter referred to as "Aton"), on 17-Mar-2004. Merck has submitted the financial disclosure information of the clinical investigators in two parts. Part I represents the clinical investigators' financial interests and arrangements in Merck. Part II represents the clinical investigators' financial interest and arrangements in Aton.
- Protocol 002 [redacted] was solely conducted by Aton and completed prior to the date of acquisition, therefore, the study is not included in Part I. Protocols 001, 005, and 006 were ongoing at the time of the acquisition. The Form FDA 1572s, where required, were amended to include additional clinical investigators at the sites after the date of acquisition for the ongoing studies.

**Process used to collect information**

- Investigators who met the definition of Clinical Investigator were requested to provide information related to their financial interests and/or arrangements in Merck. In compliance with the regulatory requirement for the Sponsor to demonstrate "due diligence", multiple requests for this information were made, when possible, to clinical investigators who did not respond.
- Merck Corporate Finance conducted an internal search for all payments that met the definition of "significant payments of other sorts" and reported the information, as appropriate. "Significant payments of other sorts" are calculated cumulatively when an investigator is involved in more than one protocol in a submission.

**Summary of findings**

**Part I**

- Total number of Merck Clinical Investigators and Sub-investigators was 123
- None of these Clinical Investigators was a full or part time employee of the Merck
- Total number of Clinical Investigators and Sub-investigators who are certified regarding an absence of financial arrangements is 114 (92.6%)
- Eight (8) investigators who did not return the Financial Disclosure certification were no longer at the study sites
- One investigator reported that he was —

—

- Merck has not entered into any financial arrangement with its Clinical Investigators whereby the value of the compensation to the investigator could be affected by the outcome of the study (21 CFR 54.2(a)).

**Part II**

- Total number of Merck/Aton Clinical Investigators and Sub-investigators was 51
- None of these Clinical Investigators was a full or part time employee of the Merck
- Total number of Clinical Investigators and Sub-investigators who are certified regarding an absence of financial arrangements is 46 (90.2%)
- Five (5) investigators did not return the Financial Disclosure certification, one is known to be no longer at the study site

***Reviewer Comments:*** *the pivotal trial supporting the NDA is a single-arm open-label Phase-2 study. The primary efficacy endpoint of the trial—objective response rate using physician assessed SWAT score—was supported by the patients' photographs. Thus, the efficacy findings of the trial could be confirmed.*

# 5 CLINICAL PHARMACOLOGY

## 5.1 Pharmacokinetics

Vorinostat will be available as 100-mg immediate-release, hard-gelatin capsules.

**Absorption**

Following oral administration of the 400 mg dose, Vorinostat is rapidly absorbed with a mean peak concentration of 319±140 ng/mL occurring between 0.5-14 hours (Median = 4 hours after dosing).

**Bioavailability**

The absolute bioavailability averages 42.5±16.1% in the fasted state.

**Effect of Food Intake**

Food intake increases the extent and rate of Vorinostat absorption. Following a high-fat breakfast, the mean $AUC_{Inf}$ of Vorinostat was increased by 38% and its $T_{max}$ was prolonged by 2.5 hours. CTCL patients were administered Vorinostat with food (if possible) during the pivotal trial (Protocol 001). The product label indicates that Vorinostat dosage should be administered with food.

**Distribution**

Vorinostat is extensively distributed throughout the body following intravenous administration of a 400 mg dose; its volume of distribution ($V_z$) averaged 150±51 L, which greatly exceeds total body water (42 L).

Vorinostat is moderately bound to human plasma proteins (71%) over a 0.5 – 50 µg/mL concentration range.

**Metabolism and Clearance**

Vorinostat is a high clearance drug with a short elimination half-life. The total plasma clearance and elimination half-life averaged 150±24 L/h and 0.71±0.26 hour, respectively, following intravenous (IV) administration of a 400 mg dose to eight patients. The elimination half-life of Vorinostat was longer following oral administration than IV administration (1.7±1.0 hours vs. 0.71± 0.6 hour, respectively), suggesting that the disposition of Vorinostat after oral administration may be absorption rate limited.

Vorinostat did not accumulate after 400 mg QD dosing for 28 days.

Vorinostat exhibits linear pharmacokinetics over the doses of 200-600 mg.

*In vitro* studies with human (S9) liver fractions indicate that Vorinostat is extensively metabolized in the liver by direct glucuronidation to form the *O*-glucuronide metabolite of Vorinostat followed by hydrolysis of the hydroxamic functional group to form 8-anilino-8-oxooctanoic acid. *In vitro* studies with human hepatocytes identified a β-oxidation product, 4-anilino-4-oxobutanoic acid.

*In vitro* studies with cDNA-expressed human UDP-glucuronosyltransferases (UGTs) indicate that Vorinostat was glucuronidated by several UGTs including UGT1A1, UGT1A3, UGT1A7, UGT1A8, UGT1A9, UGT2B7, and UGT2B17.

Two pharmacologically inactive metabolites, O-glucuronide Vorinostat and 4-anilino-4-oxobutanoic acid were found in the systemic circulation and urine following oral administration of Vorinostat. The mean $AUC_{24}$ values of the metabolites were 4-fold and 13-fold higher for *O*-glucuronide and 4-anilino-4-oxobutanoic acid, respectively, than that for the parent drug.

The analysis of urine data from Study 008 indicate that Vorinostat is predominantly eliminated through metabolism as less than 1% of the dose was excreted unchanged in urine. The mean percent of the dose recovered in urine as the *O*-glucuronide metabolite and 4-anilino-4-oxobutanoic acid was 16% and 36%, respectively. Total urinary recovery of Vorinostat and its two inactive metabolites averaged 52% of the oral dose. The Applicant has not conducted a mass balance study for Vorinostat.

**Effect of Common Covariates**

Exploratory analyses of data from Studies 006 and 008 (Total N=67, 42 males and 25 Females) suggest that **age, gender, weight, or height,** had no effect on the exposure of Vorinostat.

The effect of **race** could not be assessed as most of the patients enrolled in these studies were Caucasians.

No significant relationship could be noted between exposure of Vorinostat and total **bilirubin**, aspartate aminotransferase (AST), alanine aminotransferase (ALT), or serum **creatinine** as the values of these covariates were within the normal ranges in the studied patients.

As **age** has no effect on the exposure of Vorinostat, dosage adjustment is not necessary in elderly CTCL patients.

The Applicant did not evaluate the effect of **hepatic impairment** on the pharmacokinetics of Vorinostat (see Phase 4 Commitments).

The Applicant did not evaluate the effect of **renal impairment** on the pharmacokinetics of Vorinostat. There is no need to conduct a study in this patient population as less than 1% of the administered dose was excreted as unchanged drug in urine.

No *in vivo* **drug-drug interactions** studies were conducted for Vorinostat.

Vorinostat was not a substrate of any **CYP P450** enzyme in human liver microsomes.

Vorinostat was not an inhibitor of the CYP P450 enzymes (1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4 activities) in human liver microsomes ($IC_{50} > 100$ μM, $[I]/K_i$ ratio=0.012). However, *in vitro* studies with primary cultured human hepatocytes showed some potential for inhibition of 2C9 and 3A4 activities at Vorinostat concentrations of $\geq 10$ μM.

Vorinostat was an inducer of CYP1A2 activity in primary cultured human hepatocytes. The percent induction was 24% which is lower than that proposed in the draft FDA Guidance for Drug Interaction Studies (Viz., 40%). Thus, no *in vivo* study is warranted.

No data were available to determine whether Vorinostat is a substrate and/or inhibitor for **P-glycoprotein efflux transporter** (see Phase 4 Commitments).

## 5.2 Pharmacodynamics

- A concentration-response analysis of clinical studies for Vorinostat suggests that Vorinostat may increase **QTc interval** from baseline by 40 milliseconds.
- However, these studies were not designed or controlled to adequately assess the impact of Vorinostat on QTc interval.
- At present, the impact of Vorinostat on QTc interval is unclear.

## 5.3 Exposure-Response Relationships

- Relationships between dosing schedules and either mean response rate or mean percent incidence of major toxicities (grade 3-4) were explored.
- Although the data were limited by the number of patients the findings confirmed that the 400 mg QD dosing schedule provided a reasonable efficacy and safety profiles.

## 6.1.2 General Discussion of Endpoints

The objectives and the endpoints used in the pivotal trial (Protocol 001) and the supportive trial (Protocol 005) are shown in the table below. Detailed definitions are provided following the table.

**Table 8. Objectives and Endpoints in Protocols 001 and 005**

| | **Pivotal Trial (Protocol 001)** | **Supportive Trial (Protocol 005)** |
|---|---|---|
| **Objectives** | **Primary:**<br>To determine the response rate of oral Vorinostat *in the treatment of skin disease* in patients with advanced Cutaneous T-cell Lymphoma (CTCL) (Stage IIB or higher) who have progressive, persistent, or recurrent disease<br>**Secondary:**<br>(1) To assess response duration<br>(2) To evaluate the relief of pruritis<br>(3) To assess time to progression<br>(4) To assess time to objective response | **Primary:**<br>To determine the response rate for oral Vorinostat administered to patients with Cutaneous T-cell Lymphomas or Peripheral T-Cell Lymphomas.<br>**Secondary:**<br>(1) To determine safety and tolerability<br>(2) To determine duration of response |
| **Primary response parameter** | **Response rate** was the primary endpoint. Severity-weighted Assessment Tool (SWAT) was used to quantify total skin involvement with the disease, and patient's response status was defined by the changes in the SWAT score from the baseline<br>**SWAT:**<br>The investigator measured the percentage total body surface area (%TBSA) involvement—separately for patches, plaques, and tumors—within 12 body regions using the patient's palm as a "ruler".<br>The total %TBSA for each lesion type was multiplied by a severity weighting factor (1=patch, 2=plaque, and 4=tumor) and summed to derive the SWAT score | **Response rate** was the primary endpoint. Physician's Global Assessment (PGA) was used to define patient's response status<br>**PGA:**<br>The investigator assessed improvement or worsening in the overall disease compared to the baseline, based on the overall clinical impression.<br>Index and non-index cutaneous lesions as well as cutaneous tumors, lymph nodes, and all other disease manifestations were also assessed and included in the overall clinical impression.<br>The investigator assigns a score of 0 to 6, where 0=completely clear or CCR, and 6=worse or PD |
| **Secondary response parameter** | (1) Duration of response<br>(2) Pruritis Relief<br>(3) Time to Response | (1) Duration of response<br>(2) Pruritis Relief<br>(3) Time to Response |

| | (4) Time to Progression | (4) Time to Progression |
|---|---|---|
| **Measurement of pruritis relief** | Patients completed a self-administered questionnaire that rated the intensity of pruritis over the past week on a 10 point scale (0=no itching to 10=itching as bad as it can be), and also recorded any change in the amount of medication to relieve symptoms of itching in the past week compared to the previous week | Patients were asked by the study staff to rate their pruritis on a scale of 0 (no itching) to 10 (worst imaginable itch) at baseline and each study visit |

# DETAILS OF ENDPOINTS USED IN PROTOCOL 001 (THE PIVOTAL TRIAL)

## Primary Response Parameters

## Response Rate

The primary endpoint in Protocol 001 was the response rate based on assessment of the overall skin disease measured by the Severity Weighted Assessment Tool (SWAT) in patients with Stage IIB or higher CTCL

## SWAT Evaluation

The original SWAT was developed to quantify skin disease burden in CTCL. The investigator to mapped patch, plaque or tumor lesions on a two dimensional ventral and dorsal diagram of the human body and a standardized grid placed over the figures was used to calculate the TBSA involved. The final values were weighted dependent on the type of lesion and the values were added to produce the SWAT score.

In Protocol 001, the methodology of using SWAT was modified. The lesion types were mapped onto body diagrams to document skin involvement. However, instead of a point-counting standardized grid placed on the body diagram, the patient's palm was used as a "ruler" to measure the %TBSA involvement within each of the 12 regions with a pre-assigned %TBSA, based on previously published methodology.

Figure 1 shows the percentage of total body surface area by body region. The patient's palm with 4 fingers, excluding the thumb, (measured from wrist to fingertips) was assumed to be 1% of the TBSA and the patient's palm without fingers was assumed to be 0.5% of the TBSA.

The areas of involvement were categorized as patch, plaque or tumor.

- Patch was defined as abnormal skin not elevated from normal skin
- Plaque was defined as abnormal skin elevated from normal skin by <5 mm
- Tumor was defined as a plaque elevated ≥ 5 mm (Ulceration or erythema with fissuring are treated as tumor for calculations of area involved and severity weighting)

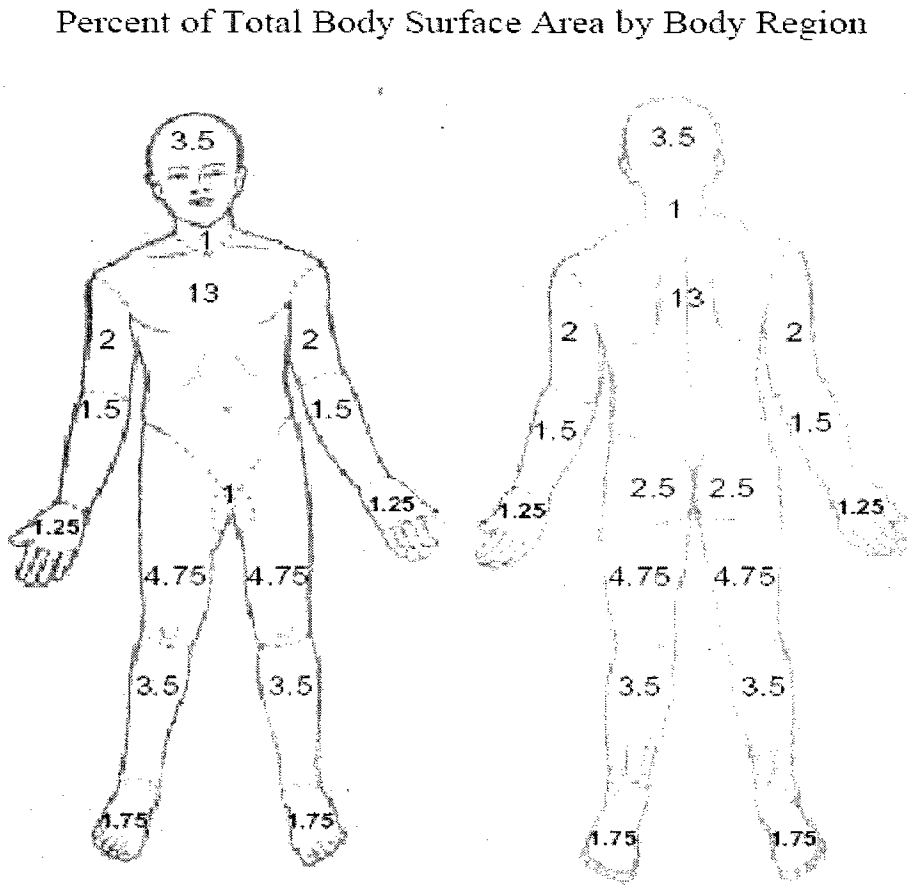
To determine the SWAT score, the areas of involvement with patch, plaque and tumor lesions were multiplied by 1, 2 and 4, respectively. The modified SWAT severity weighting is identical to that used by the European Organization for Research and Treatment of Cancer (EORTC) tumor burden index.

Figure 2 shows the case report form (CRF) used to record SWAT score. The SWAT CRF allowed the investigator to determine the percentage of TBSA involvement by skin disease and then weigh these percentages based upon the lesion type. The TBSA for each lesion type was then weighted by a multiplier (patch x 1, plaque x 2, and tumor x 4). The calculations for %

TBSA by lesion type, skin score subtotal by lesion type and skin score total were calculated by the Sponsor using a validated program, regardless of the values recorded in the gray areas of the form.

- SWAT assessment was made at baseline, every 4 weeks on treatment, and at the post-treatment visit. The response rate of overall skin improvement was estimated based on changes from baseline in the SWAT score.

**Figure 1. Percent of Total Body Surface Area by Body Regions**



Case Report Form to Record SWAT

**PHYSICIAN ASSESSMENT OF OVERALL SKIN DISEASE**

☐ Not Done

**Date of assessment:** _____ (DD MMM YYYY) **Physician's name:** _____

**Physician's signature:** _____

**Full body photographs taken:** ☐ Yes ☐ No **Date sent to Canfield:** _____ (DD / MMM / YYYY)

**Severity-Weighted Assessment Tool (SWAT)**

**Please do not leave any spaces blank. Fill in blank spaces with dashes (--).**

| Region | % TBSA for the region | % TBSA Patch (or flat erythema) | % TBSA Plaque (or elevated/ indurated erythema) | % TBSA Tumor/ Ulceration (or erythema w/fissuring, ulceration) |
|---|---|---|---|---|
| Head | 7 | | | |
| Neck | 2 | | | |
| Anterior Trunk | 13 | | | |
| Posterior Trunk | 13 | | | |
| Buttocks | 5 | | | |
| Genitalia | 1 | | | |
| Upper Arms | 8 | | | |
| Forearms | 6 | | | |
| Hands | 5 | | | |
| Thighs | 19 | | | |
| Lower Leg | 14 | | | |
| Feet | 7 | | | |
| % BSA by category | 100 | | | |
| Severity Weighting Factor | | X 1 | X 2 | X 4 |
| Skin Score Subtotal | | | | |
| Skin Score Total | | | | |

**Figure 2. Case Report Form to Record SWAT**

**Use of photographs for supportive documentation**

- Serial global half-body photographs and serial close-up photographs of distinct individual lesions were taken for supportive documentation of changes in the skin disease.
- These photographs were *only supportive,* and they were *not* used to derive SWAT skin assessment scores
- To optimize investigator objectivity and to minimize the potential for intra- or inter-investigator variability in the measurement of overall skin disease using SWAT tool, the study investigators received standardized training. They underwent training in the use of the SWAT method at the investigator meetings, and additional self-administered training was performed by all investigators through a scoring exercise of a teaching set of photographs. They were instructed to follow a standard operating procedure (SOP) outlined in the operations manual.
- Only the investigators who had received the training were permitted to conduct SWAT assessments during the clinical study.
- To avoid inter-investigator variability in the SWAT measurements for a patient, the same investigator was to perform the overall assessment of skin disease for a given patient over the course of the study, whenever possible.

**Objective Clinical Response**

- An objective clinical response was defined as either no evidence of clinical disease or a marked improvement that is $\geq$ 50% decrease in the SWAT skin assessment score compared to the baseline.
- Confirmation of response was required by a second assessment after at least 4 weeks.

**Clinical Complete Response**

- A Clinical Complete Response (CCR) required 100% improvement with no evidence of disease

**Partial Response**

- A Partial Response (PR) required at least a 50% decrease in the SWAT skin assessment scores compared to the baseline.
- Confirmation of response was required by a second assessment after at least 4 weeks.

**Confirmatory Imaging Assessment of Responding Patients**

- Patients who achieved a CCR or a PR by the SWAT scoring had a full CT scan assessment of their nodal disease after the response was confirmed by a second assessment.

- A 50% increase in the sum of the products of the greatest diameters of the index lymph nodes by CT scan while on treatment compared to baseline would render an assignment of Progressive Disease (PD).

**Stable Disease**

- Stable Disease (SD) was defined as a <50% decrease in the SWAT skin assessment scores compared to the baseline.

**Progressive Disease**

- PD required at least a 25% increase in SWAT skin assessment scores compared to the baseline *while the patient was actively taking study drug*, or at least a 50% increase in the sum of the products of the greatest diameters of pathologically positive lymph nodes (documented by biopsy) compared to the baseline, *while the patient was taking the study drug.*
- The patients assessed to have PD *required confirmation* by a second assessment 4 weeks later. This was to allow patients who experienced a temporary flare of disease due to skin infection or other intercurrent illness to continue in the study. Table below describes the response assessment criteria.

**Table 9. Definitions of CCR, PR, SD, and PD (Applicant's Table)**

| Assessment | Description | Status |
|---|---|---|
| Completely clear | No evidence of disease; 100% improvement | CCR |
| Marked improvement | Greater than or equal to 50% decrease in skin assessment scores compared to baseline and improvement is maintained for 4 weeks | PR |
| Slight improvement | Less than 50% decrease in skin assessment scores compared to baseline | SD |
| Worse | ≥ 25% increase in skin assessment scores compared to baseline while the patient is actively taking the study drug<br>or<br>≥ 50% increase in the sum of the products of the greatest diameters of pathologically positive lymph nodes (should be documented by biopsy) compared to baseline while the patient is actively taking the study drug | PD |

***Reviewer Comments:***

- *SWAT score alone determines the assignment of response status as long as the nodal disease is stable or responding. If the nodal disease shows progression, it overrides the response determined by the SWAT score.*
- *Sezary cell count is not taken into consideration to assign response status based on the SWAT score. Based on the available literature: Sezary cell counting is not highly reliable in the lower ranges, there is controversy about the number of Sezary cells that decides whether there is blood involvement or not, and discordant skin and Sezary cell responses*

*are common. According to Dr. Mark Pittelkow, the External FDA Consultant for this NDA, Sezary cell numbers can go either way—in the presence of a skin response, Sezary cell count can increase, decrease, or not change.*

**Secondary Response Parameters (Protocol 001)**

The secondary endpoints were:

- Duration of Overall Response
- Pruritis Relief
- Time to Progression
- Time to Response

**Duration of Overall Response**

- The duration of overall response was measured from the time when criteria were first met for CCR or PR (whichever was first recorded) until the first date when an increase in the skin disease SWAT score was *greater than 50% of the difference between the baseline score and the nadir score.*
- The magnitude of increase was required to be confirmed by a second assessment 1 to 4 weeks after the initial assessment.
- For patients who were still responding at the data cut-off date, the response duration was censored at the last visit before the data cut-off date

**Time to Progression**

- Time to progression was measured from the start of the treatment until the criteria for progression were first met
- Progression was defined as $\geq$ 25% increase in skin assessment scores compared to the baseline *while the patient is actively taking the study drug* or $\geq$ 50% increase in the sum of the products of the greatest diameters of pathologically positive lymph nodes (documented by biopsy when possible).
- Although it was specified in the protocol that progression of disease needed to be confirmed by a second consecutive assessment, if a patient only had one assessment of PD and no other assessment after that, it was still considered as PD in the study analyses.

**Time to Response**

- Time to response was measured from the start of the treatment to the time when the criteria were first met for CCR or PR (whichever was recorded first).

***Reviewer Comments:***

*FDA noted the possibilities of overestimations of benefits with the applicant's definitions of time to progression (patient must be actively taking the study drug and need for a confirmatory visit) and duration of overall response (increase in the SWAT score for calling progression must be greater than 50% of the difference between the baseline score and the nadir score and the loss of response must be confirmed at a second visit 1 – 4 weeks later).*

***FDA asked the applicant to recalculate these endpoints.***

For time to progression:

*For each patient in Study 001 please re-calculate Time to Progression defining progression as >25% increase in skin assessment scores compared to nadir measurements (or >50% increase in the sum of the products of the greatest diameters of pathologically positive lymph nodes, documented by biopsy when possible). Confirmation at a second visit is not required and the patient need not be actively taking study drug.*

For duration of overall response:

*For each responding patient in Study 001 please re-calculate the Duration of Overall Response measuring the duration of overall response from the time when criteria are first met for CCR or PR (whichever first recorded) until the first date when an increase in skin assessment by SWAT score is greater than 50% from the nadir score. Confirmation at a second visit is not required and the patient need not be taking study drug.*

**Pruritis Relief**

**Pruritis Assessment Questionnaire**

- The intensity of pruritis was evaluated at baseline and during each visit using a pruritis questionnaire
- The pruritis questionnaire was drafted with clinical input based on review of pruritis questionnaires used in previous CTCL clinic studies (bexarotene and denileukin diftitox)
- Pruritis assessment questionnaire was a two-part, patient-completed and self-administered questionnaire that assessed the skin itch over the past week using a 10-point scale (0 = no itching, 10 = itching as bad as it can be)
- The patient also had to provide the amount of medication taken to relieve symptoms of itching in the past week compared to the amount taken the previous week
    - Response categories for medication use: (a) did not use, (b) used less, (c) no change in use, or (d) used more
- A 3-point decrease in pruritis intensity, confirmed by a second assessment at least 4 weeks later, and without an increase (response categories a, b, or c) in the use of anti-pruritic medications, was considered clinically significant in those patients whose pruritis score was > 3 on the 0-10 point scale at the baseline.
- This 3-point improvement in pruritis intensity was pre-specified. It was based on preliminary data from Protocol 005 as the minimally important difference based on the SD of pruritis intensity at baseline among patients who had pruritis at study entry (n=10 patients, SD=2.4).
    - This 3-point improvement represents one SD, which is a more conservative estimate of minimally important difference than the 0.5 SD method presented in the literature as one of several methods used to define a minimally important difference.

***Reviewer Comments:*** *Patient reported outcomes (PROs), such as pruritis relief, cannot be reliably measured in open-label single-arm trials.*



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ON ORIGINAL

# DETAILS OF THE ENDPOINTS USED IN PROTOCOL 005 (THE SUPPORTIVE TRIAL)

- The primary endpoint in Protocol 005 was the response rate based on evaluation of overall improvement in CTCL-related conditions using Physician Global Assessment (PGA)
- Patients were assessed for response weekly during the first 4 weeks, at Week 6, and then every 3 weeks.
- See the table below that describes the PGA scores

**Primary Response Parameter(s)**

**Response Rate**

- The primary response parameter in Protocol 005 was the response rate based on the PGA
- This required the investigator to assess the overall disease compared to the baseline, and to consider index and non-index cutaneous lesions, cutaneous tumors, lymph nodes, and other disease manifestations
- Objective response was defined as a Clinical Complete Response (CCR) or Partial Response (PR) with confirmation of at least a PR 4 weeks later

**Clinical Complete Response (CCR)**

- A clinical complete response required 100% clearing of all the disease findings

**Partial Response (PR)**

- PR required at least 50% improvement in the disease findings

**Table 10. Physician's Global Assessment of Clinical Condition (Applicant's Table)**

| | | |
|---|---|---|
| 0 = Completely clear | No evidence of disease; 100% improvement | CCR |
| 1 = Almost clear | Very significant clearance (≥90% to <100%); only traces of disease remain | PR |
| 2 = Marked improvement | Significant improvement (≥75% to <90%); some evidence of disease remains | PR |
| 3 = Moderate improvement | Intermediate between slight and marked improvement; (≥50% to <75%); | PR |
| 4 = Slight improvement | Some improvement (≥25% to <50%); however, significant evidence of disease remains | SD |
| 5 = No change | Disease has not changed from baseline condition (± <25%) | SD |
| 6 = Worse | Disease is worse than at baseline evaluation by ≥25% or more | PD |
| CCR = Clinical Complete Response; PR = Partial Response; SD = Stable Disease; PD = Progressive Disease [1]: [Ref. 5.4: 27] | | |

**Secondary Response Parameters**

**Time-to-Response**

- The time-to-objective response was measured from the start of the treatment to the time when criteria were first met for partial response (PR)

**Response Duration**

- Duration of response was measured from the time when criteria were met for PR until the first date when progressive disease was documented
- If progressive disease (PD) was not observed for a responder, duration of objective response was censored on the last day of overall tumor assessment

**Time-to-Progression**

- Progressive disease was defined as a $\geq$ 25% increase in any of the parameters on the PGA.
  - This included the number or area of clinically abnormal lymph node/nodes, new pathologically positive node/nodes, or visceral disease, while the patient was actively taking the study drug.
- Patients with rising white blood cell counts or other laboratory parameters may be determined to have progressive disease based on the investigator's assessment.
- Progression of disease on treatment was confirmed by a second consecutive assessment so that patients who experienced a temporary flare of disease due to skin infection or other illnesses were not removed from the study prematurely.
- Although it was specified in the protocol that progression of disease needed to be confirmed by a second consecutive assessment, if a patient only had one assessment of PD and no other assessment after that, it was still considered as PD in the study analyses.

**Assessment of Pruritis**

- In Protocol 005, all patients were asked by the study staff to rate their pruritis on a scale of 0 (no itch) to 10 (worst imaginable itch) at each study visit (Protocol 001 utilized a self-administered two-part pruritis assessment questionnaire at each study visit)

**Complete Resolution (of Pruritis)**

- In Protocol 005, complete resolution of pruritis required a pruritis score of 0 on treatment for at least 4 continuous weeks

**Relief (from Pruritis)**

- Pruritis relief was defined as reduction of 3 or more points on a scale of 0 to 10, or complete resolution, for at least 4 continuous weeks.

***Reviewer Comments:***

- *The primary endpoint in the pivotal study (protocol 001) was objective response in cutaneous disease as defined by measurement of skin involvement using Severity Weighted Assessment Tool (SWAT)*
- *Response rate and response duration endpoints are acceptable for evaluation of therapeutic goals of CTCL treatment: reduction of disease burden and palliation of symptoms*
- *Survival measurement in CTCL trials is impractical as the mortality rate is low in most CTCL stages. Moreover, post-relapse sequential therapies may confound the survival analysis.*
- *The study prespecified that a positive result excluded the lower bound of 5% response rate (the presumptive maximum spontaneous response rate in patients with relapsed or refractory CTCL following two prior types of systemic therapies)—this is considered acceptable by the reviewer and was discussed in the SPA.*
- *The secondary endpoint was an improvement in pruritis score by at least 3 points on a 0-10 scale. This represents more than a 0.5 standard deviation (SD) of this measure, which is presented in the literature as one of several methods used to define a minimal important difference. However, evaluation of patient reported outcomes/symptoms in open-label single-arm trials is not reliable.*

**Table 11. Comparison of the Endpoints Used for Evaluation of Efficacy in Zolinza Pivotal Trial and in Previous Approvals of Systemic Therapies for CTCL**

| **Drug** | **Ontak (denileukin diftitox)<br>IV<br>Daily for 5 days, q 21 days** | **Targretin (bexarotene)<br>Oral<br>Daily** | **Zolinza/Vorinostat/SAHA<br>Oral<br>Daily** |
|---|---|---|---|
| **When approved** | Feb 1999 | Dec 1999 | N/A |
| **NDA** | 103767 | 21055 | 21991 |
| **Indication** | For treatment of patients with persistent or recurrent CTCL whose malignant cells express the CD25 component of the IL-2 receptor | For the treatment of cutaneous manifestations of CTCL in patients who are refractory to at least one prior systemic therapy | For the treatment of cutaneous manifestations of CTCL in patients who have progressive, persistent, or recurrent disease on or following two systemic therapies, |
| **Type of approval** | Accelerated | Regular | N/A |
| **Approval basis** | Response rate and duration | Response rate and duration | N/A |
| **Pivotal Trial Design** | Randomized double blind study of two doses of Ontak: 9 and 18 mcg/kg/day IV for 5 days q 21 days for 8 cycles | Two multicenter, open-label, historically controlled studies of early and advanced stage disease<br><br>Advanced disease refractory to at least one prior systemic therapy | Phase 2 multicenter clinical trial of Vorinostat in advanced CTCL<br><br>Should have failed two prior systemic therapies, one of which must be bexarotene |
| **Tumor burden assessment** | **Skin**<br>-If ≥ 10% BSA involved, then **SWAT (grid)**<br>-If ≤ 10% BSA involved, then **5 target lesions,** each measured in two dimensions and weighted score<br>**Lymph Nodes**<br>Histo + and ≥ 1 cm2 at baseline<br>**Blood**<br>Assessed in ≥ 20% circulating atypical cells | **Skin**<br>Up to five baseline-defined index lesions were observed using a **Composite Assessment (CA) of Index Lesion Disease Severity**—endpoint based on summation of the grades (of index lesions) of erythema, scaling, plaque elevation, hypo- or hyper-pigmentation, and area of involvement | **Skin**<br>**Modified SWAT**<br>Lesions are measured using patients hand area as a ruler (1%) and then weighted depending on the type of lesion, and a total SWAT score is derived |
| **Efficacy** | Demonstrated by CR and PR rates and durations | Tumor responses (CR, PR) and duration | CR and PR rates and durations |

| | | | |
|---|---|---|---|
| **Patient population** | **Disease stage Ib to III** following ≥ 4 previous therapies<br>**Stage IVa** after 1 therapy<br><br>Patients ≥ IIb 63%<br>SS 24% | **Advanced disease study (IIB to IVB)**<br>**Early disease study** (IA to IIA)<br><br>Stage IIB or III 73% | Study enrolled patients who had IB or higher disease<br>For efficacy patients with IIB or higher disease are considered<br><br>Stage ≥ IIB 82%<br>SS 40%<br>Skin Tumors 30% |
| **Primary endpoint** | Response= 50% decrease in tumor burden sustained for 6 weeks | Response duration of ≥ 4 weeks<br>A partial response was at least 50% improvement in the index lesions without worsening, or development of new cutaneous tumors or manifestations | Response is ≥ 50% decrease in SWAT, confirmed at 4 weeks. Responders had a CT confirmation of the nodal disease |
| **Secondary endpoints** | QOL assess tools used for psoriasis and atopic dermatitis studies:<br>-Physician's Erythroderma Severity Assessment<br>-Physician's Global CTCL SA<br>-Patient's Global CTCL Skin Assessment<br>-Patient's Pruritis VAS | | Time to response<br>Duration of response<br>Time to progression<br>Relief of pruritis |
| **Progressive disease** | ≥ 50% increase in measured tumor burden, or new LN (+ Histo), or new visceral disease, or 2 new skin lesions if <10% BSA involvement | Ratio of CA of Index Lesion Severity grades ≥ 1.25, or new cutaneous tumor, or new visceral disease, or new histo positive LN | Disease is called worse (Progressive Disease) when there is ≥ 25% increase in skin assessment scores compared to baseline while the patient is actively taking the study drug; must be confirmed at second visit |
| **Definitions of response duration/TTF** | **Response Duration:**<br>From first observation of response to date of relapse or initiation of new cancer treatment<br><br>**TTF:**<br>From date of first infusion until the date of relapse, new | **Response Duration:**<br>From date meeting criteria for CR, CCR, or PR to the time that patient relapses<br><br>**Duration of disease control:** from the first day on study to date of relapse | **Response Duration:**<br>From the time of CCR or PR until the first day when an increase in skin assessment by SWAT score is greater than 50% of the difference between baseline score and nadir score; patient must be actively taking the study drug and disease |

| | | | |
|---|---|---|---|
| | cancer treatment, progressive disease, or toxicities requiring discontinuation of therapy | | assessment must be confirmed at a second visit |

## 6.1.3 Study Design

Two clinical studies support the efficacy of Vorinostat in CTCL.

**Pivotal study (Protocol 001)**

- This was an open-label, single-arm, multicenter study that evaluated the effect of oral Vorinostat 400 mg once daily in 74 patients with advanced disease CTCL (Stage IB or higher).
    - Primary endpoint analysis was limited to the patients with Stage IIB and higher disease
- Patients were eligible if their disease was progressive, persistent, or recurrent on or following 2 systemic therapies, one of which must contain bexarotene unless the patient is intolerant of or not a candidate for bexarotene therapy
- Response rate was the primary end point of the study. The assessment tool used to evaluate response in this study was Severity Weighted Assessment Tool (SWAT).
- All patients began treatment with Vorinostat at a dose of 400 mg once daily and continued on the study until disease progression or intolerable toxicity
- During the first 2 months of treatment with Vorinostat, patients were seen at regular intervals every other week, during which laboratory tests and other study procedures were conducted. Patients were then followed every 4 weeks for the remainder of the study.
- Although the data cutoff for primary analysis was 6 months after the last patient initiated treatment with Vorinostat, patients who experienced clinical benefit continued treatment either on this protocol or on a continuation protocol (Protocol 007).
- Patients were treated until they met pre-defined criteria for discontinuation (disease progression, unacceptable toxicity, withdrawal of consent, uncontrolled intercurrent illness, non-compliance, lack of efficacy, Sponsor/Investigator decision).
- A post-treatment follow-up visit was conducted within 4 weeks after the last dose of the study drug or prior to the initiation of new treatment.

- Patients were also evaluated for the intensity of pruritis at baseline and during each visit using a patient-completed 10-point scale which assessed skin-itch over the past week (0 = no itching, 10 = itching as bad as it can be)
- The patient also had to provide the amount of medication taken to relieve symptoms of itching in the past week compared to the amount taken during the previous week.
- The prespecified duration of the study to analyze the data was after the last patient had been on Vorinostat therapy for 6 months.

**Protocol 005 (Initial Supportive Study)**

- In Vorinostat clinical development program, Protocol 005 was the first CTCL study that was conducted

- It was an open-label, non-randomized study in patients with a confirmed diagnosis of either CTCL or peripheral T-cell lymphoma (PTCL). While the study inclusion criteria allowed both CTCL and PTCL patients to enroll, the Investigator enrolled CTCL patients only.
- The objective of the study was to evaluate the safety and efficacy of Vorinostat in the study population.
- The primary end point of the study was objective response.
- The study tested 3 Vorinostat dosing regimens:
  - 400 mg once daily (13 patients)
  - 300 mg twice daily 3 days per week (11 patients)
  - 300 mg twice daily for 14 consecutive days followed by a 7-day rest period for each 21-day cycle (if a partial response was not achieved by day 22, the dose was changed to 200 mg twice daily) (9 patients)
- Thirty-three (33) unique patients were enrolled sequentially into 1 of 3 dosing cohorts. During the first month of treatment, patients were seen every week and laboratory tests and other study procedures were conducted. Patients were then followed every 3 weeks for the remainder of the study starting from Week 6. Patients were treated until they met pre-defined criteria for discontinuation (disease progression, unacceptable toxicity, withdrawal of consent, uncontrolled intercurrent illness, non-compliance, lack of efficacy, Sponsor/Investigator decision). A post-treatment follow-up visit was conducted within 8 weeks after the last dose study drug or prior to the initiation of new treatment.

- The assessment tool used to evaluate response in this study was the Physician's Global Assessment (PGA)—the tool used in bexarotene (Targretin®) registration trial.
- PGA was performed at baseline and every 3 weeks.

- Pruritis was assessed by the investigator during the history and review of symptoms. This was done at baseline and at every week before the examination and laboratory evaluations. Patients were asked to choose a number, representative of their itching, on a scale of 0 (no itch) to 10 (worst imaginable itch).

## 6.1.4 Efficacy Findings

**Demographic Data of the Study Population (Protocol 001 and Protocol 005)**

Demographic data for Protocol 001 and Protocol 005 study populations are shown in the table below

- In Protocol 001, the median age was 60 years while in Protocol 005, Cohort 1 (Vorinostat dose 400 mg once daily) the median age was 65 years
- The majority of patients enrolled in both studies were ≤ 65 years of age
- Protocol 001 enrolled more males than females (38/74, 51.4%) as did Protocol 005, Cohort 1 (8/13, 61.5%)
- Protocol 001 enrolled more White patients (61/74, 82.4%) than Black patients as did Protocol 005, Cohort 1 (10/13, 76.9%).

**Table 12. Baseline Demographics of the Patients in Protocol 001 and Protocol 005 (Applicant's Table)**

Baseline Demographics: Protocol 001 and Protocol 005

| Characteristic | Protocol 001 | Protocol 005 | | |
|---|---|---|---|---|
| | 400 mg once daily (N=74) | Cohort 1 (N=13) | Cohort 2 (N=11) | Cohort 3 (N=9) |
| **Age** | | | | |
| Mean | 61.2 | 61.7 | 60.9 | 67.4 |
| Median | 60.0 | 65.0 | 69.0 | 67.0 |
| Min-Max | 39.0-83.0 | 37.0-82.0 | 26.0-80.0 | 49.0-78.0 |
| Number (%) ≤65 years | 45 (60.8%) | 7 (53.9%) | 5 (45.5%) | 3 (33.3%) |
| Number (%) >65 years | 29 (39.2%) | 6 (46.2%) | 6 (54.6%) | 6 (66.7%) |
| **Gender (n, %)** | | | | |
| Female | 36 (48.6%) | 5 (38.5%) | 6 (54.5%) | 4 (44.4%) |
| Male | 38 (51.4%) | 8 (61.5%) | 5 (45.5%) | 5 (55.6%) |
| **Race (n, %)** | | | | |
| Asian | 1 (1.4%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Black | 11 (14.9%) | 3 (23.1%) | 4 (36.4%) | 1 (11.1%) |
| White | 61 (82.4%) | 10 (76.9%) | 7 (63.6%) | 8 (88.9%) |
| Other | 1 (1.4%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Protocol 005, Cohort 1: 400 mg once daily x7d/wk; Cohort 2: 300 mg twice daily x 3d/wk; Cohort 3: Induction 300 mg twice daily, maintenance 200 mg twice daily<br>CTCL = Cutaneous T-cell Lymphoma | | | | |

[Ref. 5.3.5.2: P001] [Ref. 5.3.5.2: P005]

**Table 13. Baseline Disease Characteristics (Protocol 001 and Protocol 005) (Applicant's Table)**

Baseline Summary of CTCL Characteristics: Protocol 001 and Protocol 005

| Characteristic | Protocol 001 | Protocol 005 | | |
|---|---|---|---|---|
| Number (%) of Patients with: | 400 mg once daily (N=74) | Cohort 1 (N=13) | Cohort 2 (N=11) | Cohort 3 (N=9) |
| CTCL Stage IIB and higher, n (%) | 61 (82.4%) | 11 (84.6%) | 10 (90.0%) | 7 (77.7%) |
| Presence of clinically abnormal lymph nodes, n (%) | 34 (45.9%) | 8 (61.5%) | 7 (63.6%) | 4 (44.4%) |
| Presence of Sezary syndrome, n (%) | 30 (40.5%) | 3 (23.1%) | 4 (36.4%) | 4 (44.4%) |
| Presence of skin tumors/tumor disease, n (%) | 22 (29.7%) | 2 (15.4%) | 1 (9.1%) | 2 (22.2%) |
| Prior use of bexarotene therapy | 71 (95.9%) | 9 (69.2%) | 7 (63.6%) | 6 (66.6%) |
| Number of prior systemic treatments, median (range) | 3.0 (1.0, 12.0) | 4.0 (0.0, 8.0) | 4.0 (2.0, 11.0) | 2.0 (1.0, 8.0) |
| Pruritus scores | | | | |
| Mean (SD) | 6.0 (2.5) | 9.0 (2.3) | 6.6 (3.2) | 3.6 (3.8) |
| Median (Range) | 6.0 (0.0, 10.0) | 10.0 (3.0, 10.0) | 6.0 (1.0, 10.0) | 3.0 (0.0, 10.0) |
| Protocol 005, Cohort 1: 400 mg once daily x7d/wk; Cohort 2: 300 mg twice daily x 3d/wk; Cohort 3: Induction 300 mg twice daily, maintenance 200 mg twice daily<br>CTCL = Cutaneous T-cell Lymphoma | | | | |

[Ref. 5.3.5.2: P001] [Ref. 5.3.5.2: P005]

**Disease stage**

- The majority of the patients in both studies were CTCL Stage IIB or higher at the baseline:
  - 61/74 (82.4%) patients in Protocol 001
  - 28/33 (84.9%) patients in Protocol 005

- Sezary syndrome patients were a large number in both studies:
  - 30/74 (40.5%) patients in Protocol 001
  - 11/33 (33.3%) patients in Protocol 005

- Patients with skin tumors were nearly one-third in the pivotal trial (Protocol 001):
  - 22/74 (29.7%) patients in Protocol 001
  - 5/33 (15.2%) patients in Protocol 005

**Previous treatments**

**Protocol 001**

- Median of prior systemic therapies = 3
- 71/74 (95.9%) had used bexarotene

**Protocol 005**

- Median of prior systemic therapies = 4 (in Cohort 1)
- 9/13 (69.2%) had used bexarotene)

## EFFICACY RESULTS

### Efficacy Results of Vorinostat Monotherapy in Patients with Advanced CTCL (Protocol 001)

### Patients

Total patients enrolled in the study = 74
CTCL Stage IIB or higher = 61

### All Patients as Treated (APaT) Population

- All patients (74) who received at least one dose of study drug constitute the All Patients as Treated (APaT) population
- This population was used in the primary efficacy and safety analysis

### Per Protocol (PP) Population

- This population excludes the protocol-violators
- Nine (9) patients were considered protocol-violators and were excluded from the supportive Per-Protocol (PP) efficacy analysis

***Reviewer Comments:*** *Only one patient who was protocol violator (AN 1044) was a responder. This was a stage III patient with Sezary syndrome*

### Analysis of All Patients as Treated Population

- Median age = 60.0 years (range 39.0 to 83.0 years)
- Male = 51.4%
- Female = 48.6%
- White = 82.4%
- CTCL history = 2.6 years (median, range 0.0 to 27.3 years)
- Prior systemic therapies for CTCL = 3 (median, range 1 to 12)
- Bexarotene therapy = 71/74 (95.9%)
- Interferon therapy = 47/74 (63.5%)
- Photopheresis therapy = 27/74 (36.5%)

**CTCL Disease Stages and Characteristics**

- Stage IIB or higher = 61 (82.4%)
- T3 skin tumor = 22 (29.7%)
- Sezary Syndrome (SS) = 30 (40.5%)
- Clinical abnormal lymph nodes at entry = 34 (45.9%)
- Histologically involved lymph node = 19 (25.7%)

**Body surface area (BSA) involvement at baseline (Median)**

- Patch = 15.6%
- Plaque = 5.9%
- Tumor = 0.0% (only 22 of 74 patients had tumor stage CTCL)

**Duration of drug exposure to oral Vorinostat**

- Median = 115
- Mean = 130 days (range of 2 to 365 days)
- All patients started at a dose of 400 mg once daily. During study treatment, 10 patients required at least one Vorinostat dose reduction.

**Objective Response Rates**

**Table 14. Objective Response Rates with Vorinostat in Protocol 001: All Patients as Treated (Applicant's Table)**

Number of Patients Treated with Vorinostat with an Objective Response[†]
(Protocol 001: All Patients As Treated)

| Population | N | Patients with an Objective Response[†] | | | | |
|---|---|---|---|---|---|---|
| | | n (%) | (95% CI) | Time to Objective Response[†] (days) Median (Range) | Duration of Objective Response (days) Median (Range) | Time to Progressive Disease (days) Median (Range) |
| All Patients | 74 | 22 (29.7%) | (19.7, 41.5) | 55 (28, 171) | . (34+, 322+) | . (78+, 365+) |
| Stage IIB or Higher[‡] | 61 | 18 (29.5%) | (18.5, 42.6) | 56 (28, 171) | . (34+, 280+) | . (85, 365+) |
| Patients with Sezary syndrome | 30 | 10 (33.3%) | (17.3, 52.8) | 56 (28, 171) | . (34+, 244+) | . (85, 365+) |
| Patients with tumor disease | 22 | 5 (22.7%) | (7.8, 45.4) | 31 (29, 87) | . (55, 280+) | . (148, 317+) |

[†] Objective Response: confirmed complete response or partial response.
[‡] Stages IIB, III, IVA, and IVB.
CI = Confidence Interval.
+ = Response ongoing.

[Ref. 5.3.5.2: P001]

- APaT population = 29.7% (22/74; 95% CI = 19.7 to 41.5)
- Stage IIB and higher disease = 29.5% (18/61; 95% CI = 18.5 to 42.6)
- Sezary Syndrome = 33.3% (10/30; 95% CI = 17.3 to 52.8)
- T3 tumor disease = 22.7% (5/22; 95% CI = 7.8 to 45.4)

The primary response rate met the pre-specified criteria for a positive trial defined as an observed response rate of at least 20% with the lower boundary of the corresponding 95% confidence interval excluding 5% (The 5% lower boundary of the 95% CI was based on a conservative estimate of the maximum theoretical spontaneous response rate)

**Table 15. Objective Response Rates with Vorinostat in Protocol 001: Per Protocol (PP) Population (Applicant's Table)**

| Population | N | Patients with an Objective Response[†] | | | | |
|---|---|---|---|---|---|---|
| | | n (%) | (95% CI) | Time to Objective Response[†] (days) Median (Range) | Duration of Objective Response (days) Median (Range) | Time to Progressive Disease (days) Median (Range) |
| All Patients | 65 | 21 (32.3%) | (21.2, 45.1) | 55 (28, 143) | . (48+, 322+) | . (78+, 365+) |
| Stage IIB or Higher[‡] | 54 | 17 (31.5%) | (19.5, 45.6) | 55 (28, 143) | . (55, 280+) | . (85, 365+) |
| Patients with Sezary syndrome | 27 | 9 (33.3%) | (16.5, 54.0) | 55 (28, 142) | . (56, 244+) | . (85, 365+) |
| Patients with tumor disease | 20 | 5 (25.0%) | (8.7, 49.1) | 31 (29, 87) | . (55, 280+) | . (148, 317+) |

[†] Objective Response: confirmed complete response or partial response.
[‡] Stages IIB, III, IVA, and IVB.
CI = Confidence Interval.
+ = Response ongoing.

[Ref. 5.3.5.2: P001]

- All stages = 32.3% (21/65; 95% CI = 21.2 to 45.1)
- Stage IIB and higher disease = 31.5% (17/54; 95% CI = 19.5 to 45.6)
- Sezary Syndrome = 33.3% (9/27; 95% CI = 16.5 to 54.0)
- T3 tumor disease = 25.0% (5/20; 95% CI = 8.7 to 49.1)

For patients with Stage IIB and higher disease in the PP population the lower boundary of the 95% confidence interval for the objective response approaches 20%

- All responses (except one) were partial responses (PR)
- One patient (AN1025) had a clinical complete response (CCR) after 281 days of Vorinostat treatment

**Table 16. List of Responders, Time to Objective Response, and Duration of Objective Response (Original Analysis of the Pivotal Trial—Protocol 001; Data cut-off Nov 2005) (Applicant's Table)**

| Site | Allocation Number | Stage | Sezary (Yes/No) | Tumor (Yes/No) | Time to objective response* (days) | Duration of objective response (days)** | Time to Progressive Disease (days) | Patient Status |
|---|---|---|---|---|---|---|---|---|
| 0004 | 1009 | IVA | Yes | No | 29 | 112 | 141 | discontinued |
| | 1010 | IB | No | No | 57 | 56 | 113 | discontinued |
| 0005 | 1034 | III | Yes | No | 55 | 244+[§] | 299+[§] | discontinued |
| | 1035 | IB | No | No | 55 | 105 | 160 | discontinued |
| 0006 | 1030 | IVA | No | No | 57 | 266+[§] | 323+[§] | pat. extended |
| 0007 | 1016 | IVB | Yes | No | 142 | 223+[§] | 365+[§] | pat. completed |
| 0009 | 1008 | III | Yes | No | 28 | 185+[§] | 213+[§] | discontinued |
| | 1040 | IVA | Yes | No | 29 | 59 | 88 | discontinued |
| 0010 | 1014 | IB | No | No | 30 | 322+[§] | 352+[§] | pat. contin. trial |
| | 1027 | IIB | No | Yes | 87 | 55 | 317+[§] | pat. contin. trial |
| 0011 | 1024 | III | Yes | No | 29 | 56 | 85 | discontinued |
| 0012 | 1025 | IIB | No | Yes | 29 | 280+[§] | 309+[§] | pat. contin. trial |
| | 1029 | IVA | No | Yes | 31 | 117 | 148 | discontinued |
| 0013 | 1038 | IVA | No | No | 143 | 133+[§] | 276+[§] | pat. contin. trial |
| | 1065 | III | No | No | 31 | 105 | 136+[§] | discontinued |
| 0014 | 1044 | III | Yes | No | 171 | 34+[§] | 205+[§] | discontinued |
| 0015 | 1058 | IIB | No | Yes | 87 | 137+[§] | 224+[§] | pat. contin. trial |
| | 1068 | IIB | No | Yes | 29 | 170+[§] | 199+[§] | pat. contin. trial |
| 0018 | 1059 | III | Yes | No | 57 | 145+[§] | 202+[§] | discontinued |
| 0020 | 1079 | III | Yes | No | 61 | 106+[§] | 167+[§] | pat. contin. trial |
| 0021 | 1053 | IVA | Yes | No | 114 | 119+[§] | 233+[§] | pat. contin. trial |
| 0022 | 1042 | IB | No | No | 30 | 48+[§] | 78+[§] | discontinued |

* Objective Response: confirmed complete response or partial response

** End of response is defined as the average of baseline and best response.

§ Response ongoing.

AN1027 had a second confirmed response with duration of 84+ days. Only the first response is included in the analysis.

AN1025 achieved complete response after 281 days of treatment and was sustained for 28+ days.

[Ref. 5.3.5.2: P001]

**Median Time to Objective Response:**

- All stages = 55 days
- Stage IIB and higher disease = 56 days
- Sezary Syndrome = 56 days
- T3 tumor disease = 31 days

Objective responses were seen as early as 28 days, however, responses meeting PR criteria occurred up to 6-months

**Median Response Duration**

- The median response duration for the responders had not been reached by the data cut-off date for this marketing application and the study was still ongoing; however, the median response duration was estimated to be at least 4 months

**Median Time to Progression**

- The median time to progression in patients with Stage IIB and higher disease had not been reached either, but it was estimated to be at least 5 months

***Recalculated Median Duration of Objective Response and Median Time to Progressive Disease Using the FDA Criteria***

**Using the original 23rd of Nov 2005 data cut-off date**

- The median duration of objective response for all patients is 168 days (95% CI 34 to 280+), and it is 170 days (95% CI 34 to 280+) for patients with stage IIB or higher disease
- The median time to progressive disease for all patients is 202 days (95% CI 78 to 323), and it is 205 days (95% CI 85 to 323) for patients with stage IIB or higher disease

**Using the updated 11th of April 2006 data cut-off date**

- The median duration of objective response for all patients is 169 days (95% CI 34 to 329), and it is 170 days (95% CI 34 to 329) for patients with stage IIB or higher disease
- The median time to progressive disease for all patients is 205 days (95% CI 78 to 380), and it is 213 days (95% CI 85 to 380) for patients with stage IIB or higher disease

**Updated and Recalculated Times to Progressive Disease and Durations of Objective Responses**

The following table shows the recalculated and updated times to progressive disease and durations of objective responses

- Durations of Objective Responses and Time to Progressive Disease decreased for 6 patients on recalculation (AN 1034, 1016, 1014, 1029, 1038, and 1058)
- In the original analysis, the medians of duration of objective response and time to progressive disease were not reached; however, recalculations using the FDA revised definitions, these medians could be calculated (see the last page)

**Table 17. Updated and Recalculated Times to Progressive Disease and Durations of Objective Responses (Applicant's Table)**

| Site | Allocation Number | Stage | Sezary (Yes/No) | Tumor (Yes/No) | Time to objective response[†] (days) | Duration of objective response (days)[‡] | Updated[§] Duration of objective response (days) | Time to Progressive Disease (days) | Updated[§] Time to Progressive Disease (days) |
|---|---|---|---|---|---|---|---|---|---|
| 0004 | 1009 | IVA | Yes | No | 29 | 112+ | 112+ | 141+ | 141+ |
| | 1010 | IB | No | No | 57 | 56 | 56 | 113 | 113 |
| 0005 | 1034 | III | Yes | No | 55 | 168 | 168 | 167 | 167 |
| | 1035 | IB | No | No | 55 | 105 | 105 | 160 | 160 |
| 0006 | 1030 | IVA | No | No | 57 | 266 | 266 | 323 | 323 |
| 0007 | 1016 | IVB | Yes | No | 142 | 83 | 83 | 225 | 225 |
| 0009 | 1008 | III | Yes | No | 28 | 185 | 185 | 213 | 213 |
| | 1040 | IVA | Yes | No | 29 | 59+ | 59+ | 88+ | 88+ |
| 0010 | 1014 | IB | No | No | 30 | 266 | 266 | 296 | 296 |
| | 1027 | IIB | No | Yes | 87 | 230+ | 293 | 317+ | 380 |
| 0011 | 1024 | III | Yes | No | 29 | 56 | 56 | 85 | 85 |
| 0012 | 1025 | IIB | No | Yes | 29 | 280+ | 329 | 309+ | 358 |
| | 1029 | IVA | No | Yes | 31 | 117+ | 117+ | 85 | 85 |
| 0013 | 1038 | IVA | No | No | 143 | 110 | 229+ | 253 | 372+ |
| | 1065 | III | No | No | 31 | 105 | 105 | 136 | 136 |
| 0014 | 1044 | III | Yes | No | 171 | 34 | 34 | 205 | 205 |
| 0015 | 1058 | IIB | No | Yes | 87 | 82 | 82 | 169 | 169 |
| | 1068 | IIB | No | Yes | 29 | 170 | 170 | 199 | 199 |
| 0018 | 1059 | III | Yes | No | 57 | 145+ | 145+ | 202 | 202 |
| 0020 | 1079 | III | Yes | No | 61 | 106+ | 169 | 167+ | 230 |
| 0021 | 1053 | IVA | Yes | No | 114 | 119+ | 149+ | 233+ | 263+ |
| 0022 | 1042 | IB | No | No | 30 | 48 | 48 | 78 | 78 |

[†] Objective Response: confirmed complete response or partial response

+ Response ongoing

[‡] As of 23-November-2005 as per Original Submission

[§] As of 11-April-2006 study closure as per updated efficacy data

**Outcomes of Patients Meeting the Criteria for an Objective Response**

22 responders in the APaT population met the criteria for objective response:

- 14 (14/22, 63.6%) continued to show response at the time of their last assessment
- Two (2/22, 9.1%) had SWAT scores which no longer qualified as response values; however, they did not meet the criteria for disease progression
- Six (6/22, 27.3%) patients met the criteria for progressive disease

- The time to progressive disease for patients censored at the time of data cut-off who showed ongoing response ranged from 136+ to 365+ days.

**Table 18. Outcomes of the Patients Not Meeting the criteria for Objective Response (stable disease designation)**

| | |
|---|---|
| **Patients who met the Criteria for Stable Disease (absence of disease progression or response for 24 weeks or longer)** | 24 patients (17 with Stage IIB or higher) |
| **One time reduction of ≥ 50% in the SWAT score** | 7 patients (5 with Stage IIB or higher disease) |
| **One time reduction of 25 to 50%in the SWAT score** | 17 patients (12 with Stage IIB and higher disease) |

**Patients with Objective Response *or* Stable Disease**

- 33/74 (44.6%) patients of all disease stages, and 28/61 (45.9%) patients with Stage IIB and higher disease, demonstrated either an objective response or ≥24 weeks of stable disease

**Update of Protocol 001**

- Ten (10) of the 22 responding patients from Protocol 001 continued Vorinostat treatment on continuation Protocol 007.
- Two (2) of these patients have discontinued treatment.
- Eight (8) patients (AN 1030, AN 1014, AN 1025, AN 1038, AN 1058, AN 1068, AN 1079, AN 1053) are continuing to receive Vorinostat treatment.

- Five (5) additional patients who did not meet the criteria for objective response also continued Vorinostat treatment on Protocol 007 (AN 1045, AN 1050, AN 1069, AN 1076, AN 1078).
- Of these, 1 patient (AN 1045) has discontinued treatment.

As of 26-June-2006, with cumulative Vorinostat exposure exceeding one year, 12 patients originally enrolled on Protocol 001 are continuing treatment on Protocol 007.

**Impact of Response to Previous Therapy**

- No obvious impact of the response to last treatment, either to bexarotene or to other therapies, was observed on the efficacy of Vorinostat.
- Response to any previous systemic therapy does not appear to be predictive of response to Vorinostat.

**Table 19. Response to the last systemic therapy the patient received prior to taking Vorinostat and response to Vorinostat (Applicant's Table)**

| Population | N | Responder to Vorinostat | |
|---|---|---|---|
| | | n (%) | (95% CI) |
| Patients on bexarotene as last systemic therapy | | | |
| Responder | 7 | 2 (28.6%) | (3.7, 71.0) |
| Non-responder | 16 | 5 (31.3%) | (11.0, 58.7) |
| Patients not on bexarotene as last systemic therapy | | | |
| Responder | 15 | 5 (33.3%) | (11.8, 61.6) |
| Non-responder | 36 | 10 (27.8%) | (14.2, 45.2) |

† Objective Response: confirmed complete response or partial response.
‡ Excludes systemic procedures as response data to procedures is unavailable.
CI = confidence Interval.

[Ref. 5.3.5.2: P001]

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**Exploratory Analysis for the Factors Predictive of Objective Response to Treatment with Vorinostat**

- A multivariate logistic regression analysis using several pre-specified baseline characteristics (age, gender, baseline ECOG, serum LDH, disease stage and disease type, and response to prior therapy) did not reveal any factors which were predictive of response (See the table below)
- A lack of weight effect suggests that dose adjustments to the patients' body weight for efficacy improvement are not warranted
- Borderline statistically significant difference at the 5% level (P Value = 0.048) in response rates by race favoring White vs. Non-white is unlikely to be of any clinical significance

**Table 20. Exploratory Analyses for the Factors Predictive of Objective Response to Vorinostat (Logistic Regression; Protocol 001: All Patients as Treated) (Applicant's Table)**

| Variable/Covariate | Odds Ratio Estimate | p-Value |
|---|---|---|
| Gender (Male vs Female) | 0.463 | 0.278 |
| Age (>60 vs ≤ 60) | 1.550 | 0.481 |
| Race (White vs. Non-white) | 10.798 | 0.048 |
| Baseline SWAT | 1.002 | 0.694 |
| Normalized Dose by Body Weight (mg/kg) | 0.867 | 0.654 |
| Baseline ECOG (0, 1, 2) | 1.419 | 0.420 |
| LDH (<1 X normal vs ≥ 1 X normal) | 1.214 | 0.802 |
| CTCL Stage (III/IV vs I/II) | 1.438 | 0.676 |
| Sezary Syndrome (Yes vs No) | 0.784 | 0.792 |
| Response to Prior Systemic Therapy (Yes vs No) | 0.694 | 0.540 |

[Ref. 5.3.5.2: P001]

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**Assessment of Pruritis Relief in Protocol 001**

- Patient reported pruritis relief was a secondary endpoint in protocol 001 and it was assessed using the Pruritis Assessment Questionnaire at baseline and during each follow-up visit
- The Pruritis Assessment Questionnaire was a patient-completed, self-administered, two-part questionnaire that assessed skin itch over the past week using a 10-point scale (0 = no itching, 10 = itching as bad as it can be).
- The Questionnaire also considered the amount of medication taken to relieve symptoms of itching during the past week compared to the amount taken the previous week.
    - Response categories for medication taken included:
        - (a) did not use
        - (b) used less
        - (c) no change in use
        - (d) used more
- A 3-point decrease in pruritis intensity confirmed by a second assessment at least 4 weeks later—without an increase in the use of anti-pruritic medications—was considered clinically significant in those whose pruritis score at baseline was > 3 on the 0-10 point scale
- End of pruritis relief was defined as a return of pruritis score to baseline or higher

**Results**

- Two (2) patients were excluded from the pruritis assessment as they lacked a baseline assessment

- Pruritis relief (maintained for at least four weeks without an increase in anti-pruritic medications, in patients with a baseline pruritis score of ≥ 3 points):
    - All stages = 32.3% (21/65)
    - Stage IIB and higher disease = 30.2% (16/53)
        - 6 patients with Stage IIB and higher disease achieved a complete resolution of pruritis (pruritis score of 0)

**Relationship between an Objective Response and Pruritis Relief**

Depending on whether an objective response occurred or not, differences in **the frequency, time to, and duration of pruritis relief** are observed:

**Table 21. Frequency of pruritis relief:**

| | **All stages** | **Stage IIB and higher** |
|---|---|---|
| Pruritis relief rate **in presence** of objective response | 47.1% | 53.8% |
| Pruritis relief rate **in absence** of objective response | 27.1% | 22.5% |

**Table 22. Time to pruritis relief (stage IIB and higher):**

| In **presence** of objective response | In **absence** of objective response |
|---|---|
| 29 days (median) | 15 days |

**Table 23. Duration of pruritis relief (stage IIB and higher):**

| In **presence** of objective response | In **absence** of objective response |
|---|---|
| 160 days (median) | 71 days |

**≥25% reduction in Sezary (CD4+/CD26-) cells:**

- 14/27 (51.9%) of the patients with Sezary syndrome had a ≥ 25% reduction in Sezary (CD4+/CD26-) cells

**≥50% reduction in the product of the greatest diameters of index lymph nodes:**

- 10/24 (41.7%) patients with palpable clinically abnormal lymph nodes had a ≥ 50% reduction in the products of the greatest diameters of their index lymph nodes

**≥50% reduction in body surface area covered by tumor:**

- 9/16 (56.3%) of the patients with T3 tumor disease had a ≥ 50% reduction in body surface area covered by tumor

# EFFICACY FINDINGS FROM PROTOCOL 005 (THE SUPPORTIVE TRIAL)

- Chronologically, the supportive trial (Protocol 005) preceded the pivotal trial (Protocol 001)

The study conducted under protocol 005 is submitted as a supportive study in this NDA to support the efficacy of Vorinostat in the treatment of patients with CTCL unresponsive to conventional treatment (based on the data from the pivotal trial). Although the study design allowed for recruitment of patients with CTCL and PTCL, only patients with CTCL were enrolled in the study. This single-center, open-label, nonrandomized, Phase II study was conducted by Madeleine Duvic, M.D, at the MD Anderson Cancer Center in patients with a confirmed diagnosis of either CTCL or PTCL refractory or intolerant to conventional therapies.

- Oral Vorinostat was administered to the eligible patients until disease progression or intolerable toxicity
- Evaluations were every week for the first 4 weeks, at Week 6, and every 3 weeks thereafter
- The Physician Global Assessment (PGA) was used to determine the objective response rate. PGA required the investigator to assess the overall disease compared to the baseline, and to consider index and non-index cutaneous lesions, cutaneous tumors, lymph nodes, and other disease manifestations. Confirmation of response required a second assessment at least 4 weeks apart from the initial assessment.

Thirty three (33) unique CTCL patients were enrolled sequentially into 3 dosing cohorts

- Cohort 1 (n = 13)
  - The first 3 patients were dosed by body surface area (BSA) at 250 mg/m2/d with either a 500 mg or 550 mg once daily dose. The remaining patients in this cohort were treated at a fixed dose of 400 mg once daily continuously.

- Cohort 2 (n = 11)
  - The initial dose schedule was 300 mg twice daily for 3 days per week. The protocol was later amended to allow for intra-patient dose escalation to 300 mg twice daily up to 5 days per week.

- Cohort 3 (n = 9)
  - Initially these patients received an induction of 300 mg twice daily for 14 consecutive days followed by 7 days of rest. Later, per the fourth amendment, if a PR was not achieved after the first 3 weeks of treatment, patients were maintained at 200 mg twice daily.
  - Two (2) patients in this cohort received more than 1 cycle of therapy on the original schedule because these patients were recruited prior to the fourth amendment and both achieved PR.

- This study did not prohibit patients previously treated with Vorinostat from entering another subsequent dose cohort. As a result, four (4) patients participated in 2 cohorts. These patients were counted once when overall efficacy was calculated and their overall efficacy data were assigned to their initial cohort; however, for safety reporting by dose level, they were counted independently in each cohort.
- The analysis of primary endpoint response rate was based upon an All Patients as Treated approach (APaT)

**Disease Characteristics of the overall population of 33 CTCL patients in Protocol 005:**

| | |
|---|---|
| Number of prior therapies | = 4 (median; range 0 to 11) |
| Bexarotene as prior therapy | = 22 (67%) |
| CTCL history (median) | = 3.3 years (range 0.2 to 27.2 years) |
| Stage IIB or higher disease | = 28 (85%) |
| BSA involvement (median) | = 45% (range 2.2 to 100.0) |
| Sezary Syndrome | = 11 patients (33%) |
| Clinically abnormal lymph nodes | = 19 patients (58%) |

There was no obvious disparity among the baseline characteristics of age, gender, ethnic background, disease stage and clinical characteristics among the 3 cohorts.

**Treatment Durations in Protocol 005**

**Number of days on treatment (median)**

- Overall = 86 days (range 28 to 255 days)
- Cohort 1 = 86.0 days
- Cohort 2 = 46 days
- Cohort 3 = 46.5 days

**Days of active treatment (median)**

- Cohort 1 = 86 days
- Cohort 2 = 20 days
- Cohort 3 = 39 days

- Patients in Cohort 1 received the treatment for the longest time—notably the treatment regimen for Cohort 1 is the same as the regimen in Protocol 001.
- Three (3) patients, one (1) in each cohort, required dose modifications due to adverse experiences.

***Reviewer Comments:*** *The time on treatment was likely influenced by both the efficacy and the tolerability of the treatment, as was also seen in the pivotal trial (Protocol 001)*

**Objective Response Rates in Protocol 005 (APaT population)**

The table below summarizes the response rate in the overall (all cohorts) population and in the populations by cohort.

- All responses were PRs (there were no CRs)

**Table 24. PGA Response Rates, Overall (all cohorts) and by Cohort (All Patients as Treated) (Applicant's Table)**

| Population | N | Patients with an Objective Response† n (%) | Response Rate (95% CI) |
|---|---|---|---|
| Overall | | | |
| All Patients | 33 | 8 (24.2%) | (11.1, 42.3) |
| Stage IA – IIA | 5 | 1 (20.0%) | (0.5, 71.6) |
| Stage IIB or Higher‡ | 28 | 7 (25.0%) | (10.7, 44.9) |
| Patients with Sezary syndrome | 11 | 4 (36.4%) | (10.9, 69.2) |
| Cohort 1: 400 mg once daily | | | |
| All Patients | 13 | 4 (30.8%) | (9.1, 61.4) |
| Stage IA – IIA | 2 | 0 (0.0%) | (0.0, 84.2) |
| Stage IIB or Higher‡ | 11 | 4 (36.4%) | (10.9, 69.2) |
| Patients with Sezary syndrome | 3 | 1 (33.3%) | (0.8, 90.6) |
| Cohort 2: 300 mg twice daily x 3d/wk | | | |
| All Patients | 11 | 1 (9.1%) | (0.2, 41.3) |
| Stage IA – IIA | 1 | 0 (0.0%) | (0.0, 97.5) |
| Stage IIB or Higher‡ | 10 | 1 (10.0%) | (0.3, 44.5) |
| Patients with Sezary syndrome | 4 | 1 (25.0%) | (0.6, 80.6) |
| Cohort 3: Induction 300 mg twice daily x 14d/wk, maintenance 200 mg twice daily | | | |
| All Patients | 9 | 3 (33.3%) | (7.5, 70.1) |
| Stage IA - IIA | 2 | 1 (50.0%) | (1.3, 98.7) |
| Stage IIB or Higher‡ | 7 | 2 (28.6%) | (3.7, 71.0) |
| Patients with Sezary syndrome | 4 | 2 (50.0%) | (6.8, 93.2) |

† Objective Response: complete response or partial response.
‡ Stages IIB, III, IVA, and IVB.
CI=Confidence Interval.

[Ref. 5.3.5.2: P005]

**Overall Response Rate (n = 33)**

- Stage IIB or higher disease = 25% (7/28)
- Sezary Syndrome = 36% (4/11)
- Overall population = 24% (8/33)

Applicant commented that similar response rates were observed in Cohort 1 and 3. In Cohort 1 the objective response rates were 30% for all patients, 36% for patients with Stage IIB or higher disease, and 33% for patients with SS. Corresponding rates for Cohort 3 were 33%, 28%, and 50%; and for Cohort 2 the corresponding rates were 10%, 25%, and 9%. In cohort 2, however, not only the response rate was numerically lower, but also the duration of the observed response (one) was the shortest (see below). This suggested that the Cohort 2 dose and regimen were suboptimal for the protocol defined patient population.

**Time to Response and Response Duration**

- Time-to-response and response duration for the responders are summarized in the table

**Table 25. Time to Objective Response and Duration of Objective Response in Patients who had an Objective Response (Protocol 005; All Patients as Treated) (Applicant's Table)**

| Cohort | Allocation Number | Time-to-Objective Response(Days) | Duration of Objective Response (Days) |
|---|---|---|---|
| 1 | 1001 | 143 | 113 |
| 1 | 1007 | 114 | 113 |
| 1 | 1008 | 62 | 136 |
| 1 | 1012 | 29 | 70 |
| 2 | 1019 | 29 | 66 |
| 3 | 1027 | 153 | 99+ |
| 3 | 1028 | 105 | 106+ |
| 3 | 1031 | 25 | 106 |
| | Median (range) | 83.5 (25.0, 153.0) | 106.0 (66.0, 136.0) |

† Objective Response: complete clinical response or partial clinical response.
+Response ongoing.
Cohort 1: 400 mg once daily x 7d/wk.
Cohort 2: 300 mg twice daily x 3d/wk.
Cohort 3: Induction 300 mg twice daily, maintenance 200 mg twice daily.

[Ref. 5.3.5.2: P005]

**Time to objective response (median)**

- 83 days (range 25 to 153 days)

**Duration of objective response (median) in the 8 responders**

- 106 days (median; range 66 to 136 days)
    - Cohort 1 = 100 + days
    - Cohort 2 = 66 days
    - Cohort 3 = approximately 100 days

**Time to progressive disease (median)**

- 211 days (range 94 to 255 days)

**Patients who had improvement of the overall disease condition but did not qualify as responders**

- Overall Study Population = 11 (33.3%)
  - Cohort 1 = 5 (38.5%)
  - Cohort 2 = 3 (27.3%)
  - Cohort 3 = 3 (33.3%)

**Time to progressive disease for the patients who had clinical improvement (but did not qualify as responders)**

- 85 days (median)

**Time to progressive disease for the patients with no response at all**

- 35 days (median)

**Stable disease**

- Eight (8) patients were identified as having stable disease
- Four (4) of the 8 patients with stable disease assessment were from Cohort 1

**Prior Treatment (Protocol 005)**

- The table summarizes the patient response status to the most recent bexarotene therapy and the response status to Vorinostat. It also shows the response rate in patients who were not on bexarotene therapy. In total, 66.7% (22 of 33) of the patients had received bexarotene therapy prior to enrollment into the study.
- Response to the last treatment, whether bexarotene or other, did not show an impact on the subsequent efficacy of Vorinostat.

**Table 26. Response to the most Recent Bexarotene Systemic Therapy and Response to Vorinostat (Protocol 005: All Patients as treated) (Applicant's Table)**

| | | Responder to Vorinostat |
|---|---|---|
| Population | N | n (%) |
| Patients who responded to the most recent bexarotene therapy[†] | 10 | 2 (20.0%) |
| Patients who didn't respond to the most recent bexarotene therapy[‡] | 12 | 3 (25.0%) |
| Patients who were not on bexarotene as a prior systemic therapy | 11 | 3 (27.3%) |
| [†] Complete response or partial response. | | |
| [‡] Stable disease or progressive disease or unknown. | | |

[Ref. 5.3.5.2: P005]

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**Pruritis relief (Protocol 005)**

All patients were asked to rate their pruritis on a scale of 0 to 10 at each study visit. Thirty-one (31) patients who had a baseline pruritis score were included in the pruritis relief analysis

- Overall, in all three cohorts, 26 patients had a baseline pruritis score of ≥ 3
  - 50% (13/26) had pruritis relief
    - 8% (2/26) had complete resolution of pruritis
    - 42% (11/26) had a sustained reduction in pruritis of ≥ 3 for at least 4 continuous weeks.

**Cohort-wise frequency of pruritis relief** (both complete and partial relief; for those patients with a baseline pruritis score of ≥ 3)

- Cohort 1 = 73% (8/11)
- Cohort 2 = 20% (2/10)
- Cohort 3 = 60% (3/5)

Applicant commented that these data further support the conclusion that the Cohort 2 dose and schedule is suboptimal and provides some evidence that the Cohort 1 schedule is perhaps the most effective dose and schedule.

**Median time-to-pruritis relief** (for those who had baseline pruritis scores of ≥ 3 and who experienced a ≥ 3 pruritis score reduction)

- Overall population = 25 days (range 8 to 63)
- Cohort 1 = 15 days (range 8 to 43)
- Cohort 2 = 27 days (range 25 to 28)
- Cohort 3 = 29 days (range 8 to 63)

**Median duration of pruritis relief** (end of pruritis relief defined as a return to the baseline or higher score)

- Overall population = 57 days (range 31+ to 155)
- Cohort 1 = 64 days (range 36+ to 155)
- Cohort 2 = 45 days (range 31+, 59+)
- Cohort 3 = 38 days (range 36+, 106)

**Exploratory Analyses (Protocol 005)**

**Patients with Clinically Abnormal Lymph Nodes**

- Clinically abnormal lymph nodes were detected in 13 evaluable patients at baseline
- Ten (10) patients (10/13, 76.9%) had a reduction ≥ 50% of their clinical abnormal lymph nodes
- All of the patients with clinically abnormal lymph nodes in Cohort 3 met the criterion of 50% reduction compared to the baseline; rate of lymph node improvement in Cohort 1 was 80% (4/5) and in Cohort 2 it was 50.0% (2/4)

**Patients with a Baseline Measurement of Index Lesions**

- Nineteen (19) patients had a baseline measurement of index lesions (18 mycosis fungoides patients and 1 Sezary syndrome patient)
- 5 patients (26.3%) had a ≥ 50% reduction of index lesions
- Observed rate of index lesion reduction was 80% in Cohort 3

Applicant commented that overall Protocol 005 study results support the results of Protocol 001 study in demonstrating that Vorinostat provides clinically meaningful responses in a substantial number of patients with relapsed or refractory CTCL. Of the three dose cohorts investigated under Protocol 005, the combined evidence for safety and efficacy supports the use of Vorinostat 400 mg once daily continuously. Clinical benefit from Vorinostat therapy is observed in advanced clinical stage CTCL including Sezary syndrome patients as well as in earlier clinical stage patients. Clinical benefit does not appear to correlate with response to the most recent previous CTCL treatment or response to prior bexarotene therapy. The duration of clinical benefit from Vorinostat therapy is clinically meaningful. Vorinostat provides clinically meaningful reduction in pruritis in a substantial number of symptomatic patients with CTCL refractory to or intolerant of prior therapy.

**Comparison and Analyses of the Efficacy Results across Studies (Protocols 005 and 001)**

Two studies of Vorinostat in relapsed and refractory CTCL patients were conducted: an initial supportive study assessing several dosing regimens (Protocol 005) and a pivotal study (Protocol 001). Concurrence for the design of Protocol 001 was reached with Food and Drug Administration (FDA) as part of a Special Protocol Assessment (SPA).

- The initial supportive study (Protocol 005) enrolled a total of 33 patients with mycosis fungoides or Sezary syndrome.
- The size of the study prohibited definitive conclusions regarding the optimal dose and schedule; however, the data showed that 400 mg once daily dose yielded the numerically highest response rate in patients with Stage IIB and higher disease. Response rate was measured by the Physician's Global Assessment (PGA).
- Relief of pruritis, as assessed by history, was also more frequently observed in the 400 mg once daily cohort than in the other cohorts.

- Protocol 001 was designed to more specifically assess the response of Stage IB and higher CTCL patients to a regimen of Vorinostat administered at 400 mg once daily.
- Efficacy was assessed by a modified Severity Weighted Assessment Tool (SWAT) score.
- 74 patients were enrolled.
- The observed response rate was 29.5% in patients with ≥ IIB disease.

Pooled analyses of the efficacy results from the pivotal study (Protocol 001) and the initial supportive study (Protocol 005) were not conducted as the two studies used different inclusion and exclusion criteria and methodologies for assessing response to treatment. However, corroborative conclusions can be made regarding clinical efficacy of Vorinostat in patients with CTCL based on the results from both studies. The following sections detail and compare the analyses of the results from both studies.

**Study Populations (Protocol 001 and Protocol 005)**

- The All Patients as Treated (APaT) approach was used in the efficacy evaluations for Protocol 001 and Protocol 005. The APaT populations for each study was categorized based on Vorinostat dose and schedule, and two clinical characteristics: clinical Stage IIB and higher, and Sezary syndrome. Some analyses also took into consideration the extent of T3 tumor disease.
- Because of different dosing regimens, the overall combined efficacy of the two protocols was evaluated by including only those patients on Protocol 005 who were enrolled in Cohort 1—they were treated at the same Vorinostat dose and schedule (400 mg once daily) as in Protocol 001.
- The combined efficacy analysis, thus, utilizes the APaT patient population of Protocol 001 (74 patients) and Protocol 005, Cohort 1 (13 patients) for a total of 87 patients.
- This combined efficacy population can be further examined by subgroups: patients with Stage IIB and higher, and patients with Sezary syndrome.
- In the combined efficacy population, 72/87 (82.8%) patients were Stage IIB and higher and 33/87 (37.9%) patients had Sezary syndrome.

**Population Characteristics**

Demographic data and baseline CTCL disease characteristics for Protocol 001 and Protocol 005 are shown in the tables below.

- Age, gender, race, and baseline CTCL disease characteristics were comparable across the treatment groups within each study as well as between the 2 studies.
- The majority of patients enrolled in both studies were less than or equal to 65 years of age.
    - In Protocol 001, the median age was 60 years
    - In Protocol 005, Cohort 1, the median age was 65 years.
- Protocol 001 enrolled more males than females (38/74, 51.4%) as did Protocol 005, Cohort 1 (8/13, 61.5%)
- Protocol 001 enrolled more White patients (61/74, 82.4%) than Black patients as did Protocol 005, Cohort 1 (10/13, 76.9%).

**Table 27. Baseline Demographics in: Protocol 001 and Protocol 005 (Applicant's Table)**

| Characteristic | Protocol 001 | Protocol 005 | | |
|---|---|---|---|---|
| | 400 mg once daily (N=74) | Cohort 1 (N=13) | Cohort 2 (N=11) | Cohort 3 (N=9) |
| **Age** | | | | |
| Mean | 61.2 | 61.7 | 60.9 | 67.4 |
| Median | 60.0 | 65.0 | 69.0 | 67.0 |
| Min-Max | 39.0-83.0 | 37.0-82.0 | 26.0-80.0 | 49.0-78.0 |
| Number (%) ≤65 years | 45 (60.8%) | 7 (53.9%) | 5 (45.5%) | 3 (33.3%) |
| Number (%) >65 years | 29 (39.2%) | 6 (46.2%) | 6 (54.6%) | 6 (66.7%) |
| **Gender (n, %)** | | | | |
| Female | 36 (48.6%) | 5 (38.5%) | 6 (54.5%) | 4 (44.4%) |
| Male | 38 (51.4%) | 8 (61.5%) | 5 (45.5%) | 5 (55.6%) |
| **Race (n, %)** | | | | |
| Asian | 1 (1.4%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Black | 11 (14.9%) | 3 (23.1%) | 4 (36.4%) | 1 (11.1%) |
| White | 61 (82.4%) | 10 (76.9%) | 7 (63.6%) | 8 (88.9%) |
| Other | 1 (1.4%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Protocol 005, Cohort 1: 400 mg once daily x7d/wk; Cohort 2: 300 mg twice daily x 3d/wk; Cohort 3: Induction 300 mg twice daily, maintenance 200 mg twice daily<br>CTCL = Cutaneous T-cell Lymphoma | | | | |

[Ref. 5.3.5.2: P001] [Ref. 5.3.5.2: P005]

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## Baseline CTCL Characteristics (Protocol 001 and Protocol 005)

### Table 28. Baseline Summary of CTCL Characteristics: Protocol 001 and Protocol 005 (Applicant's Table)

| Characteristic | Protocol 001 | Protocol 005 | | |
|---|---|---|---|---|
| Number (%) of Patients with: | 400 mg once daily (N=74) | Cohort 1 (N=13) | Cohort 2 (N=11) | Cohort 3 (N=9) |
| CTCL Stage IIB and higher, n (%) | 61 (82.4%) | 11 (84.6%) | 10 (90.0%) | 7 (77.7%) |
| Presence of clinically abnormal lymph nodes, n (%) | 34 (45.9%) | 8 (61.5%) | 7 (63.6%) | 4 (44.4%) |
| Presence of Sezary syndrome, n (%) | 30 (40.5%) | 3 (23.1%) | 4 (36.4%) | 4 (44.4%) |
| Presence of skin tumors/tumor disease, n (%) | 22 (29.7%) | 2 (15.4%) | 1 (9.1%) | 2 (22.2%) |
| Prior use of bexarotene therapy | 71 (95.9%) | 9 (69.2%) | 7 (63.6%) | 6 (66.6%) |
| Number of prior systemic treatments, median (range) | 3.0 (1.0, 12.0) | 4.0 (0.0, 8.0) | 4.0 (2.0, 11.0) | 2.0 (1.0, 8.0) |
| Pruritus scores | | | | |
| Mean (SD) | 6.0 (2.5) | 9.0 (2.3) | 6.6 (3.2) | 3.6 (3.8) |
| Median (Range) | 6.0 (0.0, 10.0) | 10.0 (3.0, 10.0) | 6.0 (1.0, 10.0) | 3.0 (0.0, 10.0) |
| Protocol 005, Cohort 1: 400 mg once daily x7d/wk; Cohort 2: 300 mg twice daily x 3d/wk; Cohort 3: Induction 300 mg twice daily, maintenance 200 mg twice daily<br>CTCL = Cutaneous T-cell Lymphoma | | | | |

[Ref. 5.3.5.2: P001] [Ref. 5.3.5.2: P005]

### Protocol 005

- 33 unique patients were enrolled in the three primary dosing cohorts in Protocol 005
- 13 patients (those enrolled in Cohort 1) received the Vorinostat dose and regimen comparable to that of Protocol 001 (400 mg once daily).
- All 13 of these patients had a histological diagnosis of CTCL Stage IB or higher

### CTCL Stage IIB and higher:

- 61/74 (82.4%) patients in Protocol 001
- 28/33 (84.9%) patients in Protocol 005

### Sezary syndrome patients:

- 30/74 (40.5%) patients in Protocol 001
- 11/33 (33.3%) patients in Protocol 005

### Patients with skin tumors/T3 tumor disease:

- 22/74 (29.7%) in Protocol 001

- 5/33 (15.2%) in Protocol 005

**Exposure to Previous Treatments:**

**Protocol 001**

- Median of 3 prior systemic therapies
- 71/74, 95.9% had used bexarotene

**Protocol 005**

- Median of 4 prior systemic therapies
- 9/13, 69.2% had used bexarotene, in Cohort 1

Comparable **baseline mean pruritis scores** were also noted in both studies.

These data support the similarities in the baseline characteristics for patients included in analysis of the subpopulations.

**Subpopulations for Comparison**

4 subpopulations were defined for comparison between the All Patients as Treated (APaT) evaluation for these two studies. These subpopulations are summarized in discussions of the primary endpoint: response rate, and also in the discussions for secondary endpoints: time to objective response, duration of response, time to progression, and pruritis relief. Additionally, analysis is provided for reduction of index lesions by physical examination.

(1) The overall population
(2) The CTCL Stage IIB and higher population
(3) The Sezary syndrome population
(4) Patients who were treated with oral Vorinostat 400 mg once daily

**Comparison of Efficacy Results**

A comparison of efficacy analyses was performed using data from Protocol 001 and Protocol 005. These comparisons were possible as both studies:

(1) Used oral administration of Vorinostat at a comparable dose and regimen (400 mg capsules once daily)
(2) Vorinostat capsules administered in the two studies were similar in formulation, composition, potency assay and manufacturing process
(3) Study designs were similar with respect to baseline characteristics (e.g., tumor staging, tumor disease, prior use of bexarotene), patient population and efficacy evaluations; and
(4) Two studies used similar clinical and laboratory efficacy definitions.

**The inclusion criteria of Protocol 001 and Protocol 005 differed in the following aspects:**

- Patients with CTCL with any stage of the disease were eligible for enrollment on Protocol 005, whereas patients enrolled on Protocol 001 were eligible only if they were diagnosed with CTCL Stage IB or higher
- Protocol 005 was open to enrollment for patients with either CTCL or PTCL, whereas only patients with CTCL were eligible for enrollment on Protocol 001
- Patients enrolled on Protocol 005 must have received at least 1 prior systemic therapy for CTCL, whereas patients enrolled on Protocol 001 must have received at least 2 prior systemic therapies for CTCL, one of which must have contained bexarotene unless contraindicated
- For patients enrolled on Protocol 005 the study site must have a confirmed histological diagnosis of CTCL, whereas on Protocol 001 histological diagnosis of CTCL must have been confirmed by biopsy within 1 year prior to enrollment.

**Primary Endpoints**

The primary efficacy objective for both Protocol 001 and Protocol 005 was to determine the response rate of oral Vorinostat in the treatment of skin disease in patients with CTCL. In both studies, the primary endpoint was the proportion of patients achieving an objective response.

- The primary efficacy analysis for Protocol 001 included only patients with CTCL Stage IIB and higher, utilizing a modified Severity Weighted Assessment Tool to measure the objective response.
- In Protocol 001, the lesion types (patch, plaque, or tumor) were mapped onto body diagrams to document skin involvement and this body diagram served as a worksheet for the deriving SWAT scores
    - Patch: abnormal skin not elevated from normal skin
    - Plaque: abnormal skin elevated from normal skin by <5 mm
    - Tumor: a plaque elevated ≥ 5 mm
- The patient's palm was used as a "ruler" to measure the %TBSA involvement within each of 12 regions with pre-assigned %TBSA
- The patient's palm with 4 fingers (measured from wrist to fingertips, excluding the thumb) was assumed to be 1% of TBSA, and the patient's palm without fingers was assumed to be 0.5% of TBSA.
- To determine the SWAT score, the areas of involvement with patch, plaque and tumor lesions were multiplied by 1, 2 and 4, respectively. This is in contrast to the weighting factor of 3 used in the original SWAT method. The modified SWAT gives more weight to responses in tumor lesions than does the original SWAT.

- By comparison, Protocol 005 measured the objective response by the Physician's Global Assessment (PGA)
- Assessment by PGA required the investigator to assess for overall tumor response by assigning a specific term based on their overall impression (e.g., completely clear, almost

clear, marked improvement, moderate improvement, slight improvement, no change, worse)

- Since the measurement tools for determining objective response in each study were different, it was not possible to conduct a pooled analysis of the primary endpoint data

A side-by-side comparison of the primary efficacy endpoints for both studies, including definitions for objective, complete, and partial response, is provided in the table below:

**Table 29. Endpoint Variables in CTCL Efficacy: Protocol 001 and Protocol 005 (Applicant's Table)**

| Parameter | Definitions / Descriptions | |
|---|---|---|
| | Protocol 001 | Protocol 005 |
| Baseline CTCL Staging Criteria | Stage IB, IIA, IIB, III, IVA, IVB | Stage IA, IB, IIA, IIB, III, IVA, IVB |
| Primary Efficacy Endpoint: Assessment Tools | SWAT | PGA |
| Primary Efficacy Endpoint: Objective Response | CR or PR: Confirmation of response required a second assessment at least 4 weeks later. | CR or PR: Confirmation of response required a second assessment at least 4 weeks later. |
| Complete Clear Response (CCR) | No evidence of disease; 100% improvement | No evidence of disease; 100% improvement |
| Partial Response (PR) | ≥50% decrease in skin scores compared to baseline and improvement is maintained for 4 weeks | ≥50% improvement in disease findings |
| Duration of Response | Measured from the time measurement criteria were first met for a response until the first date when an increase from nadir in skin score was greater than 50% of the difference between the baseline score and nadir score and if that magnitude of increase in skin score was conformed by a second assessment at 1-4 weeks later. | Measured from the time measurement criteria were met for PR until the first date that progressive disease was documented. |
| Time to Progression (TTP) | Measure from the start of the treatment until the criteria for progression are first met | Measure from the start of the treatment to the time of documented disease progression. |
| Time to Response (TTR) | Measured from start of treatment to the time when criteria are first met for CCR or PR (whichever is first recorded). | Measured from start of treatment to time when criteria were first met for PR. |
| CTCL: Cutaneous T-cell Lymphoma<br>PGA: Physician's Global Assessment<br>SWAT: Severity Weighted Assessment Tool | | |

[Ref. 5.3.5.2: P001] [Ref. 5.3.5.2: P005]

**Response Rates (Protocol 001 and Protocol 005)**

The following table shows that the objective response rates in various subpopulations are comparable between Protocol 001 and Protocol 005 (Cohort 1)—the 400 mg once daily subpopulation.

- Of the **overall population** in Protocol 001, 22/74 (29.7%) patients achieved an objective response, and in Protocol 005, cohort 1, 4/13 (30.8%)
- Of the **Stage IIB and higher patients** in Protocol 001, 18/61 (29.5%) patients achieved an objective response, and in Protocol 005, cohort 1, 4/11 (36.4%)
- Of the **Sezary syndrome patients** in Protocol 001, 10/30 (33.3%) patients achieved an objective response, and in Protocol 005, cohort 1, 1/3 (33.3%)
- Of the patients who had **bexarotene as prior systemic therapy** in Protocol 001, 21/71 (29.6%) patients achieved an objective response, and in Protocol 005, cohort 1, 4/9 (44.4%)

Although the methods for evaluating responses differed between the two studies, the outcome by response rates were similar

**Table 30. Objective Response Rate in Patients Treated with Vorinostat 400 mg Once Daily (Protocol 001 and Protocol 005 Cohort 1) (Applicant's Table)**

| Population | Patients with Objective Response Rate[†] | | | |
|---|---|---|---|---|
| | Protocol 001 (APaT) N=74 | | Protocol 005 Cohort 1 (APaT) N=13 | |
| | % (n/N) | (95% CI) | % (n/N) | (95% CI) |
| All Patients | 29.7% (22/74) | (19.7, 41.5) | 30.8% (4/13) | (9.1, 61.4) |
| Stage IIB and higher[‡] | 29.5% (18/61) | (18.5, 42.6) | 36.4% (4/11) | (10.9, 69.2) |
| Patients with Sezary syndrome | 33.3% (10/30) | (17.3, 52.8) | 33.3% (1/3) | (0.8, 90.6) |
| Patients with prior bexarotene as systemic therapy | 29.6% (21/71) | (19.3, 41.6) | 44.4% (4/9) | (13.7, 78.8) |

[†] Objective Response Rate: % of patients with complete response or partial response.
[‡] Stages IIB, III, IVA, and IVB.
Protocol 005, Cohort 1: 400 mg once daily x7d/wk; Cohort 2: 300 mg twice daily x 3d/wk; Cohort 3: Induction 300 mg twice daily, maintenance 200 mg twice daily
CI=Confidence Interval.

[Ref. 5.3.5.2: P001] [Ref. 5.3.5.2: P005]

**Patients with Clinical Benefit with/without an Objective Response (Protocol 001)**

Several patients treated on Protocol 001 had improvement in their SWAT scores at one or more time points but did not meet the criteria for objective response. This reflects some clinical benefit.

**≥50% Reduction in SWAT Skin Assessment Score**

- Overall = 29/74 (39.2%)
- Stage IIB and higher disease = 23/61 (37.7%)
- Sezary syndrome = 13/30 (43.3%)
- T3 tumor disease = 7/22 (31.8%)

**≥ 25% to 49% Reduction in SWAT Skin Assessment Score**

- Overall = 17/74 (23.0%)
- Stage IIB and higher disease = 12/61 (19.7%)
- Sezary syndrome = 6/30 (20.0%)
- T3 tumor disease = 4/22 (18.2%)

**Some (>0%) Reduction in SWAT Score at some time during evaluation**

- Overall = 60/74 (81.1%)
- Stage IIB and higher disease = 47/61 (77.0%)
- Sezary syndrome = 24/30 (80.0%)
- T3 tumor disease = 16/22 (72.7%)

**Patients with Clinical Benefit with/without an Objective Response (Protocol 005)**

- In Protocol 005, improvement in the overall disease condition was observed among patients who did not qualify as responders
- In Cohort 1, 5/13 (38.5%) patients were non-responders but had improvement in PGA for one or more visits
- Two (2) of 13 (15.4%) patients were non-responders with improvement for at least 2 consecutive visits or at the last visit.

The applicant comments that these data suggest that in some patients, although the full objective response as defined by the protocols, is not achieved, the patients may have some clinical benefit.

**Secondary Endpoints (Protocol 001 and Protocol 005)**

- In Protocol 001, secondary efficacy endpoints included response duration, relief of pruritis, time to progression, and time to objective response.
- The Protocol 005 prespecified secondary objective was to determine duration of response. Times to response and pruritis relief were also analyzed *post hoc* and are presented in the following sections.

**Time to Objective Response**

In Protocol 001, the median time to objective response was slightly less than two months:

- Overall = 55 days
- Stage IIB and higher = 56 days
- Sezary syndrome = 56 days
- T3 tumor disease = 31 days

In Protocol 005, Cohort 1, overall, the median time to objective response was 88 days (approximately 3 months)
Between the two studies, time to objective response ranged from about 2 to 3 months.

**Duration of Response**

In Protocol 001, the overall median response duration had not been reached, but exceeded 4 months (original analysis)

- Overall patient population = the range for days of response: 34+ to 322+
- Stage IIB and higher population = the range for days of response: 34+ to 280+
- Sezary syndrome patients = the range for days of response: 34+ to 244+
- T3 tumor disease patients = the range for days of response: 55 to 280+

In Protocol 005, Cohort 1, in the overall population, the median response duration was 113 days.

One patient had a rapid response (time to response of 29 days) and the response lasted 70 days. This patient withdrew consent after 28 days on the study but re-enrolled in Cohort 2 twelve weeks later into Cohort 2. This patient had a delayed but durable response with time to response of 104 days and response duration of 386 days. The combined total number of days on study for this patient from Cohort 1 and Cohort 2 were 495 days.

**Time to Progression**

In Protocol 001, the overall median time to progressive disease was not reached (original analysis). Patients included in the censored data showed time to progressive disease ranging from 78+ to 365+ days and ongoing response. Therefore, in the overall population, the median time to progression was not reached and was estimated to exceed 5 months.

Range of Time to Disease Progression in days:

- Overall patient population = 78+ to 365+
- Stage IIB and higher = 85 to 365+ days
- Sezary syndrome = 85 to 365+ days
- T3 tumor disease = 148 to 317+ days

In Protocol 005, if progressive disease was not observed for a patient, time to progression was censored at the last overall tumor assessment date. There were 11 such patients overall.
In the overall population, the median time to progression was 85 days with a range of 21 to 255 days.

**Relief of Pruritis (Protocol 001 and Protocol 005)**

**Protocol 001**

- Pruritis relief required maintenance of effect for at least 4 weeks without an increase in the use of pruritis medication
- The results were similar for the overall patient population with pruritis (intensity $\geq 3$ points at baseline) and patients with Sezary syndrome.

**Table 31. Frequency of Pruritis Relief and Complete Resolution of Pruritis (Protocol 001)**

| Patient Population | Pruritis Relief | Complete Resolution of Pruritis |
|---|---|---|
| Overall | 23/72 (31.9%) | 8/72 (11.1%) |
| Stage IIB and higher | 18/59 (30.5%) | 8/59 (13.6%) |
| Sezary syndrome | 9/30 (30.0%) | 3/30 (10.0%) |
| T3 tumor disease | 4/20 (20.0%) | 2/20 (10.0%) |

**Protocol 005**

- Pruritis relief was most evident in Cohort 1 (400 mg once daily)
- Pruritis relief was exhibited as a decrease in mean pruritis score from approximately a score of 9 to a score of less than 4 at the end of the study.
  - 8/11 (72.7%) patients experienced pruritis relief (maintained for at least 4 weeks)
  - 1/11 (9.1%) patient achieved complete resolution of pruritis

**Other Measures of Efficacy (Protocol 001 and Protocol 005)**

**Reduction in Index Lesions (Lymph Nodes) Measurements by Physical Examination**

**Protocol 001**

Twenty-four of 74 (32.4%) patients had palpable, *clinically abnormal* **index** *lymph nodes* (index lesions). Overall, 34 patients in the study had *clinically abnormal lymph nodes.*

- 10/24 (41.7%) patients had ≥ 50% reduction in the sum of products of the greatest diameters of the index lymph nodes
- 6/24 (25.0%) patients achieved an objective response (by SWAT)
  - 4/6 patients had an objective response and also a ≥ 50% reduction of their index lymph nodes

***Reviewer Comments:*** *When patients had the skin disease and clinically abnormal lymph nodes, the proportion with clinically abnormal lymph nodes who had a nodal response was higher than the proportion of patients who had an objective response in their skin disease by SWAT.*

**Protocol 005 (Cohort 1)**

5/13 (38.5%) patients in cohort 1 had clinically detectable abnormal lymph nodes at baseline—these were not considered index lesions, however.

- 4/5 (80.0%) patients had a ≥ 50% reduction in the sum of products of the greatest diameters of lymph nodes by physical examination
- The majority of the patients in this subpopulation who presented with clinically abnormal lymph nodes showed clinical improvement from baseline

***Reviewer Comments:*** *It is also stated that of the 7 patients in Protocol 005 who had a baseline measurement for index lesions, none experienced a ≥ 50% reduction in the sum of products of the greatest diameters of index lesions by physical examination.*

**Persistence of Efficacy and/or Tolerance Effects**

Pre-specified primary observation period in Protocol 001 was 6 months from the last enrolled patient's first day of treatment and this limited the ability to document the persistence of efficacy; however, patients showing clinical benefit were permitted to continue treatment following completion of the 6-month treatment period

- As of the data cut-off date of 23-Nov-2005, fifteen (15) patients initially enrolled in Protocol 001 had received Vorinostat treatment beyond 6-months—either as a part of ongoing Protocol 001, or on a treatment extension study Protocol 007 (developed to enable any patient showing clinical benefit in Protocol 001 to continue receiving treatment with Vorinostat)
  - 1/15 patients experienced a CR (AN 1025) and 8 had an objective response of PR at the time of data cut off

- 14/15 patients were receiving 400 mg once daily continuously and 1/15 patient was receiving 300 mg once daily continuously as of data cut-off date. The patient receiving 300 mg once daily continuously had a previous dose reduction in the base protocol due to an adverse experience.
- One patient enrolled in Protocol 005 was rechallenged with Vorinostat after discontinuing enrollment in the first cohort due to adverse experiences. This patient (AN 1012/1015) responded a second time for a period of time beyond 386 days.

- The response rates for all the patients treated with Vorinostat at the dose and schedule proposed for clinical use (400 mg, orally, once daily, continuously) were 30.7% (4/13) in the initial supportive study (Protocol 005) and 29.7% (22/74) in the pivotal study (Protocol 001); for patients with Stage IIB or higher CTCL, the response rates were 36.4% (4/11) and 29.5% (18/61), respectively; and for Sezary syndrome patients, the response rates was 33.3% (1/3 and 10/30) in both studies.

    - Thus, although the required prior therapy and evaluation of response differed between the two studies, response rates were similar.

- In Protocol 001, the median response duration for the responders was not reached as of the data cut-off for this marketing application as the study was ongoing; however, the median response duration was estimated to be at least 4 months.
- The median time-to-progression in patients with Stage IIB and higher was not reached either, but was estimated to be at least 5 months.

***Reviewer Comments:*** *See previous comments regarding recalculation of the response duration and time to progression (using the FDA criteria to define loss of response) on page 73.*

**Outcomes of Objective Responders in Protocol 001**

The table below lists the 22 patients (APaT population) who had an objective response in Protocol 001. Some of these patients subsequently developed disease progression.

- All responses were partial
    - 1 patient (AN 1025) had a PR as the first response but achieved CCR after 281 days of treatment.
    - Another patient (AN 1027) also experienced a second PR with a duration of 84+ days.
- 14/22 (63.6%) responders continued to show response at the time of their last assessment
- 2/22 (9.1%) patients (AN1027 and AN1065) eventually had SWAT scores which no longer qualified as response values; however these patients did not meet the criteria for disease progression.
- 6/22 (27.3%) patients who achieved an objective response met the criteria for progressive disease.

**Table 32. Responders in Protocol 001: Duration of Objective Response and Time to Progression (APaT Population) (Applicant's Table)**

| Site | Number | Stage | Sezary (Yes/No) | Tumor (Yes/No) | Time to objective Response† (Days) | Duration of objective Response (Days) | Time to Progression Disease (Days) |
|---|---|---|---|---|---|---|---|
| 0004 | **1009§** | **IVA** | **Yes** | **No** | **29** | **112** | **141** |
| | **1010§** | **IB** | **No** | **No** | **57** | **56** | **113** |
| 0005 | 1034 | III | Yes | No | 55 | 244+‡ | 299+‡ |
| | **1035§** | **IB** | **No** | **No** | **55** | **105** | **160** |
| 0006 | 1030 | IVA | No | No | 57 | 266+‡ | 323+‡ |
| 0007 | 1016 | IVB | Yes | No | 142 | 223+‡ | 365+‡ |
| 0009 | 1008 | III | Yes | No | 28 | 185+‡ | 213+‡ |
| | **1040§** | **IVA** | **Yes** | **No** | **29** | **59** | **88** |
| 0010 | 1014 | IB | No | No | 30 | 322+‡ | 352+‡ |
| | 1027 | IIB | No | Yes | 87 | 55 | 317+‡ |
| 0011 | **1024§** | **III** | **Yes** | **No** | **29** | **56** | **85** |
| 0012 | 1025 | IIB | No | Yes | 29 | 280+‡ | 309+‡ |
| | **1029§** | **IVA** | **No** | **Yes** | **31** | **117** | **148** |
| 0013 | 1038 | IVA | No | No | 143 | 133+‡ | 276+‡ |
| | 1065 | III | No | No | 31 | 105 | 136+‡ |
| 0014 | 1044 | III | Yes | No | 171 | 34+‡ | 205+‡ |
| 0015 | 1058 | IIB | No | Yes | 87 | 137+‡ | 224+‡ |
| | 1068 | IIB | No | Yes | 29 | 170+‡ | 199+‡ |
| 0018 | 1059 | III | Yes | No | 57 | 145+‡ | 202+‡ |
| 0020 | 1079 | III | Yes | No | 61 | 106+‡ | 167+‡ |
| 0021 | 1053 | IVA | Yes | No | 114 | 119+‡ | 233+‡ |
| 0022 | 1042 | IB | No | No | 30 | 48+‡ | 78+‡ |

† Objective Response: confirmed complete response or partial response
‡ Response ongoing
§ 6 Patients that progressed after an objective response are noted in bold
AN1027 had a second confirmed response with duration of 84+ days. Only the first response is included in the analysis.
AN1025 achieved complete response after 281 days of treatment and was sustained for 28+ days.

[Ref. 5.3.5.2: P001]

- Based on the persistence of histone acetylation and no dramatic changes in pharmacokinetics, there is no anticipation that Vorinostat treatment would lead to tolerance [Ref. 5.3.3.2: P008] [Ref. 5.3.5.4: P006].

## 6.1.5 Clinical Microbiology

- Not applicable (Vorinostat is a HDAC inhibitor to be used for treatment of cancers; it has no microbiological application)

## 6.1.6 Efficacy Conclusions

**Conclusions**

- The pivotal study (Protocol 001) demonstrated that Vorinostat provided clinically meaningful responses in a substantial number of patients with advanced CTCL (Stage IIB and higher) who had progressive, persistent, or recurrent disease on or following 2 systemic therapies—including prior bexarotene therapy

- Vorinostat provided clinically meaningful responses in a substantial number of patients within the 3 prespecified subgroups: patients with stage IIB or higher disease, Sezary syndrome patients, and T3 tumor patients.
- Similar responses were noted in the overall population, including the lower clinical stage patients
- Both the median duration of objective response and the median time-to-progression were clinically meaningful:
- Median duration of objective response had not been reached (ongoing study) but exceeded 4 months. *(Updated and recalculated analysis showed this to be 168 days for all patients and 170 days for patients with stage IIB or higher disease).*
- Median time to progression had not been reached (ongoing study) but was estimated to exceed 5 months. *(Updated and recalculated analysis showed this to be 202 days for all patients and 205 days for patients with stage IIB or higher disease).*
- The median time to response was less than 2 months (55 days)
- Vorinostat provided clinically meaningful reduction in pruritis in a substantial number of symptomatic patients with CTCL who were refractory to or intolerant of at least 2 prior therapies including bexarotene.
- No impact of response to last treatment, or response to prior bexarotene treatment, was discernable on subsequent efficacy of Vorinostat.

**Review and discussion of Vorinostat efficacy**

- Efficacy of Vorinostat for the proposed indication of cutaneous T-cell lymphoma (CTCL) has been demonstrated in 2 Phase II studies: Protocols 001 and 005.
- Both studies were open-label non-randomized studies due to low prevalence of CTCL and absence of a standard effective therapy to compare against Vorinostat in the refractory or relapsed CTCL population.
- Protocol 005 was conducted before Protocol 001 and provided the basis for the design of the pivotal study.

- Most cases of primary CTCL are not curable. A majority of patients with early stage disease die of causes unrelated to CTCL.
- Five-year survival rates vary by clinical stage:
  - Stage I 80-90%
  - Stage II 60-70%
  - Stage III 40-50%
  - Stage IV 25-35%

- CTCL patients with superficial skin involvement (clinical Stages I and IIA according to World Health Organization–European Organization for Research and Treatment of Cancer [WHO-EORTC] classification of cutaneous lymphomas) have a median survival of more than 12 years
- However, the long-term survival of patients with T2, T3 and T4 disease is shorter than that of a matched control population. Patients with more advanced stage disease: plaque,

tumor, erythroderma, and lymph node or blood involvement, but no visceral involvement, (Stages IIB, III, and IVA) have a median survival of 5 years.

- More than 50% of patients with Stage III through Stage IV disease die of mycosis fungoides, with a median survival of less than 5 years
- Survival for advanced stage disease is short. Median survivals have been reported for Stage IV disease ranging from 1.1-2.5 years. Patients with visceral involvement have a median survival of 2.5 years or less

- Treatment choices for MF and SS are type-, stage-, and practitioner- dependent.
- For early stage patients, palliative skin-directed treatments are commonly used. These treatments tend to be associated with a high relapse rate.
- For the more advanced stages (with worse prognosis) systemic approaches similar to other low-grade lymphomas are appropriate, either alone or in combination. However, combination chemotherapies do not cure the disease and periods of remission become shorter with each subsequent treatment.
- A widely acceptable standard therapy to effectively treat advanced CTCL is not available. In the absence of curative treatment, palliation is currently the goal of therapy. Thus, new drugs or approaches are still being developed with the goal of altering the disease state in patients with advanced disease.

In the Vorinostat CTCL program, the two key Phase II studies differ in the following areas:

**Eligibility**

- Protocol 005 had no requirements of minimum stage, number of previous systemic therapies, or prior bexarotene therapy.
- Protocol 001 had more stringent inclusion criteria to recruit more advanced CTCL patients for whom the general prognosis was poor and effective treatment options were absent.
- Patients must have had advanced disease documented as Stage IB or higher including Sezary syndrome, with progressive, persistent, or recurrent disease on or following two systemic therapies, one of which must have contained bexarotene unless the patient was intolerant of or not a candidate for bexarotene therapy.
    - Persistent disease was defined as a lack of at least 50% improvement of disease on therapy for at least 3 months unless the patient is intolerant of therapy because of toxicities.
    - Systemic therapies were defined as photopheresis and antineoplastic agents including investigational drugs or biological therapy administered parenterally or orally.
    - Patients were considered intolerant of bexarotene therapy if they were discontinued from bexarotene therapy because of toxicities.
    - Patients were considered not to be candidates for bexarotene therapy if they had risk factors for pancreatitis (e.g., prior pancreatitis, uncontrolled hyperlipidemia, excessive alcohol consumption, uncontrolled diabetes mellitus, biliary tract

disease, and medications known to increase triglyceride levels or to be associated with pancreatic toxicity), as described in the bexarotene package insert

**Assessment of Primary Endpoint**

**Protocol 005**

- Efficacy in Protocol 005 was primarily assessed using the composite endpoint of Physician's Global Assessment (PGA) which measured the extent of skin involvement as well as lymph node size.
- The PGA endpoint is widely used by physicians in treating CTCL patients, and was adopted in the registration study of bexarotene for its indication in CTCL

**Protocol 001**

- For Protocol 001, a modified Severity-Weighted Assessment Tool (SWAT) was chosen for assessing skin disease. The SWAT was used in the registration study of denileukin diftitox
- In a separate study, SWAT scores were shown to correlate with PGA scores
- Protocol 001 modified the SWAT to introduce a different weighting factor for the tumor stage and use a predefined % regional skin area rather than a calculation using a point-counting grid placed on a body diagram of the involved skin areas. This modification with the use of a weighted scoring system for type of lesion is consistent with the tumor burden index used by the EORTC. *To avoid a potential discrepancy in a composite endpoint between the tumor volume assessment and cutaneous assessment using the SWAT tool, a response algorithm was proposed based solely on the SWAT tool (noted in the SPA)*
- Protocol 001 was amended and the Investigator were instructed to limit examinations of patients to experienced clinicians and the same patients be evaluated by the same clinician throughout the study period to avoid inter-Investigator variability. In addition, Investigators had been trained in the use of SWAT and a SOP for the SWAT was provided to the Investigators.
- Serial, close-up digital photographs of distinct individual lesions, as well as global half-body photographs, were also taken as supportive documentation of change in skin disease. These photographs were supportive only and were not used to derive SWAT skin assessment scores.

**Treatment Duration**

- There was no pre-specified duration of treatment in Protocol 005.
- In Protocol 001, the primary data analysis was based on a minimum follow-up of 6 months from the time the last patient began treatment. Patients remained on study treatment for the 6 month period unless there was disease progression, intolerable toxicity, withdrawal of consent or the physician determined that it was in the best interest of the patient to withdraw.

- Patients who continued to demonstrate clinical benefit from Vorinostat at the end of the treatment phase were allowed to be transitioned into a continuation study, Protocol 007.
- The 6 month duration of treatment was considered sufficient to allow for evaluation of the proportion of patients who would respond to Vorinostat and would provide confidence in a minimal duration of treatment benefit that would be clinically relevant to patients and their treating physicians.

**Doses and Schedules**

- Protocol 005 sequentially tested one continuous (400 mg once daily) and two intermittent doses and schedules of Vorinostat (300 mg twice daily for 3 consecutive days every 7 days, and 300 mg twice daily for 14 consecutive days every 21 days).
- Based on the safety profile and proof of efficacy of the 400 mg once daily dose in Protocol 005 and the safety profile for the same dose established in other Phase I studies, 400 mg once daily was selected as the dose of Vorinostat to be evaluated in Protocol 001.
- Additional safety data for the 400 mg once daily continuous dose had been obtained in Protocol 006 and Protocol 002, further supporting this selection.

**Pruritis Intensity Assessment**

As CTCL affects the quality of life by its impact on skin appearance and symptom of pruritis, symptomatic relief of pruritis was closely monitored in both Protocol 005 and Protocol 001 as a secondary efficacy endpoint

- In previous clinical trials in CTCL patients, different non-validated instruments were used to measure the severity of pruritis:
  - Patients rated severity of itch on a 10 cm Visual Analog Scale, anchored by 0 (no itch) and 10 (worst imaginable itch)
  - Patients using a 5 point Likert-type scale from 1: no itchiness to 5: extreme itchiness answered "Over the past four weeks, how much itchiness have you noted from your CTCL skin lesions?" as part of a non-validated CTCL-specific questionnaire
- In Protocol 005, all patients were asked to rate their pruritis on a non-validated 10-point scale at baseline and during each visit in response to questioning by the study staff to assess skin itch over the past week (0 = no itching, 10 = worst imaginable itching)
- In Protocol 001, on a self-administered pruritis assessment questionnaire, patients rated the severity of their pruritis using a 10-point scale (0 = no itching, 10 = itching as bad as it can be) and also recorded the amount of medication taken to relieve symptoms of itching in the past week compared to the amount taken in the previous week.
  - A 3-point decrease in pruritis intensity confirmed by a second assessment at least 4 weeks after the initial assessment without an increase in the use of anti-pruritis medications was considered to be clinically significant in those whose pruritis score was $\geq 3$ at the baseline.
  - A 3-point improvement in pruritis intensity represented the SD of pruritis intensity at baseline among Protocol 001 patients who had pruritis at study entry (N=72 patients, SD of pruritis score =2.5). The 1 SD approach was a more

conservative estimate of minimal important difference than the 0.5 SD method presented in the literature as one of several methods used to define a minimal important difference

**Patients and disease characteristics in protocols 005 and 001 and discussion of the observed results**

- The characteristics of the patients recruited in both Protocol 005 and Protocol 001 were representative of the targeted advanced CTCL population with relapsed or refractory disease.
    - These characteristics were similar to those reported in other CTCL registration trials.
- The demographics in age, sex, number of previous systemic therapies, number of years since CTCL diagnosis, presence of clinically abnormal lymph nodes, proportion of advanced disease, proportion with T3 tumor and proportion of SS were consistent with those expected for a population with aggressive disease in need of new therapeutic options.
- The primary population in Protocol 001 was patients with CTCL clinical Stage IIB or greater.
    - Of the 74 patients enrolled on Protocol 001, 61 were diagnosed with CTCL clinical Stage IIB or above, among these 30 had SS and 22 had T3 tumor.
- Thirteen (13) patients with Stage IB and higher enrolled on Protocol 005 were treated with 400 mg daily dose of Vorinostat.
    - Of these, 11 were clinical Stage IIB or higher and 3 had SS.
- The combined total of patients who had CTCL clinical Stage IIB or greater and who received Vorinostat at a dose of 400 mg daily was 72 patients
- 87/107 CTCL patients received the proposed clinical dose of Vorinostat of 400 mg daily. (Additional 20 CTCL patients treated on Protocol 005 received different doses of Vorinostat)

Protocol 005 was the first trial to positively demonstrate Vorinostat anti-tumor activity in CTCL.

- In 13 relapsed or refractory CTCL patients treated with 400 mg once daily continuously, the objective response rate (ORR) denoted as CR and PR was 30.8% (4/13). In 11 patients with Stage IIB and higher disease, the ORR was 36.4% and in patients with SS the ORR was 33.3% (1/3).
- When the continuous dosing cohort was combined with the 2 intermittent dosing cohorts, a total of 33 unique patients were included in the overall population. The ORR was 24.2% (8/33) in the overall population, 25.0% (7/28) in advanced CTCL (Stage IIB and higher) and
- 36.4% (4/11) in SS patients.
- The response rate was higher in the continuous dosing cohort than the two intermittent dosing cohorts, and duration of response was longer.

- Although the small sample size of Protocol 005, Cohort 1, precluded a statistically meaningful analysis for all the efficacy endpoints, and the primary endpoint assessment tool was different than that in Protocol 001, the response rates achieved were similar to those later observed in Protocol 001.

- Overall, the results observed in Protocol 005 support those for Protocol 001 in both the primary and secondary assessments.

**Protocol 001**

- In Protocol 001, Vorinostat treatment resulted in a response rate of 29.5% (95% CI: 18.5% to 42.6%) in patients with CTCL (Stage IIB or higher) who had progressive, persistent, or recurrent disease on or following 2 systemic therapies, one of which contained bexarotene unless the patient was intolerant of or not a candidate for bexarotene. This met the pre-specified criteria for a positive trial as defined by an observed response rate of at least 20% with the lower boundary of the corresponding 95% confidence interval excluding 5%. The 5% lower boundary of the
- 95% CI was based on a conservative estimate of the maximum theoretical spontaneous response rate. The same estimate was adopted in the bexarotene registration trial. Not only does the lower boundary of the 95% confidence interval for the objective response in patients with Stage IIB and higher disease exceed 5%, in fact it approaches the pre-specified target response rate of 20%.
- Similar response rates were observed in all subgroups studied in Protocol 001: both early and advanced stage CTCL, Sezary syndrome patients, and patients with T3 tumor disease.
- The appreciable response rate in Sezary syndrome patients was particularly notable as this is a population with poor prognosis. The presence of Sezary cells generally correlate with a more advanced stage of CTCL. The majority (14 of 27 or 52% in the per-protocol analysis) of Sezary syndrome patients had a greater than 25% reduction in Sezary cell count. There were 9 SWAT responses (33.3%) in this subgroup. Thus some patients (5) *without* a cutaneous objective response did also show a reduction in Sezary cell count. Reductions in Sezary cell count support the activity of Vorinostat in patients with advanced disease.
- Patients with a tumor component on SWAT assessment demonstrate response. There is a $\geq$ 50% reduction in total tumor body surface area in 56.3% of patients with T3 tumor disease at baseline and $\geq$ 50% reduction in the sum of products for the greatest diameters of index lymph nodes by physical exam in 41.7% of patients with measurable lymph nodes at baseline. These reductions in tumor BSA, index lymph nodes, and physical exam were documented not only in patients who achieved an objective response but in those in whom the criteria for PR based on SWAT score was not met.
- The median response duration for the responders of Protocol 001 exceeds 4 months as the majority of patients who responded continued to respond at the time of data cut-off and fifteen (15) patients continued on study therapy at the time of the data cut-off date.

*(Updated and recalculated analysis using the FDA criteria showed this to be 168 days for all patients and 170 days for patients with stage IIB or higher disease).*

- Most responses were noted during the first 2 months of treatment, although some patients showed initial improvement but did not meet the criteria for response until beyond 4 months of evaluation.

Definition of response duration in the Vorinostat pivotal study differs from that in the other CTCL registration trials. The table below provides 3 randomly selected Protocol 001 responders to illustrate the differences in response duration.

**Table 33. A Comparison of Response Durations in CTCL Pivotal Trials (Applicant's Table)**

| | | Vorinostat Pivotal Study (Protocol 001) | Bexarotene Pivotal Study | Denileukin Diftitox Pivotal Study |
|---|---|---|---|---|
| **Definitions** | | The time interval from when criteria were first met for a response until the first date when an increase from nadir in skin score was greater than 50% of the difference between baseline score and nadir score. | The time interval from the start of therapy to the time of relapse | The interval from the first dose of study drug to the time of loss of maximum response. |
| **Duration of response estimated for 3 randomly selected patients from vorinostat Protocol 001 based on the 3 unique definitions** | AN1058 | 137+ days | 224 days | 141 days |
| | AN1029 | 117 days | 148 days | 85 days |
| | AN1030 | 266+ days | 323 days | 323 days |
| **Comparison of duration of response results** | | Not Applicable | Duration of response estimated by bexarotene pivotal study definition is longer than the vorinostat pivotal study. | Duration of response estimated by the denileukin diftitox pivotal study definition tend to be longer than the vorinostat pivotal study. However, some duration of response may be shorter than the vorinostat pivotal study definition. |

- Median time to progression in Protocol 001 had not been reached but is estimated to exceed 5 months. *(Updated and recalculated analysis using the FDA criteria showed this to be 202 days for all patients and 205 days for patients with stage IIB or higher disease).*
- In addition to the patients who met the criteria for an objective response by SWAT score reduction, a considerable proportion of patients experienced a reduction in SWAT scores of between 25% and 50% for at least one time point in the study.
- Among the patients with Stage IIB and higher disease, 12/61 (19.7%) patients experienced this level of reduction at one time, and a rate of 17/74 (23.0%) was seen in the overall population.
- Improvement in skin disease, as measured in terms of best response in SWAT score reduction of > 0%, is attained in 60/74 (81.1%) patients treated with Vorinostat.
- In addition to the 22 patients who had demonstrated an objective response, 10 patients with Stage IIB or higher and 1 patient with Stage IB had experienced a stable disease (SD) defined as absence of disease progression or response for 24 weeks.
- Therefore, 33 of 74 (44.6%) patients of all stages and 28 of 61 (45.9%) of patients Stage
- IIB or above demonstrated either objective response or 24 weeks of stable disease.

- In Protocol 001, response rates to Vorinostat were similar whether or not patients responded to bexarotene or other last systemic therapy. The proportion of patients who did not respond to bexarotene but responded to Vorinostat was similar to the proportion of patients who did respond to bexarotene and subsequently responded to Vorinostat. Presence or absence of response to the last systemic therapy preceding Vorinostat did not alter the proportion of patients who responded to Vorinostat. This suggests that the clinical activity of Vorinostat is not cross-resistant to bexarotene or to other available marketed and investigational therapies for CTCL.

- Although response rates with new treatment regimens such as bexarotene have been higher than those previously attained with older therapies, the need for additional therapies exists because the majority of CTCL patients remain refractory to or relapse on currently available treatments. Moreover, not all patients are candidates for bexarotene therapy due to its side effect profile. There was no discernable impact of response to last treatment or response to prior bexarotene treatment on subsequent efficacy of Vorinostat. Vorinostat responses were observed in 7/20 (35.0%) of patients who had failed to respond to bexarotene as their most recent prior systemic therapy and in 10/39 (25.6%) of patients who had failed prior bexarotene therapy at any time.

- The responses to Vorinostat were not restricted to any identifiable demographic subgroup or clinical characteristic.

- The symptom of pruritis significantly impacts the quality of life of CTCL patients. In Protocol 001, most patients presented at baseline with considerable pruritis as reflected by a mean baseline pruritis score of 6.
- Pruritis relief was rapid with nearly a 2 point decrease in mean pruritis score by Week 4 of therapy with Vorinostat. By Week 17, the mean pruritis score continued to decline to just above 3. Overall 23/72 (31.9%) patients had pruritis relief and 8/72 (11.1%) had complete resolution of their pruritis. Eighteen (18/59, 30.5%) patients with CTCL Stage IIB and higher had pruritis relief without an increase in the use of anti-pruritic medications. By using a conservative criterion (reduction of at least 3 points), 21/65 (32.3%) patients had improvement in the intensity of this symptom and 6/65 (9.2%) patients had complete resolution of pruritis.

- Twenty-seven (27/61, 44.3%) patients with CTCL Stage IIB and higher had evidence of clinical benefit as indicated by either a response defined by SWAT or pruritis relief or both.

- The clinical value of Vorinostat therapy can also be measured by the length of time that patients remained on therapy either with stable disease or with objective response. As of the data cut-off, the median time to progressive disease in Protocol 001 has not been reached and is estimated to exceed 5 months. Similarly, median response duration has not been reached and exceeds 4 months. The median and mean duration of exposure to study drug were 115.5 and 130.7 days, respectively. Thirty-eight (38/74, 51.4%) patients

remained on study therapy for more than 16 weeks and 20/74 (27.0%) patients remained on study therapy for more than 24 weeks.

## Conclusions

- In the two CTCL studies, Protocol 001 (pivotal study) and Protocol 005 (initial supportive study), a total of 107 patients with CTCL were treated. Eighty nine (89) of these patients had Stage IIB or higher disease, and 87 (87/89) were treated at Vorinostat 400 mg once daily, the dose and schedule proposed for clinical use in this application.
- The eligibility criteria required that the patients should have failed at least two systemic therapies (in Protocol 001) and one prior therapy (in Protocol 005). In this refractory population treated at 400 mg once daily, the response rates were 29.7% (22/74) and 30.8% (4/13) for pivotal and supportive studies, respectively. For patients with Stage IIB and higher CTCL, the response rates to Vorinostat 400 mg once daily were 29.5% (18/61) and 36.4% (4/11), respectively. For SS patients, the response rate was 33.3% (10/30 and 1/3) in both studies. Thus, even though required prior therapy and evaluation of response differed between the two studies, response rates were quite similar.
- The table below presents the objective response rate (the primary endpoint for both studies) in the 2 CTCL studies (APaT population) for patients treated with 400 mg once daily.

**Table 34. Objective Response Rate in Patients Treated with Vorinostat 400mg Once Daily in Protocol 001 and Protocol 005 (Cohort 1) (APaT Population) (Applicant's Table)**

| Population | Patients With Objective Response Rate[†] | | | |
|---|---|---|---|---|
| | Protocol 001 (APaT) N=74 | | Protocol 005 Cohort 1 (APaT) N=13 | |
| | % (n/*N*) | (95% CI) | % (n/*N*) | (95% CI) |
| All Patients | 29.7% (22/74) | (19.7, 41.5) | 30.8% (4/13) | (9.1, 61.4) |
| Stage IIB or Higher[‡] | 29.5% (18/61) | (18.5, 42.6) | 36.4% (4/11) | (10.9, 69.2) |
| Patients with Sezary syndrome | 33.3% (10/30) | (17.3, 52.8) | 33.3% (1/3) | (0.8, 90.6) |
| Patients with prior bexarotene as systemic therapy | 29.6% (21/71) | (19.3, 41.6) | 44.4% (4/9) | (13.7, 78.8) |

[†] Objective Response Rate: % of patients with complete response or partial response.
[‡] Stages IIB, III, IVA, and IVB.
CI=Confidence Interval.

[Ref. 5.3.5.2: P001, P005]

# 7 INTEGRATED REVIEW OF SAFETY

## 7.1 Methods and Findings

### Data Sources

- Data for safety review of this NDA comes from 12 (5 completed and 7 ongoing) clinical studies which examined Vorinostat in various cancer types and at various oral doses, both as a monotherapy or as a combination therapy.
- The data cut-off date for all the studies, except for the pivotal trial (Protocol 001), was 24-Oct-2005
- For the pivotal trial (Protocol 001) the data cut-off date was 25-Nov-2005

- An ongoing blinded study, Protocol 014, contributed only summarized serious adverse experience data and had a data cut-off date of 30-Nov-2005

### Patient Populations for Safety

Patients from the above 12 studies are categorized into 5 populations (based on disease types and therapies):

**1. Vorinostat Monotherapy – CTCL:** patients with CTCL treated with Vorinostat monotherapy.
**2. Vorinostat Monotherapy – CTCL Stage IIB and Higher:** patients with CTCL clinical Stage IIB and higher treated with Vorinostat monotherapy
**3. Vorinostat Monotherapy – Solid Tumors:** patients with solid tumors treated with Vorinostat monotherapy
**4. Vorinostat Monotherapy – Hematologic Malignancies:** patients with hematologic cancers treated with Vorinostat monotherapy
**5. Vorinostat Combination Therapies:** patients treated with Vorinostat in combination with other anti-cancer therapies.

***Reviewer Comments:***
*1. Patients in population 2 are a subset of the population 1, i.e. Vorinostat Monotherapy – CTCL population.*
*2. At least some AE experiences of populations 3, 4, and 5 can be expected to be different from those of populations 1 and 2 due to different clinical behaviors of the diseases and different past treatments for those. For example, bone marrow involvement and lower marrow reserve can be expected in hematological malignancies, and many patients with solid tumors might have been exposed to CDDP—this affects the observed hematology and renal toxicity profiles.*

The following table provides an overview of the populations and shows the total patients and the total patient exposures in each population.



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**Table 35. Patient Populations: Definitions, Protocols, Number of Patients, and Number of Patient Exposures (Applicant's Table)**

| Population Definition | Protocols | Total Patients Per Population | Total Patient Exposure Per Population |
|---|---|---|---|
| Vorinostat Monotherapy-CTCL | 001, 005 | 107 | 111[†] |
| Vorinostat Monotherapy-CTCL Stage IIB and Higher | 001, 005 – only Stage IIB and higher | 89[‡] | 93[‡] |
| Vorinostat Monotherapy – Solid Tumors | 002, 008 (Part I), 011, 006 (solid tumor patients) | 101 | 101 |
| Vorinostat Monotherapy – Hematologic Malignancies | 003, 004, 013, 006 (hematologic malignancy patients) | 87 | 87 |
| Vorinostat Combination Therapies | 012, 015, 016 | 10 | 10 |
| Total Patients | | 305 | 309 |

[†] In Protocol 005, 4 patients were exposed to 2 different dose cohorts.
[‡] These patients are a subset of the those in the Vorinostat Monotherapy – CTCL population.
Protocol 014, an on-going double-blind monotherapy study, provided summarized serious adverse experience data only.

[Ref. 5.3.5.2: P008] [Ref. 5.3.5.2: P001, P005] [Ref. 5.3.5.4: P002, P003V1, P004V1, P006, P011V1, P012V1, P013V1, P014V1, P015V1, P016V1, P029V1, P030V1]

- Clinical safety of Vorinostat is supported by data from **305 patients** and **309 patient exposures**. (Four additional patient exposures occurred in Protocol 005 in which patients enrolled in 1 cohort were permitted to enroll in a subsequent cohort at a later time point. As a result, 4 patients participated in 2 dosing cohorts each. Accordingly, the total number of patients in the Vorinostat Monotherapy – CTCL Population was 107 and the total number of patient exposures was 111. Similarly, the total number of patients in the Vorinostat Monotherapy – CTCL Stage IIB and Higher subset was 89 and the total number of patient exposures was 93).
- The first population analyzed (Vorinostat Monotherapy – CTCL) corresponds to the population used to establish the clinical efficacy of Vorinostat. The subset population (Vorinostat Monotherapy - CTCL Stage IIB and Higher) supports the primary endpoint defined in the pivotal clinical study (Protocol 001) and allows for analysis of the safety and tolerability of Vorinostat monotherapy in the target indication

- Distinct clinical differences (both the disease biology and the therapy) among the 5 patient populations warrant separate reviews of the safety data.
  - CTCL patients do not have the clinical characteristics of the heavily pre-treated patients with solid tumors
  - Patients with hematologic malignancies have underlying bone marrow involvement and differ from CTCL patients in their hematological adverse experiences
  - Patients treated with Vorinostat in combination with other chemotherapy agents, which are known to precipitate adverse experiences, require separate analysis.

All of the studies (completed and ongoing; Vorinostat monotherapy and combinations) included in this report are summarized in the tables below:

- Safety was assessed by the Investigators throughout the studies and up to a 30-day post-treatment visit.

- The total number of patients enrolled represents patients whose data was received by the data cutoff date.
- Additional Phase I studies of Vorinostat monotherapy have been initiated in (Protocol 029 and Protocol 030); however only preliminary data on 3 patients from Protocol 029 were available at the data cut-off date. Data from Protocol 029 and Protocol 030 are not included in the integrated analysis tables or listing tables.

***Reviewer Comments:***

*Please make a special note of protocol 016: Phase I Study of Vorinostat in Combination with Bexarotene in Patients with Advanced CTCL.*

## Table 36. Completed Vorinostat Monotherapy Studies with full Clinical Study Reports (Applicant's Table)

| Protocol | Phase | Study Title | Dose | Study Objectives | n |
|---|---|---|---|---|---|
| 001 | IIb | Phase IIb Study in Advanced Cutaneous T-Cell Lymphoma (CTCL) | 400 mg once daily | Primary:<br>To determine the response rate of oral Vorinostat in the treatment of skin disease in patients with advanced CTCL.<br>Secondary:<br>1) to assess response duration<br>2) to evaluate relief of pruritis<br>3) to assess time to progression<br>4) to assess time to objective response<br>5) to assess safety and tolerability of oral Vorinostat | 74 |
| 002 | | | 400 mg once daily | Primary:<br><br>Secondary:<br>1) to determine the safety and tolerability of oral Vorinostat administered continuously | 12 |
| 005 | IIa | Phase IIa Study in Cutaneous T-Cell Lymphomas and Peripheral T-Cell Lymphomas Unresponsive to Conventional Therapy | 1) 400 mg once daily<br>2) 300 mg twice daily 3 out of 7 days<br>3) 300 mg twice daily 14 out of 21 days | Primary:<br>To determine the response rate for oral Vorinostat administered to patients with Cutaneous T-cell Lymphomas or Peripheral T-Cell Lymphomas.<br>Secondary:<br>1) to determine safety and tolerability<br>2) to determine duration of response | 33† |
| 006 | I | Phase I Study in Advanced Solid Tumors and Hematological Malignancies | 1) 200, 400, or 600 mg once daily<br>2) 200, 300, or 400 mg every 12 hours<br>3) 300, or 400 mg every 12 hours daily<br>for 3 out of 7 days | Primary:<br>To define a safe daily oral regimen of Vorinostat for phase II studies.<br>Secondary:<br>1) To evaluate the pharmacokinetic profile of the oral formulation of Vorinostat<br>2) To determine the oral bioavailability<br>3) To document any anti-tumor effects.<br>Additional: to assess the biological effects of Vorinostat on normal tissues and tumor cells and correlate outcomes of response with histone acetylation levels. | 73 |
| 008 | I | Phase I Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Vorinostat in Patients With Advanced Cancer | Part 1: A single 400 mg dose of Vorinostat administered on **Day 1** in the fasted state and on **Day 5** following a standard high fat meal with pharmacokinetic sampling for 48 hours post-dose. Continuous dosing with 400 mg once daily on **Days 7 to 28.** Dosing on Day 28 followed a standard high fat meal with pharmacokinetic sampling for 24 hours post-dose.<br><br>Part 2: **Continuous dosing** with 300 mg twice daily Vorinostat for 14 out of 21 days. The a.m. dose on **Days 1 and 14** administered following a standard high fat breakfast with pharmacokinetic sampling for 12 hours post-dose. | Primary:<br>1) to evaluate the safety and tolerability<br>2) to obtain serum pharmacokinetics after single and multiple-dose administration<br>3) to obtain single-dose serum pharmacokinetics in the fed versus fasted state<br>Secondary:<br>To evaluate the urinary excretion of Vorinostat.<br>Exploratory: to evaluate Pharmacodynamic biomarkers. | 23 |

## Table 37. Ongoing Open-Label Monotherapy Studies of Vorinostat (Applicant's Table)

| Protocol | Phase | Study Title | Dose | Study Objectives | n |
|---|---|---|---|---|---|
| 003 | 1 | Phase I Study in Advanced Leukemias or Myelodysplastic Syndromes | **Starting dose** at 100 mg three times daily, then escalation in the increments of 50 mg three times daily or 100 mg twice daily for 14 days out of 21 days<br>**Second schedule** tested 300 mg twice daily for 14 out of 21 days deescalated to 200 mg twice daily. | Primary:<br>To determine Maximum Tolerated Dose (MTD) of Vorinostat administered every 8 hours or every 12 hours for 14 out of 21 days.<br>Secondary: | 41 |
| 004 | 1 | Phase I/II Study in Advanced Multiple Myeloma | **Original Dosing Regimen:**<br>Starting dose at 200 mg administered every 12 hours for 5 out of 7 days. Escalation in the increments of 50 mg every 12 hours (total daily dose of 100 mg).<br>**Amended Dosing Regimen:**<br>Starting dose at 200 mg administered every 12 hours for 14 out of 21 days. Escalation in the increments of 100 mg every 12 hours (total daily dose of 200 mg). | Old Primary for Phase I:<br>To determine the MTD of Vorinostat administered every 12 hours for 5 out of 7 days during the first cycle (i.e., first 4 weeks).<br>New Primary for Phase I:<br>To determine the MTD of Vorinostat administered every 12 hours for 14 out of 21 days during the first 2 cycles (i.e., first 6 weeks).<br>Primary for Phase II:<br>To assess the safety and overall response rate to Vorinostat.<br>Secondary: | 13 |
| 011 | II | Phase II Study in Patients with Relapsed or Refractory Breast, Colorectal, and Non-Small Cell Lung Cancer | **Original Dosing Regimen:**<br>400 mg twice daily for 14 out of 21 days.<br>**Amended Dosing Regimen:**<br>300 mg twice daily for 14 out of 21 days.<br>**Amended Dosing Regimen:**<br>200 mg twice daily for 14 out of 21 days. | Primary:<br>3) To evaluate the safety and tolerability.<br>Exploratory: | 16 |
| 013 | II | Phase II Study in Relapsed Diffuse Large B-Cell Lymphoma | **Original Dosing Regimen:**<br>300 mg twice daily x 14 days every 21 days.<br>**Amended Dosing Regimen:**<br>300 mg twice daily x 3 days every 7 days. | 2) To assess the safety or oral Vorinostat in this patient population. | 10 |

## Table 38. Ongoing Open-Label Combination Therapy Studies (Applicant's Table)

| Protocol | Phase | Study Title | Dose | Study Objectives | n |
|---|---|---|---|---|---|
| 012 | 1 | A Phase 1 Clinical Trial of Oral Suberoylanilide Hydroxamic Acid in Combination with Pemetrexed and Cisplatin in Patients with Advanced Cancer | **Initial Dose Level:** Vorinostat 200 mg twice daily for 14 out of 21 days + pemetrexed and cisplatin **Amended Design:** Cohort A (Vorinostat twice daily + pemetrexed and cisplatin): Dose Level 1 - 300 mg twice daily for 3 out of 7 days for first week, then 2 weeks off Dose Level 2 - 300 mg twice daily for 3 out of 7 days for first 2 weeks, then 1 week off Dose Level 3 - 300 mg twice daily for 3 out of 7 days repeated weekly for 3 weeks Cohort B (Vorinostat once daily + pemetrexed and cisplatin): Dose Level 1 - 400 mg daily for 7 days Dose Level 2 - 500 mg daily for 7 days Dose Level 3 - 600 mg daily for 7 days | Primary: 1) To determine the (MTD) of Vorinostat when administered in repeated 21-day cycles in combination with standard doses of pemetrexed and cisplatin in patients with advanced solid tumors 2) To determine the MTD of Vorinostat when administered in repeated 21-day cycles in combination with standard doses of pemetrexed in patients with advanced solid tumors 3) To assess at the MTD the pharmacokinetics of Vorinostat, pemetrexed, and cisplatin when administered in combination. Secondary: To assess the safety and tolerability of these combination regimens. | 6 |
| 015 | 1 | Phase 1 Clinical Trial of Oral Suberoylanilide Hydroxamic Acid (L-001079038) in Combination With Bortezomib in Patients With Advanced Multiple Myeloma | Combination of Vorinostat + increasing doses of bortezomib Dose Level 1 – 200 mg twice daily for 14 days Dose Level 2 – 200 mg twice daily for 14 out of 21 days Dose Level 3 – 300 mg twice daily for 14 out of 21 days Dose Level 4 – 300 mg twice daily for 14 out of 21 days Dose Level 5 – 300 mg twice daily for 14 out of 21 days. | Primary: To determine the MTD for the combination of oral Vorinostat and standard doses of bortezomib in patients with advanced multiple myeloma. Secondary: To assess the safety and tolerability of the combination regimen of Vorinostat and bortezomib. Exploratory: 1) To assess the pharmacokinetics of Vorinostat alone and when administered in combination with bortezomib | 1 |
| **016** | 1 | **Phase I Study in Combination with Bexarotene in Patients with Advanced CTCL** | Starting dose at 200 mg once daily Vorinostat + 150 mg/m2 bexarotene once daily then escalating to 400 mg once daily Vorinostat in 100 mg increments followed by escalating to 300 mg/m2 bexarotene in 75 mg increments. No intra-patient dose escalation. | Primary: To determine MTD of Vorinostat administered once daily x 28 days in repeated cycles in combination with escalating doses of up to 300 mg/m2 bexarotene. Secondary: (1) To assess the safety and tolerability this regimen | 6 |

## Table 39. Ongoing Blinded Monotherapy Studies (Applicant's Table)

| Protocol | Phase | Study Title | Dose | Study Objectives | n |
|---|---|---|---|---|---|
| 014 | III | A Phase III, Randomized, Double-Blind Placebo-controlled Trial of Oral Suberoylanilide Hydroxamic Acid in Patients With Advanced Malignant Pleural Mesothelioma Previously Treated With Systemic Chemotherapy | Original Dose:<br>300 mg twice daily for 14 out of 21 days.<br>Amended Dose:<br>300 mg twice daily for 3 out of 7 days. | Primary:<br>[redacted]<br>patients with advanced malignant pleural mesothelioma who have failed prior chemotherapy that had included pemetrexed in combination with either cisplatin or carboplatin and to determine the overall safety and toxicity of Vorinostat in this population. | 10 |

## Table 40. Ongoing Monotherapy Studies ) with Interim Safety Reports (Applicant's Table)

| Protocol | Phase | Study Title | Dose | Study Objectives | n |
|---|---|---|---|---|---|
| 029 | I | A Phase I Clinical Trial of Vorinostat (MK-0683) in Patients With Solid Tumors | Vorinostat will be administered orally once daily on Days 1 (fasted), 3 (fed) and 19 (fed) as well as twice daily on Days 5-18. The dose escalation on each patient is prohibited during this period. Cohorts are as follows:<br>1 – 100 mg twice daily<br>2 – 200 mg twice daily<br>3 – 300 mg twice daily<br>4 – 400 mg twice daily<br>In addition, the following dose level will be conducted in concurrence with dose level 3 above:<br>3 – 400 mg once daily | Primary:<br>1) To determine the MTD, or the maximum acceptable dose (MAD) and evaluate the dose limiting toxicity (DLT) of Vorinostat in patients with solid tumors<br>2) To evaluate the overall safety profile of Vorinostat in the first cycle<br>Secondary:<br>1) To obtain pharmacokinetics of Vorinostat after 14 days administration with once daily or twice daily regimen<br>2) To obtain pharmacokinetics of Vorinostat in the fasted and fed state<br>3) To evaluate the overall safety profile of Vorinostat in subsequent cycles | 15 |
| 030 | I | A Phase I Clinical Trial of Vorinostat | Vorinostat will be administered orally once daily on Days 1 and 17 as well as twice daily on Days 3-16. The dose escalation on each patient is prohibited during this period.<br>Cohorts are as follows:<br>1 – 100 mg twice daily<br>2 – 200 mg twice daily<br>3 – 300 mg twice daily<br>4 – 400 mg twice daily | Primary:<br>1) To determine the MTD, or the MAD, and evaluate the DLT of Vorinostat in the first cycle;<br>2) To evaluate the overall safety profile of Vorinostat in the first cycle.<br>Secondary:<br>1) To obtain pharmacokinetics of Vorinostat<br>2) To evaluate the overall safety profile of Vorinostat in subsequent cycles | 12 |

**Dosing Schedules across Studies:**

- Continuous dosing:
  - Once daily (QD)
  - Twice daily (BID)
- Discontinuous dosing (few days of dosing in the whole treatment cycle):
  - Twice daily
  - Three times daily (TID)

- The lowest daily dose of Vorinostat:
  - 200 mg (once daily)
- The highest total daily doses:
  - 600 mg (once daily)
  - 800 mg (400 mg twice daily)
  - 900 mg (300 mg three times daily)

**Schedules of Vorinostat administration with tolerable toxicities:**

Patients included in the Summary of Clinical Safety were enrolled on several Phase I trials. These trials used several dosing regimens to control dose limiting toxicities and to improve efficacy. Thus the safety analysis is based on the results from several studies.

- In Protocols 003, 004, 005, 011, 012, 013, 014 and 015, a twice daily Vorinostat administration for **14 consecutive days followed by a 7-day rest period in a 21-day cycle** was tested either alone or in combination with other chemotherapy agents
  - In protocols 003 and 004, a **200 mg twice daily dose** on this schedule was tolerable
- In Protocol 006, a **200 mg twice daily** dose was tolerable on a **continuous basis**
- In Protocols 011 and 013, dose levels of **400 and 300 mg twice daily for 14 consecutive days** followed by a 7 day rest **exceeded the MTD** due to thrombocytopenia.

**Summary of DLT and MTD experience in Phase 1 studies**

**Patients with solid tumors**

- When solid tumor patients were given Vorinostat monotherapy at 400 mg twice daily for 14 consecutive days followed by a 7-day rest, all 6 initial patients required treatment interruption for either Grade 3-4 thrombocytopenia or gastrointestinal symptoms (nausea, vomiting, anorexia, or dehydration)
- At the next dose reduction of 300 mg twice daily for 14 consecutive days followed by a 7-day rest, 3 of the 6 patients experienced dose limiting adverse experiences of either Grade 4 thrombocytopenia or asthenia and weight loss.
- Therefore, this study enrolled patients only at 200 mg twice daily on this schedule.

**Patients with Hematological Malignancies**

When patients with Hematologic Malignancies were given Vorinostat Monotherapy, similar findings were noted in Protocol 013

- Two (2) of 7 patients experienced dose limiting thrombocytopenia in the 300 mg twice daily dose on the 14 consecutive day followed by a 7-day rest schedule

**These studies demonstrated that thrombocytopenia, gastrointestinal symptoms (nausea, vomiting, and anorexia), dehydration, asthenia, and weight loss were the commonly observed dose limiting toxicities (at 600 to 800 daily doses given for 14 days).**

**MTD**

The maximum tolerated dose (MTD) was determined based on the dose limiting toxicities observed in Protocol 006 (Phase I Study in Advanced Solid Tumors and Hematological Malignancies; Cohorts: 1. 200, 400, or 600 mg once daily, 2. 200, 300, or 400 mg every 12 hours, 3. 300, or 400 mg every 12 hours daily for 3 out of 7 days):

- The maximum tolerated once daily dose was 400 mg
  - The 600 mg once daily dose given continuously was not tolerated
- The maximum tolerated twice daily dose is 200 mg.
  - The 300 mg twice daily dose given continuously was not tolerated.
- The maximum tolerated three times per day dose is 200 mg for 14 consecutive days followed by 7 days of rest.
  - The 300 mg dose given three times daily on this schedule was not tolerated.
- The maximum tolerated twice daily dose for 3 consecutive days per week is 300 mg.
  - The 400 mg twice daily dose on this schedule was not tolerated.

**CTCL patients at MTD**

- When CTCL patients were given Vorinostat Monotherapy at 400 mg once daily dose, 4 out of 86 patients (4.7%) experienced Grade 3 or Grade 4 thrombocytopenia

**"Treatment Categories" of Vorinostat dosing based on the doses administered** are shown below. These categories are according to Protocol 006. There are 5 categories of doses:

- 400 mg once daily (the clinically recommended dose and schedule)
- 300 mg twice daily for 3 consecutive days per week
- 200 mg twice daily
- Doses that exceed the maximum tolerated dose (MTD)
- Doses below the MTD

**Descriptions of Safety Analysis**

A safety summary is presented for each disease based population. For each of these 5 populations, the following analyses are presented:

- Demographic characteristics
- Age, race, gender, and secondary diagnoses
- Extent of exposure and duration of therapy
- Disposition of the patients

Each section of the Clinical Summary of Safety for Vorinostat is divided into:

- General safety overview
- Review of clinical and laboratory safety data for each of the 5 populations
  - Clinical and laboratory adverse experiences (AEs)
  - Serious adverse experiences (SAEs)
  - Discontinuations due to AEs (separately for all occurrences and for drug-related adverse experiences)

- Parameters of special interest:
  - Gastrointestinal AEs
  - Hematologic AEs
  - Constitutional AEs

**Analyses:**

- Subgroup analyses of clinical and laboratory AEs based on demographic categories (age, race, gender)
- Detailed listings of serious clinical or laboratory AEs and discontinuations from therapy due to adverse experiences
- Frequencies of clinical adverse experiences by Common Terminology Criteria for Adverse Experience (CTCAE) Grade 3 or higher
- Adverse experiences resulting in death
- Adverse experiences resulting in dose modification and discontinuation

- A listing of all laboratory abnormalities is presented (also those deemed clinically significant and reported by the investigator as laboratory AEs)
- All laboratory data were analyzed using CTCAE version 3.0 for shifts in CTCAE grade from baseline values

- Cardiac conduction system adverse experiences have been observed with the clinical use of other histone deacetylase (HDAC) inhibitors; therefore, separate listings of adverse experiences reported on electrocardiograms (ECGs) are provided.
  - A table of QT measurements is provided for clinical studies of Vorinostat where these data were obtained.

**Overall Extent of Exposure**

This section provides the extent of exposure to Vorinostat for the five patient populations and "treatment categories" as defined above

- The extent of exposure is presented at ANY DOSE and at the TOTAL DAILY DOSE by weeks
  - **The number of weeks at ANY DOSE** represents *the exposure duration of an individual patient regardless of* **the initial dose** (Although some patients may have taken 2 or more different doses, they are **counted once** in the ANY DOSE row)
    - ***Reviewer Comments:*** *Number of weeks an individual patient received Vorinostat (at any dose).*
  - **The number of weeks at any TOTAL DAILY DOSE** represents *the exposure duration at* **the initial dose** *and the exposure duration at* **modified doses** (if applicable)
    - Patients who took 2 or more different daily doses are **counted more than once** (in each different daily dose category)
    - Dose modification may have occurred as a result of
      - A protocol amendment
      - An adverse experience
      - Dose escalation

**Vorinostat Monotherapy – CTCL**

The overall extent of exposure for patients in this *population* is summarized in the table below. Vorinostat Monotherapy CTCL patients from Protocol 001 and Protocol 005 are included regardless of initial starting dose of Vorinostat; Protocol 001 used a 28-day treatment cycle and Protocol 005 used a 21-day treatment cycle.

- Ninety-six (96) of 111 (86.5%) received a 400 mg total daily dose (initial or modified)
- The mean number of days on drug was highest in the 400 mg total daily dose at 109 days, with a range of 2 to 365 days. *(This is the recommended dose for the label).*
- At any dose, the mean number of days on Vorinostat was 110 days with range of 2 to 365 days

**Table 41. Number of Patients on Study Drug by Dose and Actual Duration of Treatment (Vorinostat Monotherapy – CTCL – Overall) (Applicant's Table)**

| MK-0683 Total Daily Dose | <2 wks | >2 wks to <4 wks | >4 wks to <6 wks | >6 wks to <12 wks | >12 wks to ≤16 wks | >16 wks to ≤20 wks | >20 wks to ≤24 wks | >24 weeks | Total | Range of Days on Drug | Mean Number of Days on Drug |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ANY DOSE | 8 | 11 | 9 | 26 | 12 | 10 | 10 | 25 | 111 | 2 to 365 | 110.4 |
| 300 mg | 1 | 4 | 0 | 0 | 1 | 1 | 1 | 1 | 9 | 13 to 291 | 84.4 |
| 350 mg | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 2 | 31 to 165 | 98.0 |
| 400 mg | 5 | 11 | 7 | 24 | 11 | 10 | 8 | 20 | 96 | 2 to 365 | 109.6 |
| 500 mg | 2 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 3 | 5 to 154 | 57.0 |
| 550 mg | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 19 to 19 | 19.0 |
| 600 mg | 16 | 3 | 2 | 5 | 0 | 0 | 0 | 0 | 26 | 3 to 57 | 22.4 |
| Although some patients may have taken two or more different dosages, they have been counted only one time each, on the 'ANY DOSE' row. | | | | | | | | | | | |

[Ref. 5.3.5.2: P001, P005]

**Cohort 1 of Protocol 005 (initial dose of Vorinostat of 400 mg once daily continuously)**

- 11 patients in Cohort 1 received 400 mg once daily as the initial prescribed dose
- Initial Vorinostat dose was based upon body surface area (BSA) (n = 3 patients). Two (2) patients received a 500 mg total daily dose of Vorinostat for < 2 weeks, and one patient 550 mg once daily for ≤ 4 weeks
  - 2 patients – dose modified to 400 mg once daily per protocol amendment
  - 1 patient – dose modified to 350 mg once daily

**Cohort given Vorinostat at a dose of 400 mg once daily (initial or modified dose)**

The table below summarizes the extent of exposure for the patients with the initial starting dose of 400 mg once daily therapy (in Protocol 001 and 005) and those patients (in Protocol 005) who received 400 mg total daily after a dose modification.

- Eighty-six (86) patients were exposed to 400 mg once daily as the initial prescribed dose
- The mean number of days on drug was highest in the 400 mg daily dose: 116 days with a range of 2 to 365 days.
- At any dose, the mean number of days on Vorinostat was 126 days with a range of 2 to 365 days

**Table 42. Number of Patients on Study Drug by Dose and Actual Duration of Treatment (Vorinostat Monotherapy – CTCL – 400 mg once daily 7d/wk) (Applicant's Table)**

| MK-0683 Total Daily Dose | <=2 wks | >2 wks to <=4 wks | >4 wks to <=6 wks | >6 wks to <=12 wks | >12 wks to <=16 wks | >16 wks to <=20 wks | >20 wks to <=24 wks | >24 weeks | Total | Range of Days on Drug | Mean Number of Days on Drug |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ANY DOSE | 2 | 5 | 5 | 22 | 11 | 10 | 9 | 23 | 87 | 2 to 365 | 126.4 |
| 300 mg | 1 | 4 | 0 | 0 | 1 | 1 | 1 | 1 | 9 | 13 to 291 | 84.4 |
| 350 mg | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 2 | 31 to 165 | 98.0 |
| 400 mg | 2 | 8 | 7 | 23 | 9 | 10 | 7 | 20 | 86 | 2 to 365 | 116.2 |
| 500 mg | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 5 to 12 | 8.5 |
| 550 mg | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 19 to 19 | 19.0 |
| 600 mg | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 3 to 6 | 4.5 |
| Although some patients may have taken two or more different dosages, they have been counted only one time each, on the 'ANY DOSE' row. | | | | | | | | | | | |

[Ref. 5.3.5.2: P001, P005]

**Cohort given initial Vorinostat dose of 300 mg twice daily for 3 days per week**

- This group is small as only the initial patients in Cohort 2 of Protocol 005 received this dose: patients received 300 mg twice daily for 3 consecutive days followed by a 4-day rest period. Dose could be increased to 300 mg twice daily for 5 consecutive days followed by a 2-day rest period if no partial response was received after 1 cycle or 21 days.
- At any dose, the mean number of days on Vorinostat was 36.7 days with a range of 3 to 188 days.
- The time on treatment was likely influenced by the efficacy as well as tolerability. No patients in this treatment category received a 400 mg daily dose. One (1) patient had the dose modified to 250 mg twice daily.

**Table 43. Number of Patients on Study Drug by Dose and Actual Duration of Treatment (Vorinostat Monotherapy – CTCL – Allocated to 300 mg twice daily x 3d/wk) (Applicant's Table)**

| MK-0683 Total Daily Dose | <=2 wks | >2 wks to <=4 wks | >4 wks to <=6 wks | >6 wks to <=12 wks | >12 wks to <=16 wks | >16 wks to <=20 wks | >20 wks to <=24 wks | >24 weeks | Total | Range of Days on Drug | Mean Number of Days on Drug |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ANY DOSE | 5 | 3 | 1 | 2 | 0 | 0 | 0 | 1 | 12 | 3 to 188 | 36.7 |
| 300 mg | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | . |
| 350 mg | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | . |
| 400 mg | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | . |
| 500 mg | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 154 to 154 | 154.0 |
| 550 mg | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | . |
| 600 mg | 5 | 3 | 2 | 2 | 0 | 0 | 0 | 0 | 12 | 3 to 57 | 23.8 |
| Although some patients may have taken two or more different dosages, they have been counted only one time each, on the 'ANY DOSE' row. | | | | | | | | | | | |

[Ref. 5.3.5.2: P005]

**Cohort given Vorinostat dose of 300 mg twice daily for 14 days followed by a 7 day rest period**

This is a small group. Patients who did not obtain at least a partial response after 3 weeks had their dose modified to 200 mg twice daily without a rest period.

- At any dose, the mean number of days on Vorinostat was 67.8 days with a range of 14 to 214 days.
- Ten (10) of 12 patients (83.3%) were exposed to 400 mg daily. These 10 patients received 200 mg twice daily per protocol Amendment 4.
- The mean number of days on study was highest in the 400 mg daily dose at 52.6 days.

**Table 44. Number of Patients on Study Drug by Dose and Actual Duration of Treatment (Vorinostat Monotherapy – CTCL – Allocated to 300 mg twice daily x 14d/3wk) (Applicant's Table)**

| MK-0683 Total Daily Dose | <=2 wks | >2 wks to <=4 wks | >4 wks to <=6 wks | >6 wks to <=12 wks | >12 wks to <=16 wks | >16 wks to <=20 wks | >20 wks to <=24 wks | >24 weeks | Total | Range of Days on Drug | Mean Number of Days on Drug |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ANY DOSE | 1 | 3 | 3 | 2 | 1 | 0 | 1 | 1 | 12 | 14 to 214 | 67.8 |
| 300 mg | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | . |
| 350 mg | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | . |
| 400 mg | 3 | 3 | 0 | 1 | 2 | 0 | 1 | 0 | 10 | 12 to 158 | 52.6 |
| 500 mg | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | . |
| 550 mg | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | . |
| 600 mg | 9 | 0 | 0 | 3 | 0 | 0 | 0 | 0 | 12 | 6 to 57 | 23.9 |

Although some patients may have taken two or more different dosages, they have been counted only one time each, on the 'ANY DOSE' row.
[Ref. 5.3.5.2: P005]

**Cohort with exposure to doses above MTD**

The table below summarizes the extent of exposure to Vorinostat at doses above the MTD. Doses above the MTD consist of twice daily dosing for 14 days followed by 7 days off the study drug.
This group contains only the patients from Cohort 3 of Protocol 005. Most of the patients received 1 cycle of induction and then switched to the twice daily dosing. Two patients received more than 1 course on the induction regimen because of initial evidence of response.

**Table 45. Number of Patients on Study Drug by Dose and Actual Duration of Treatment (Vorinostat Monotherapy – CTCL – Doses above MTD) (Applicant's Table)**

| MK-0683 Total Daily Dose | <=2 wks | >2 wks to <=4 wks | >4 wks to <=6 wks | >6 wks to <=12 wks | >12 wks to <=16 wks | >16 wks to <=20 wks | >20 wks to <=24 wks | >24 weeks | Total | Range of Days on Drug | Mean Number Days on Drug |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ANY DOSE | 9 | 0 | 0 | 3 | 0 | 0 | 0 | 0 | 12 | 6 to 57 | 23.9 |
| 300 mg | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | . |
| 350 mg | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | . |
| 400 mg | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | . |
| 500 mg | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | . |
| 550 mg | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | . |
| 600 mg | 9 | 0 | 0 | 3 | 0 | 0 | 0 | 0 | 12 | 6 to 57 | 23.9 |

Although some patients may have taken two or more different dosages, they have been counted only one time each, on the 'ANY DOSE' row.
[Ref. 5.3.5.2: P005]

**Cohort exposed to Vorinostat at doses below MTD**

The table shows the dose levels that patients received as a result of a dose modification.

- In Protocol 001, nine (9) patients had their dose modified to 300 mg once daily for 7 consecutive days in a 28-day cycle, and 3 of these had their dose further reduced to 300 mg once daily for 5 days followed by 2 days off study drug.
- In Protocol 005, five (5) patients had their dose modified to 300 mg twice daily for 5 days followed by 2 days off study drug per protocol Amendment 2. Two (2) of the 5 returned to 300 mg twice for 3 days due adverse experiences. Two patients from Cohort 1 that initially began dosing at 400 mg once daily were dose reduced to 300 mg twice daily 3 days per week.
- The mean number of days on drug was highest in the 350 mg daily dose at 98 days with a range of 31 to 165 days.

**Table 46. Number of Patients on Study Drug by Dose and Actual Duration of Treatment Vorinostat Monotherapy – CTCL – Doses below MTD (Applicant's Table)**

| MK-0683 Total Daily Dose | <=2 wks | >2 wks to <=4 wks | >4 wks to <=6 wks | >6 wks to <=12 wks | >12 wks to <=16 wks | >16 wks to <=20 wks | >20 wks to <=24 wks | >24 weeks | Total | Range of Days on Drug | Mean Number Days on Drug |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ANY DOSE | 2 | 9 | 2 | 1 | 1 | 1 | 2 | 2 | 20 | 5 to 291 | 66.0 |
| 300 mg | 1 | 4 | 0 | 0 | 1 | 1 | 1 | 1 | 9 | 13 to 291 | 84.4 |
| 350 mg | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 2 | 31 to 165 | 98.0 |
| 400 mg | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 2 | 16 to 40 | 28.0 |
| 500 mg | 2 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 3 | 5 to 154 | 57.0 |
| 550 mg | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 19 to 19 | 19.0 |
| 600 mg | 1 | 3 | 0 | 1 | 0 | 0 | 0 | 0 | 5 | 11 to 45 | 23.4 |
| Although some patients may have taken two or more different dosages, they have been counted only one time each, on the 'ANY DOSE' row. | | | | | | | | | | | |

[Ref. 5.3.5.2: P001, P005]

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**Vorinostat Monotherapy – CTCL Stage IIB and Higher**

The overall extent of exposure to Vorinostat in patients with CTCL Stage IIB and higher is summarized in the table below. **As this population is a subset of the Vorinostat Monotherapy – CTCL Population, the duration of exposure is similar.**

- Seventy-nine (79) of 93 patients (84.9%) were exposed 400 mg total daily.
- The mean number of days on drug was highest in this dose at 106.4 days with a range 2 to 365 days.
- At any dose, the mean number of days on treatment was 107.9 with a range of 2 to 365 days.

**Table 47. Number of Patients on Study Drug by Dose and Actual Duration of Treatment Vorinostat Monotherapy – CTCL Stage IIB and Higher – Overall (Applicant's Table)**

| MK-0683 Total Daily Dose | ≤2 wks | >2 wks to ≤4 wks | >4 wks to ≤6 wks | >6 wks to ≤12 wks | >12 wks to ≤16 wks | >16 wks to ≤20 wks | >20 wks to ≤24 wks | >24 weeks | Total | Range of Days on Drug | Mean Number of Days on Drug |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ANY DOSE | 8 | 10 | 9 | 23 | 7 | 6 | 8 | 22 | 93 | 2 to 365 | 107.9 |
| 300 mg | 1 | 4 | 0 | 0 | 1 | 1 | 1 | 1 | 9 | 13 to 291 | 84.4 |
| 350 mg | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 2 | 31 to 165 | 98.0 |
| 400 mg | 5 | 11 | 7 | 21 | 6 | 6 | 5 | 18 | 79 | 2 to 365 | 106.4 |
| 500 mg | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 2 | 12 to 154 | 83.0 |
| 550 mg | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 19 to 19 | 19.0 |
| 600 mg | 15 | 2 | 2 | 4 | 0 | 0 | 0 | 0 | 23 | 3 to 57 | 21.1 |
| Although some patients may have taken two or more different dosages, they have been counted only one time each, on the 'ANY DOSE' row. | | | | | | | | | | | |

[Ref. 5.3.5.2: P001, P005]

**Cohort of CTCL Stage IIB or higher that received 400 mg daily dose (initial and modified)**

The extent of exposure to Vorinostat in patients with CTCL Stage IIB or higher who received a 400 mg total daily as the initial prescribed dose (Protocol 001 and one of 3 cohorts of 005) and the patients from Protocol 005 who received 400 mg total daily after a dose modification is summarized.

- The mean number of days on drug was highest at 400 mg daily dose at 114.1 days (range of 2 to 365 days)
- This table also reflects the dose modifications in this subset population. At any dose, the mean number of days on drug was 126.3 days with maximum exposure of 365 days (consistent with Vorinostat Monotherapy CTCL population)

**Table 48. Number of Patients on Study Drug by Dose and Actual Duration of Treatment (Vorinostat Monotherapy – CTCL Stage IIB and Higher) (Applicant's Table)**

| MK-0683 Total Daily Dose | ≤2 wks | >2 wks to ≤4 wks | >4 wks to ≤6 wks | >6 wks to ≤12 wks | >12 wks to ≤16 wks | >16 wks to ≤20 wks | >20 wks to ≤24 wks | >24 weeks | Total | Range of Days on Drug | Mean Number of Days on Drug |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ANY DOSE | 2 | 5 | 5 | 20 | 6 | 6 | 7 | 21 | 72 | 2 to 365 | 126.3 |
| 300 mg | 1 | 4 | 0 | 0 | 1 | 1 | 1 | 1 | 9 | 13 to 291 | 84.4 |
| 350 mg | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 2 | 31 to 165 | 98.0 |
| 400 mg | 2 | 8 | 7 | 21 | 4 | 6 | 5 | 18 | 71 | 2 to 365 | 114.1 |
| 500 mg | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 12 to 12 | 12.0 |
| 550 mg | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 19 to 19 | 19.0 |
| 600 mg | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 3 to 6 | 4.5 |
| Although some patients may have taken two or more different dosages, they have been counted only one time each, on the 'ANY DOSE' row. | | | | | | | | | | | |

[Ref. 5.3.5.2: P001, P005]

**Cohort with exposure to Vorinostat at 300 mg twice daily for 3 days out of 7 days**

- At any dose, the mean number of days on drug was 37.6 days (range of 3 to 188 days).
- No patient received a 400 mg daily dose.
- One patient was dose modified to 250 mg twice daily. The mean number of days on drug was highest in the 500 mg daily dose at 154 days.

**Table 49. Number of Patients on Study Drug by Dose and Actual Duration of Treatment Vorinostat Monotherapy – CTCL Stage IIB and Higher – 300 twice daily x 3d/wk (Applicant's Table)**

| MK-0683 Total Daily Dose | ≤2 wks | >2 wks to ≤4 wks | >4 wks to ≤6 wks | >6 wks to ≤12 wks | >12 wks to ≤16 wks | >16 wks to ≤20 wks | >20 wks to ≤24 wks | >24 weeks | Total | Range of Days on Drug | Mean Number of Days on Drug |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ANY DOSE | 3 | 2 | 1 | 2 | 0 | 0 | 0 | 1 | 11 | 3 to 188 | 37.6 |
| 300 mg | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | . |
| 350 mg | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | . |
| 400 mg | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | . |
| 500 mg | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 154 to 154 | 154.0 |
| 550 mg | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | . |
| 600 mg | 3 | 2 | 2 | 2 | 0 | 0 | 0 | 0 | 11 | 3 to 57 | 23.6 |

Although some patients may have taken two or more different dosages, they have been counted only one time each, on the 'ANY DOSE' row.
[Ref. 5.3.5.2: P001, P005]

**Cohort of patients that initially received Vorinostat at a dose of 300 twice daily for 14 consecutive days in a 21-day cycle**

- This group contains only the patients from Cohort 3 of Protocol 005; they received 300 mg twice daily for 14 consecutive days followed by a 7 day rest period. Patients who did not obtain at least a partial response after 3 weeks received 200 mg twice daily without a rest period. Most of the patients received one cycle of induction and then switched to the twice daily continuous dosing.
- Two patients received more than one course on the induction regimen because of initial evidence of response.

**Table 50. Number of Patients on Study Drug by Dose and Actual Duration of Treatment Vorinostat Monotherapy – CTCL Stage IIB and Higher – Allocated to 300 BID x 14d/3wk (Applicant's Table)**

| MK-0683 Total Daily Dose | <=2 wks | >2 wks to <=4 wks | >4 wks to <=6 wks | >6 wks to <=12 wks | >12 wks to <=16 wks | >16 wks to <=20 wks | >20 wks to <=24 wks | >24 weeks | Total | Range of Days on Drug | Mean Number of Days on Drug |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ANY DOSE | 1 | 3 | 3 | 1 | 1 | 0 | 1 | 0 | 10 | 14 to 166 | 52.4 |
| 300 mg | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | . |
| 350 mg | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | . |
| 400 mg | 3 | 3 | 0 | 0 | 2 | 0 | 0 | 0 | 8 | 12 to 110 | 38.4 |
| 500 mg | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | . |
| 550 mg | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | . |
| 600 mg | 8 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 10 | 6 to 57 | 21.7 |

Although some patients may have taken two or more different dosages, they have been counted only one time each, on the 'ANY DOSE' row.
[Ref. 5.3.5.2: P001, P005]

**Vorinostat Monotherapy – Solid Tumors**

The overall extent of exposure to Vorinostat in patients with solid tumors is summarized in the table below.

- At any dose, the overall mean number of days on treatment was 104.4 days with a range of 1 to 1311 days.
- Seventy-one (71) of 101 patients (70.3%) received 400 mg total daily dose (400 mg once daily or 200 mg twice daily). The mean number of days on drug was highest at this daily dose; 91.8 days and a range of 1 to 1034 days.

**Table 51. Number of Patients on Study Drug by Dose and Actual Duration of Treatment Vorinostat Monotherapy – Solid Tumor – Overall (Applicant's Table)**

| MK-0683 Total Daily Dose | ≤2 wks | >2 wks to ≤4 wks | >4 wks to ≤6 wks | >6 wks to ≤12 wks | >12 wks to ≤16 wks | >16 wks to ≤20 wks | >20 wks to ≤24 wks | >24 weeks | Total | Range of Days on Drug | Mean Number of Days on Drug |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ANY DOSE | 22 | 14 | 13 | 29 | 7 | 2 | 5 | 9 | 101 | 1 to 1311 | 104.4 |
| 200 mg | 13 | 1 | 1 | 3 | 0 | 0 | 0 | 1 | 19 | 1 to 609 | 46.0 |
| 800 mg | 14 | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 19 | 1 to 625 | 56.1 |
| 900 mg | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 to 1 | 1.0 |
| 300 mg | 18 | 2 | 1 | 0 | 0 | 0 | 0 | 0 | 21 | 1 to 36 | 6.6 |
| 350 mg | 2 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 5 | 1 to 57 | 24.8 |
| 400 mg | 22 | 11 | 7 | 15 | 6 | 1 | 2 | 7 | 71 | 1 to 1034 | 91.8 |
| 500 mg | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 2 to 2 | 2.0 |
| 550 mg | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| 600 mg | 18 | 8 | 2 | 7 | 0 | 0 | 1 | 1 | 37 | 1 to 870 | 49.4 |

Although some patients may have taken two or more different dosages, they have been counted only one time each, on the 'ANY DOSE' row.
No patient received a 900 mg total daily dose. 900 mg appears due to a duplicate entry in Protocol 011.

[Ref. 5.3.3.2: P008] [Ref. 5.3.5.4: P002, P006, P011V1]

**400 mg total daily dose (initial dose)**

- Mean exposure was just under 16 weeks
- Twenty-six (26) of 45 (57.8%) patients were exposed to Vorinostat for more than 6 weeks
  - Eight (8) of 45 patients (17.7%) included in this analysis were exposed to some dose of Vorinostat for more than 16 weeks, and 3 patients had prolonged exposure of almost three years.
  - One patient (AN1015 exposure) exceeded 2 years; this patient was originally enrolled in Protocol 006 and subsequently enrolled in Protocol 007 (extension study). This patient had a 1393 day exposure to study drug as of 12-Dec-2005. This patient (medullary cancer) received 400 mg twice daily from 18-Feb-2002 until 10-Nov-2003 when the dose of study drug was reduced to 400 mg daily for the duration of the study.

**300 mg discontinuous twice daily dosing**

- Sixteen (16) patients were exposed to this dose. Patients began treatment at 300 mg or 400 mg twice daily, and might have undergone dose modification. Seven (7) patients (43.8%) were exposed more than 4 weeks.

**200 mg twice daily dosing each week**

- Two (2) of 8 patients remained on treatment for more the 24 weeks with maximum exposure of 776 days.
- 2 patients were treated out to >6 weeks to ≤12 weeks, and 3 patients were treated for ≤4 weeks

**200 mg twice daily dosing for 14 days followed by 7 days off the study drug**

- Eight (8) patients were exposed to drug. Patients might have started 200 mg; or 400 mg twice daily, but had dose modification.
- No patient was able to sustain the 400 mg twice daily dose beyond 6 weeks due dose limiting toxicities.

**Doses above the MTD**

- Thirty-two (32) patients started treatments at doses above the MTD but had a dose modification
- Nine (9) of 32 patients (28.1 %) were exposed for more than 4 weeks above the MTD and 2 of the 32 (6.2%) patients remained on Vorinostat for beyond 24 weeks with a maximum exposure of 885 days

## Vorinostat Monotherapy – Hematologic Malignancies

The overall extent of exposure for patients in this population is summarized in the table below

- At any dose, the mean number of days on drug was 48.5 days (range 1 to 341 days)
- Forty-two (42) of 87 (48.2%) patients received 400 mg daily dose. The mean number of days on drug was highest at this dose; 52.7 days and a range of 1 to 319 days.

**Table 52. Number of Patients on Study Drug by Dose and Actual Duration of Treatment (Vorinostat Monotherapy – Hematologic Malignancies – Overall) (Applicant's Table)**

| MK-0683 Total Daily Dose | ≤2 wks | >2 wks to ≤4 wks | >4 wks to ≤6 wks | >6 wks to ≤12 wks | >12 wks to ≤16 wks | >16 wks to ≤20 wks | >20 wks to ≤24 wks | >24 weeks | Total | Range of Days on Drug | Mean Number of Days on Drug |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ANY DOSE | 21 | 18 | 18 | 17 | 6 | 3 | 0 | 4 | 87 | 1 to 341 | 48.5 |
| 200 mg | 8 | 0 | 2 | 2 | 0 | 0 | 0 | 1 | 13 | 1 to 190 | 30.5 |
| 250 mg | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 5 | 1 to 2 | 1.6 |
| 300 mg | 9 | 2 | 1 | 0 | 1 | 0 | 0 | 0 | 13 | 1 to 89 | 15.2 |
| 350 mg | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| 400 mg | 11 | 7 | 8 | 9 | 3 | 1 | 0 | 3 | 42 | 1 to 319 | 52.7 |
| 450 mg | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 3 | 13 to 29 | 19.0 |
| 500 mg | 3 | 1 | 2 | 1 | 2 | 0 | 0 | 0 | 9 | 1 to 102 | 38.4 |
| 600 mg | 15 | 11 | 4 | 3 | 0 | 0 | 0 | 0 | 33 | 1 to 70 | 23.1 |
| 750 mg | 8 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 9 | 5 to 21 | 13.6 |
| 800 mg | 2 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 7 to 22 | 13.7 |
| 900 mg | 3 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 4 | 6 to 56 | 19.3 |

Although some patients may have taken two or more different dosages, they have been counted only one time each, on the 'ANY DOSE' row.
[Ref. 5.3.5.4: P003V1, P004V1, P006, P013V1]

## Cohort exposed to 400 mg total daily dose continuously (initial or modified)

Patients in Protocol 006 received this dosing regimen

- Sixteen (16) patients were exposed to 400 mg total daily either as the initial regimen, or as a result of dose modifications
- Seven (7) of 16 patients (43.7%) were exposed for more than six weeks
- Two patients remained on this dose of Vorinostat for more than 24 weeks with a maximum exposure of 318 days. The mean number of days of exposure for this dose schedule was 71.5 days.

## 300 mg twice daily discontinuous dosing group

- Three (3) patients from Protocol 013 were exposed to this regimen
- As this trial is ongoing, and the data provided are limited to the time of data cut-off, these do not reflect the true tolerability of exposure at this dose

## 200 mg twice daily dosing

- Only patients in Protocol 006 got this dosing regimen
- Three (3) of 6 patients were able to tolerate Vorinostat for more than six weeks and one patient was able to tolerate Vorinostat for more than 16 weeks

- Mean number of days on treatment was relatively short (48 days), but the range of days on treatment extended to 117 days. This represents a patient who began treatment at 200 mg twice daily who was dose reduced to 200 mg once daily.

**200 mg twice-daily dosing for 14 days on study drug followed by 7 days off**

- These patients were enrolled in the ongoing studies Protocol 003, Protocol 004, and Protocol 013 and follow-up data were limited at the time of data cut-off date.
- Patients began treatment at either 200 mg or 300 mg twice daily, but might have had a dose modification
- Four (4) of 14 patients (28.5%) were exposed more than 6 weeks.
- The mean number of days of exposure in this group was 38 days. The longest exposure at the time of data cut-off was 98 days.

**Exposure to Vorinostat above the MTD**

- Fourteen (14) of 18 patients were exposed to Vorinostat for 4 weeks or less.
- Three (3) patients remained on Vorinostat up to six weeks and one patient was exposed for more than 6 weeks with a maximum exposure of 45 days.
- The mean number of days of exposure in this group was 19.7 days.

**Exposure to Vorinostat below the MTD**

- Thirty-one (31) of 45 patients were exposed to Vorinostat for 6 weeks or less
- Nine (9) patients remained on Vorinostat up to 12 weeks and 2 patients were exposed more than 24 weeks with a maximum exposure of 190 days.
- The mean number of days of exposure in this group was 41.3 days.

## Vorinostat Combination Therapies

Three study protocols that used Vorinostat Combination Therapies are summarized below:

**Table 53. Table of Protocols Using Vorinostat Combination Therapies (Applicant's Table)**

| Protocol Number | Phase | Study Title |
|---|---|---|
| 012 | I | A Phase I Clinical Trial of Oral Suberoylanilide Hydroxamic Acid in Combination with Pemetrexed and Cisplatin in Patients with Advanced Cancer |
| 015 | I | Phase I Clinical Trial of Oral Suberoylanilide Hydroxamic Acid (L-001079038) in Combination With Bortezomib in Patients With Advanced Multiple Myeloma |
| 016 | I | Phase I Study in Combination with Bexarotene in Patients with Advanced CTCL |

[Ref. 5.3.5.4: P012V1, P015V1, P016V1]

## Exposure (overall)

The overall extent of exposure for patients who received combination therapies is summarized in the table below.

- By the data cut-off date, the mean number of days on the study drug (any dose) for these ongoing studies was 36.9 (range 9 to 86 days).
- Seven (7) of 10 (70%) patients received the 400 mg total daily dose; the mean number of days of exposure to this dose is 19
- The mean number of days on drug was highest in the 300 mg daily dose; 41 days (range of 22 to 57 days)

**Table 54. Number of Patients on Vorinostat by Dose and Duration of Treatment (Vorinostat Combination Therapy Protocols – Overall) (Applicant's Table)**

| MK-0683 Total Daily Dose | ≤2 wks | >2 wks to ≤4 wks | >4 wks to ≤6 wks | >6 wks to ≤12 wks | >12 wks to ≤16 wks | >16 wks to ≤20 wks | >20 wks to ≤24 wks | >24 weeks | Total | Range of Days on Drug | Mean Number of Days on Drug |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ANY DOSE | 3 | 2 | 2 | 2 | 1 | 0 | 0 | 0 | 10 | 9 to 86 | 36.9 |
| 200 mg | 5 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 7 | 1 to 27 | 10.0 |
| 300 mg | 0 | 2 | 0 | 2 | 0 | 0 | 0 | 0 | 4 | 22 to 57 | 41.0 |
| 400 mg | 3 | 3 | 1 | 0 | 0 | 0 | 0 | 0 | 7 | 7 to 29 | 19.1 |
| 600 mg | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 to 1 | 1.0 |
| Although some patients may have taken two or more different dosages, they have been counted only one time each, on the 'ANY DOSE' row. | | | | | | | | | | | |

[Ref. 5.3.5.4: P012V1, P015V1, P016V1]

## Demographic and Other Characteristics of Study Population

### Summary Comparison of Demographics

- Demographics including age, gender and race were similar across all the study populations and at various doses within each population (exception: a slightly higher male predominance and a slightly higher median age in the non-CTCL group).
    - The majority of patients enrolled were white and male.
- Both CTCL and non-CTCL patients had several non-tumor related concomitant conditions (co-morbidities) as can be expected for their ages, and they had tumor-related conditions relevant to their primary diseases.
- Patients were receiving a variety of medications for both the concomitant medical conditions and for symptomatic and supportive care of their tumor related conditions.
- Each protocol enrolled selected patients—there were restrictions on the severity of concomitant medical conditions and organ dysfunction allowed. For example, patients with severe hematologic abnormalities and moderate to severe hepatic and renal abnormalities, defined by the limits in the individual protocols, were excluded from these studies. Therefore, although the enrolled patients had a wide variety of other medical conditions, these were not of a severity expected to interfere with the study therapy.

The details of demographics, concomitant medical conditions, and concomitant medications are summarized for each of the 5 study populations in the sections below.

### Vorinostat Monotherapy – CTCL

- In Protocol 001 and Protocol 005, Vorinostat monotherapy was administered to patients diagnosed with CTCL who were refractory to or intolerant of other prior therapy.
- In Protocol 001, the inclusion requirements included treatment failure for two systemic therapies. One (1) of the therapies must have contained bexarotene unless the patient was intolerant or not a candidate for bexarotene therapy. Patients with a history of treatment with any HDAC inhibitor were ineligible.
- In Protocol 005 the inclusion criteria required a staging of $\geq$ IA and treatment failure for at least one prior therapy. Patients who had previously enrolled on 1 cohort of this study were eligible for enrollment in a subsequent cohort. Four (4) patients participated in two cohorts.
- In Protocol 001, Sezary Syndrome patients who had been on systemic corticosteroids for the last 3 months prior to study entry and who were on a stable daily dose of corticosteroids equivalent to $\leq$ 10 mg of prednisone during the four weeks immediately prior to study entry *were eligible.*
- Patients on topical corticosteroids with a potency that did not exceed 0.1% triamcinolone acetonide cream or similar strength corticosteroid cream during the four weeks immediately prior to study entry *were eligible.*
- In Protocol 005, patients on stable doses of antihistamines and/or topical anti-pruritic agents, including topical corticosteroids *were eligible.*

- A total of 107 patients with CTCL were enrolled in this population, the total patient exposure to Vorinostat was 111 patients. The baseline characteristics of patients who participated in these protocols are summarized in the table below for the 111 patients in all treatment groups.
- All of the CTCL patients exposed to at least one dose of study drug were ≥26 years of age.
- The **median age** of these patients at the time of enrollment was **63 years**.
  - Forty-nine (49) of the 111 patients (44.1%) were 66 years of age or older.
- The study population was predominantly White (79.3%).
- More men (51.4%) participated in these studies than women (48.6%).
- Eighty-seven (87) of 111 (78.4%) patients received 400 mg total daily dosing (initial dose). This is the clinically recommended dose and schedule. The median age for this treatment group was 60 years.

**Table 55. Baseline Patient Characteristics Vorinostat Monotherapy – CTCL (Applicant's Table)**

| | | 400mg once daily continuous (N = 87) | | 300mg twice daily 3/7 (N = 12) | | Doses above MTD (N = 12) | | Total (N = 111) | |
|---|---|---|---|---|---|---|---|---|---|
| | | n | (%) | n | (%) | n | (%) | n | (%) |
| Gender | Female | 41 | (47.1) | 7 | (58.3) | 6 | (50.0) | 54 | (48.6) |
| | Male | 46 | (52.9) | 5 | (41.7) | 6 | (50.0) | 57 | (51.4) |
| Age (years) | 25 And Under | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| | 26 to 35 | 0 | (0.0) | 1 | (8.3) | 0 | (0.0) | 1 | (0.9) |
| | 36 to 45 | 9 | (10.3) | 2 | (16.7) | 1 | (8.3) | 12 | (10.8) |
| | 46 to 55 | 21 | (24.1) | 0 | (0.0) | 1 | (8.3) | 22 | (19.8) |
| | 56 to 65 | 22 | (25.3) | 2 | (16.7) | 3 | (25.0) | 27 | (24.3) |
| | 66 to 75 | 26 | (29.9) | 6 | (50.0) | 5 | (41.7) | 37 | (33.3) |
| | Over 75 | 9 | (10.3) | 1 | (8.3) | 2 | (16.7) | 12 | (10.8) |
| | MEAN | | 61.3 | | 61.9 | | 64.8 | | 61.7 |
| | SD | | 11.60 | | 16.52 | | 11.78 | | 12.15 |
| | MEDIAN | | 60.0 | | 70.5 | | 66.5 | | 63.0 |
| | RANGE | | 37 - 83 | | 26 - 80 | | 39 - 78 | | 26 - 83 |
| Race | Asian | 1 | (1.1) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| | Black | 14 | (16.1) | 4 | (33.3) | 3 | (25.0) | 21 | (18.9) |
| | Multi-Racial | 1 | (1.1) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| | White | 71 | (81.6) | 8 | (66.7) | 9 | (75.0) | 88 | (79.3) |

[Ref. 5.3.5.2: P001, P005]

**Secondary diagnoses** for Vorinostat Monotherapy CTCL population:

- Hypertension 40.5%
- Hypothyroidism 37.8%
- Depression 27.0%

- Distribution of **secondary diagnoses by SOC** was consistent with the frequencies of reported common secondary diagnoses in the overall CTCL population: vascular disorders (45.9%), endocrine disorders (41.6%), and psychiatric disorders (38.7%).

***Reviewer Comments:*** *In this population, unusually high incidence of hypothyroidism may be due to sick-euthyroid syndrome, and high incidence of endocrine disorders is due to a combination of sick euthyroid cases and secondary diabetes cases—the latter due to frequent corticosteroids use in this population.*

**Prior Chemotherapy**

- These patients were heavily pre-treated for CTCL
- A median of 5 prior therapies had been administered (range of 0 to 18 therapies) in patients who received Vorinostat 400 mg once daily. One patient from Protocol 005 had no prior chemotherapy but did have prior radiotherapy which did meet the inclusion criteria.

**Table 56. Summary of Prior Chemotherapy (Vorinostat Monotherapy – CTCL Population) (Applicant's Table)**

| Prior Therapies | 400mg once daily continuous (N=87) | 300mg twice daily 3/7 (N=12) | Doses above MTD (N=12) |
|---|---|---|---|
| Number (%) of patients with | | | |
| no prior chemotherapy | 1 (1.1%) | 0 (0.0%) | 0 (0.0%) |
| one prior chemotherapy | 3 (3.4%) | 0 (0.0%) | 0 (0.0%) |
| two prior chemotherapies | 10 (11.5%) | 0 (0.0%) | 4 (33.3%) |
| three or more prior chemotherapies | 73 (83.9%) | 12 (100.0%) | 8 (66.7%) |
| Median (Range) | 5 (0, 18) | 5 (3, 17) | 5 (2, 11) |

[Ref. 5.3.5.2: P001, P005]

**Concomitant Therapies** (Vorinostat Monotherapy – CTCL Population):

- Antibacterials 64.9%
- Dermatologic corticosteroids 55.9%
- Analgesics 55.9%

**Prior Therapies Compared to Concomitant Therapies**

Increased use of some concomitant therapies compared to prior therapies was noted. This increase is consistent with the management of adverse experiences for this patient population.

- **Anti-diarrheal agents** use increased from 4/111 (3.6%) in prior therapy to 29 (26.1%) in concomitant therapies
- **Anti-emetic** use increased from 16 (14.4%) in prior therapy to 40 (36.0%) in concomitant therapies
- **Anti-anemic** use increased from 20 (18.0%) in prior therapy to 27 (24.3%) in concomitant therapies
- **Anti-hemorrhagic** use increased from 1 (0.9%) in prior therapy to 4 (3.6%) in concomitant therapies
- **Anti-thrombotic** use increased from 10 (9.0%) in prior therapy to 19 (17.1%) in concomitant therapies

## Vorinostat Monotherapy – CTCL Stage IIB and Higher

Of the 107 CTCL patients, a total of 89 patients diagnosed with clinical staging ≥ IIB and higher received Vorinostat monotherapy. The total patient exposure to Vorinostat was 93 patients. Baseline characteristics of the 93 patients are summarized in the table below.

- The **median age** of patients at the time of enrollment was **63 years**.
- Forty-three (43) of 93 patients (46.2%) patients that participated were 66 years of age or older. The study population was predominantly White (78.5%).
- More men (51.6%) participated than women (48.4%) in these studies.
- The age, gender, and race distributions in this subset were consistent with the other CTCL patients who participated.

- Seventy-two (72) of 93 (77.4 %) patients received 400 mg once daily dosing, the clinically recommended dose and schedule.
- The median age for this group was 62 years; numerically higher than the Vorinostat Monotherapy-CTCL population. However, race and gender distributions were consistent with the Vorinostat Monotherapy – CTCL.

**Table 57. Baseline Patient Characteristics (Vorinostat Monotherapy-CTCL Stage IIB and Higher) (Applicant's Table)**

| | | 400mg QD continuous (N = 72) | | 300mg BID 3/7 (N = 11) | | Doses above MTD (N = 10) | | Total (N = 93) | |
|---|---|---|---|---|---|---|---|---|---|
| | | n | (%) | n | (%) | n | (%) | n | (%) |
| Gender | Female | 34 | (47.2) | 6 | (54.5) | 5 | (50.0) | 45 | (48.4) |
| | Male | 38 | (52.8) | 5 | (45.5) | 5 | (50.0) | 48 | (51.6) |
| Age (years) | 25 And Under | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| | 26 to 35 | 0 | (0.0) | 1 | (9.1) | 0 | (0.0) | 1 | (1.1) |
| | 36 to 45 | 6 | (8.3) | 2 | (18.2) | 1 | (10.0) | 9 | (9.7) |
| | 46 to 55 | 16 | (22.2) | 0 | (0.0) | 1 | (10.0) | 17 | (18.3) |
| | 56 to 65 | 19 | (26.4) | 2 | (18.2) | 2 | (20.0) | 23 | (24.7) |
| | 66 to 75 | 22 | (30.6) | 5 | (45.5) | 4 | (40.0) | 31 | (33.3) |
| | Over 75 | 9 | (12.5) | 1 | (9.1) | 2 | (20.0) | 12 | (12.9) |
| | MEAN | | 62.2 | | 61.3 | | 63.9 | | 62.3 |
| | SD | | 11.61 | | 17.16 | | 12.54 | | 12.33 |
| | MEDIAN | | 62.0 | | 72.0 | | 66.5 | | 63.0 |
| | RANGE | | 37 - 83 | | 26 - 80 | | 39 - 78 | | 26 - 83 |
| Race | Asian | 1 | (1.4) | 0 | (0.0) | 0 | (0.0) | 1 | (1.1) |
| | Black | 11 | (15.3) | 4 | (36.4) | 3 | (30.0) | 18 | (19.4) |
| | Multi-Racial | 1 | (1.4) | 0 | (0.0) | 0 | (0.0) | 1 | (1.1) |
| | White | 59 | (81.9) | 7 | (63.6) | 7 | (70.0) | 73 | (78.5) |

[Ref. 5.3.5.2: P001, P003]

## Secondary diagnoses:

- Hypertension 40.9%
- Hypothyroidism 38.7%
- Depression 28%

## Prior Chemotherapy

- These patients were heavily pre-treated for CTCL. A median of 4 prior therapies had been administered with a range of 1 to 18

**Table 58. Prior Chemotherapy (Vorinostat Monotherapy – CTCL Stage IIB and Higher) (Applicant's Table)**

| Prior Therapies | 400mg once daily continuous (N=72) | 300mg twice daily 3/7 (N=11) | Doses above MTD (N=10) |
|---|---|---|---|
| Number (%) of patients with | | | |
| no prior chemotherapy | 0 (0%) | 0 (0%) | 0 (0%) |
| one prior chemotherapy | 3 (4.2%) | 0 (0.0%) | 0 (0.0%) |
| two prior chemotherapies | 9 (12.5%) | 0 (0.0%) | 2 (20.0%) |
| three or more prior chemotherapies | 60 (83.3%) | 11 (100.0%) | 8 (80.0%) |
| Median (Range) | 4 (1, 18) | 5 (3, 8) | 7 (2, 11) |

[Ref. 5.3.5.2: P001, P005]

## Concomitant Therapies

The most common concomitant therapies reported were:

- Antibacterials 45.2%
- Analgesics 31.2%
- Anti-diarrheals 25.9%

## Comparison of Prior Therapy and Concomitant Therapy

An increase in the number of patients on supportive or non-study treatment was observed when comparing *prior therapy* with *concomitant therapy*. These increases are consistent with the management of the adverse experiences in this patient population.

- No **anti-diarrheals** were reported as prior therapy but 24 of 93 patients (25.9%) reported them as concomitant therapies
- **Anti-emetics** taken increased from 4 patients (4.4%) as prior therapy to 36 patients (49.5%) who took them as concomitant therapies
- **Anti-anemic** use increased from 4 patients (4.3%) to 11 (11.8%)
- No **anti-hemorrhagics** were reported in prior therapy but 4 (4.3%) patients reported them as concomitant therapies
- **Anti-thrombotics** taken increased from 5 patients (5.4%) in prior therapy to 11 (11.8%) in concomitant therapies.

**Vorinostat Monotherapy – Solid Tumors**

The following Vorinostat protocols enrolled patients with solid tumors. Some of these studies did allow patients with hematological malignancies:

- Protocol 002 required patients to have cytological or histological confirmation of [redacted] Patients were eligible to participate if they were unresponsive to or intolerant of conventional chemotherapy. Patients who refused upfront conventional chemotherapy were eligible. Failure of up to 2 prior chemotherapies including neoadjuvant or adjuvant or concomitant chemotherapy/radiation was acceptable.

- Protocol 006 required patients to have histologically documented, advanced stage, primary or metastatic adult solid tumors and hematological malignancies refractory to standard treatment or for which there was no curative standard therapy.
  - Patients with androgen-independent prostate cancer, and cancers of the breast, ovary, head and neck, non-small cell lung, bladder, and kidney were eligible.
  - Patients with multiple myeloma refractory to standard care were eligible.
  - Patients with relapsed or refractory intermediate-grade or follicular non-Hodgkin's lymphoma or Hodgkin's disease were eligible.
  - Patients with leukemia and myelodysplastic syndrome that were refractory to standard therapy or for which no curative standard therapy exist were eligible.

- Protocol 008 required patients to have a histologically confirmed malignancy that was metastatic or unresectable and for which standard curative and palliative measures did not exist. Patients with solid tumors, hematologic malignancies, and lymphoma were eligible.

- Protocol 011 required patients with a histological diagnosis of breast carcinoma, colorectal carcinoma, or non-small cell lung cancer. Patients were required to have relapsed or refractory disease following at least one chemotherapy treatment regimen. Patients with colorectal cancer must have relapsed or refractory disease following at least two treatment regimens that included fluoropyrimidines, irinotecan, and oxaliplatin. Patients with breast cancer must have relapse or refractory disease following at least one treatment regimen and must have been treated with anthracyclines and taxanes.

The demographic characteristics of patients in the Vorinostat Monotherapy-Solid Tumor population are summarized in the table below.

- A total of 101 patients, ≥26 years of age, participated.
- The **median age** of patients at the time of enrollment was 61 years. Twenty-nine (29) of 101 (28.7%) patients were 66 years of age or older.
- The Vorinostat Monotherapy Solid Tumor population was predominantly White (88.1%).
- More men (63.4%) participated than women (36.6%).

- Of the patients who received doses above the MTD, 36 of 38 patients (94.7%) were White and 26 were men (68.4%).

- Of the patients who received doses below the MTD, 5 of 6 patients (83.3%) were White and 5 were men (83.3%).
- The gender and race distributions were consistent with the Vorinostat Monotherapy-CTCL population but the median age was numerically lower in this population.

- Forty (40) of 101 (39.6 %) patients received Vorinostat at 400 mg once daily dosing. In this treatment category age, race, and gender distributions were consistent with the Vorinostat Monotherapy – CTCL – population.

**Table 59. Baseline Patient Characteristics of the Vorinostat Monotherapy – Solid Tumors Population (The first part of the table lists subsets by Vorinostat doses, and second lists all patients) (Applicant's Table)**

| | | 400mg once daily continuous (N = 40) | | 300mg twice daily 3:7 (N = 13) | | 200mg twice daily continuous (N = 4) | | Doses above MTD (N = 38) | | Doses below MTD (N = 6) | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) |
| Gender | Female | 17 | (42.5) | 6 | (46.2) | 1 | (25.0) | 12 | (31.6) | 1 | (16.7) |
| | Male | 23 | (57.5) | 7 | (53.8) | 3 | (75.0) | 26 | (68.4) | 5 | (83.3) |
| Age (years) | 25 And Under | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (16.7) |
| | 26 to 35 | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 2 | (5.3) | 0 | (0.0) |
| | 36 to 45 | 4 | (10.0) | 1 | (7.7) | 0 | (0.0) | 3 | (7.9) | 1 | (16.7) |
| | 46 to 55 | 10 | (25.0) | 2 | (15.4) | 2 | (50.0) | 9 | (23.7) | 1 | (16.7) |
| | 56 to 65 | 11 | (27.5) | 6 | (46.2) | 1 | (25.0) | 18 | (47.4) | 0 | (0.0) |
| | 66 to 75 | 10 | (25.0) | 3 | (23.1) | 1 | (25.0) | 6 | (15.8) | 2 | (33.3) |
| | Over 75 | 5 | (12.5) | 1 | (7.7) | 0 | (0.0) | 0 | (0.0) | 1 | (16.7) |
| | MEAN | | 61.2 | | 61.1 | | 59.5 | | 57.4 | | 55.0 |
| | SD | | 11.88 | | 9.95 | | 7.85 | | 10.57 | | 19.20 |
| | MEDIAN | | 63.0 | | 61.0 | | 56.5 | | 59.0 | | 59.5 |
| | RANGE | | 39 - 84 | | 42 - 76 | | 54 - 71 | | 27 - 75 | | 25 - 78 |
| Race | Asian | 2 | (5.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| | Black | 3 | (7.5) | 2 | (15.4) | 0 | (0.0) | 1 | (2.6) | 1 | (16.7) |
| | Hispanic American | 1 | (2.5) | 1 | (7.7) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| | Null | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.6) | 0 | (0.0) |
| | White | 34 | (85.0) | 10 | (76.9) | 4 | (100.0) | 36 | (94.7) | 5 | (83.3) |

| | | Total (N = 101) | |
|---|---|---|---|
| | | n | (%) |
| Gender | Female | 37 | (36.6) |
| | Male | 64 | (63.4) |
| Age (years) | 25 And Under | 1 | (1.0) |
| | 26 to 35 | 2 | (2.0) |
| | 36 to 45 | 9 | (8.9) |
| | 46 to 55 | 24 | (23.8) |
| | 56 to 65 | 36 | (35.6) |
| | 66 to 75 | 22 | (21.8) |
| | Over 75 | 7 | (6.9) |
| | MEAN | | 59.3 |
| | SD | | 11.53 |
| | MEDIAN | | 61.0 |
| | RANGE | | 25 - 84 |
| Race | Asian | 2 | (2.0) |
| | Black | 7 | (6.9) |
| | Hispanic American | 2 | (2.0) |
| | Null | 1 | (1.0) |
| | White | 89 | (88.1) |

[Ref. 5.3.3.2: P008] [Ref. 5.3.3.4: P002, P006, P011V1]

**Common Secondary Diagnoses:**

- Dyspnea 35.6%
- Hypertension 33.7%
- Fatigue 25.7%

**Prior Therapies in Vorinostat Monotherapy – Solid Tumor population:**

- Anti-neoplastic agents 75.2%
- Analgesics 40.6%
- Psycholeptics 34.7%

**Table 60. Summary of Prior Chemotherapy Regimens (Vorinostat Monotherapy – Solid Tumors) (Applicant's Table)**

| Prior Therapies | 400mg once daily continuous (N=40) | 300mg twice daily 3/7 (N=13) | 200mg twice daily continuous (N=4) | Doses above MTD (N=38) | Doses below MTD (N=6) |
|---|---|---|---|---|---|
| Number (%) of patients with | | | | | |
| no prior chemotherapy | 0 (0.0%) | 1 (7.7%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| one prior chemotherapy | 4 (10.0%) | 5 (38.5%) | 0 (0.0%) | 3 (7.9%) | 2 (33.3%) |
| two prior chemotherapies | 10 (25.0%) | 5 (38.5%) | 0 (0.0%) | 7 (18.4%) | 1 (16.7%) |
| three or more prior chemotherapies | 26 (65.0%) | 2 (15.4%) | 4 (100.0%) | 28 (73.7%) | 3 (50.0%) |
| Median (Range) | 3 (1, 10) | 2 (0, 5) | 4 (3, 6) | 4 (1, 10) | 3 (1, 6) |

[Ref. 5.3.3.2: P008] [Ref. 5.3.5.4: P002, P006, P011V1]

**Concomitant Therapies for Vorinostat Monotherapy Solid – Tumor Population:**

- Analgesics 81.2%
- Psycholeptics 63.4%
- Laxatives 60.4%

**Comparison of Prior Therapies to Concomitant Therapies**

An increase in several treatments was observed when comparing *prior therapy* with *concomitant therapy* (consistent with management of treatment related side effects):

- **Anti-diarrheals** increased from 3 of 101 (3.0%) in prior therapy to 18 (17.8%) in concomitant therapies
- **Anti-emetics** increased from 8 (7.9%) in prior therapy to 29 (28.7%) in concomitant therapies
- **Anti-anemics** increased from 18 (17.8%) to 43 (42.6%)
- **Anti-hemorrhagics** increased from one (1.0%) prior therapies to 5 (5%) in concomitant therapies
- **Anti-thrombotic** use increased from 5 (5.0%) in prior therapies to 23 (22.8%) in concomitant therapies

**Vorinostat Monotherapy – Hematologic Malignancies**

- Protocol 003 required relapsed or refractory advanced leukemia or myelodysplastic syndrome.

- Protocol 004 required an established diagnosis of multiple myeloma confirmed by bone marrow aspirate and/or biopsy and patients must have relapsed or been refractory to their most recent treatment.

- Protocol 013 required a histological diagnosis of Diffuse Large B-cell Lymphoma and relapsed disease following standard first-line chemotherapy and at least one systemic salvage therapy that may include autologous stem cell transplantation.

The demographic characteristics of patients in Vorinostat Monotherapy Hematologic Malignancies population are summarized in the table below.

- 87 patients of age ≥ 18 years were enrolled.
- The median age of patients at enrollment was 65 years.
- Thirty-nine (39) of 87 (44.8 %) patients were 66 years of age or older.

Eleven (11) patients were exposed to 400 mg once daily dosing

- In the 400 mg once daily treatment category, the study population was predominantly White (72.7%).
- More men (72.7%) participated than women (27.3%) and the median age was 41 years.
- Two (2) patients were over the age of 65 years.
- The gender and race distributions were consistent with the Vorinostat Monotherapy – CTCL – population but the median age was lower.

Fifty-one (51) patients received doses above the MTD

- The median age was 65 years.
- The population was predominantly White (84.3%).
- More men (54.9%) participated than women (45.1%).
- Twenty-nine (29) patients were over the age of 65 years.
- The gender and race distributions were consistent with the Vorinostat Monotherapy – CTCL – population but the median age was numerically higher.

**Table 61. Baseline Patient Characteristics (Vorinostat Monotherapy – Hematologic Malignancies) (The first part of the table lists subsets by Vorinostat doses, and second lists all patients) (Applicant's Table)**

| | | 400mg once daily continuous (N = 11) | | 300mg twice daily 3/7 (N = 3) | | 200mg twice daily Continuous (N = 6) | | 200mg twice daily 14/21 (N = 10) | | Doses above MTD (N = 51) | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) |
| Gender | Female | 3 | (27.3) | 1 | (33.3) | 2 | (33.3) | 3 | (30.0) | 23 | (45.1) |
| | Male | 8 | (72.7) | 2 | (66.7) | 4 | (66.7) | 7 | (70.0) | 28 | (54.9) |
| Age (years) | 25 And Under | 1 | (9.1) | 0 | (0.0) | 0 | (0.0) | 1 | (10.0) | 1 | (2.0) |
| | 26 to 35 | 4 | (36.4) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| | 36 to 45 | 2 | (18.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 6 | (11.8) |
| | 46 to 55 | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 2 | (20.0) | 7 | (13.7) |
| | 56 to 65 | 2 | (18.2) | 1 | (33.3) | 4 | (66.7) | 2 | (20.0) | 12 | (23.5) |
| | 66 to 75 | 1 | (9.1) | 0 | (0.0) | 1 | (16.7) | 4 | (40.0) | 17 | (33.3) |
| | Over 75 | 1 | (9.1) | 2 | (66.7) | 1 | (16.7) | 1 | (10.0) | 8 | (15.7) |
| | MEAN | | 45.2 | | 73.7 | | 65.5 | | 60.8 | | 63.3 |
| | SD | | 20.43 | | 8.39 | | 8.60 | | 17.49 | | 14.15 |
| | MEDIAN | | 41.0 | | 78.0 | | 63.0 | | 66.0 | | 65.0 |
| | RANGE | | 21 - 79 | | 64 - 79 | | 56 - 77 | | 18 - 76 | | 20 - 90 |
| Race | Asian | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (10.0) | 2 | (3.9) |
| | Asiatic | 1 | (9.1) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| | Black | 2 | (18.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 3 | (5.9) |
| | Hispanic American | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (10.0) | 3 | (5.9) |
| | White | 8 | (72.7) | 3 | (100.0) | 6 | (100.0) | 8 | (80.0) | 43 | (84.3) |

| | | Doses below MTD (N = 6) | | Total (N = 87) | |
|---|---|---|---|---|---|
| | | n | (%) | n | (%) |
| Gender | Female | 0 | (0.0) | 32 | (36.8) |
| | Male | 6 | (100.0) | 55 | (63.2) |
| Age (years) | 25 And Under | 0 | (0.0) | 3 | (3.4) |
| | 26 to 35 | 0 | (0.0) | 4 | (4.6) |
| | 36 to 45 | 0 | (0.0) | 8 | (9.2) |
| | 46 to 55 | 2 | (33.3) | 11 | (12.6) |
| | 56 to 65 | 1 | (16.7) | 22 | (25.3) |
| | 66 to 75 | 2 | (33.3) | 25 | (28.7) |
| | Over 75 | 1 | (16.7) | 14 | (16.1) |
| | MEAN | | 64.5 | | 61.3 |
| | SD | | 12.14 | | 15.94 |
| | MEDIAN | | 66.0 | | 65.0 |
| | RANGE | | 47 - 81 | | 18 - 90 |
| Race | Asian | 0 | (0.0) | 3 | (3.4) |
| | Asiatic | 0 | (0.0) | 1 | (1.1) |
| | Black | 0 | (0.0) | 5 | (5.7) |
| | Hispanic American | 0 | (0.0) | 4 | (4.6) |
| | White | 6 | (100.0) | 74 | (85.1) |

[Ref. 5.3.5.4. P003V1, P004V1, P006, P013V1]

**Secondary diagnoses for Vorinostat Monotherapy Hematologic Malignancies population:**

- Anemia 64.4%
- Fatigue 50.6%
- Drug hypersensitivity 41.4%

**Prior therapies for Vorinostat Monotherapy Hematologic Malignancies population:**

- Anti-neoplastic agents 86.2%
- Corticosteroids 33.3%
- Psycholeptics 24.1%

## Prior Chemotherapy

- Exposure to prior chemotherapy is summarized in the table below

**Table 62. Summary of Prior Chemotherapy Regimens (Vorinostat Monotherapy – Hematologic Malignancies) (Applicant's Table)**

| Prior Therapies | 400mg once daily continuous (N=11) | 300mg twice daily 3/7 (N=3) | 200mg twice daily continuous (N=6) | 200mg twice daily 14/21 (N=10) | Doses above MTD (N=51) | Doses below MTD (N=6) |
|---|---|---|---|---|---|---|
| Number (%) of patients with | | | | | | |
| no prior chemotherapy | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 8 (15.7%) | 1 (16.7%) |
| one prior chemotherapy | 1 (9.1%) | 0 (0.0%) | 0 (0.0%) | 1 (10.0%) | 6 (11.8%) | 1 (16.7%) |
| two prior chemotherapies | 0 (0.0%) | 1 (33.3%) | 1 (16.7%) | 2 (20.0%) | 12 (23.5%) | 3 (50.0%) |
| three or more prior chemotherapies | 10 (90.9%) | 2 (66.7%) | 5 (83.3%) | 7 (70.0%) | 25 (49.0%) | 1 (16.7%) |
| Median (Range) | 4 (1, 13) | 3 (2, 3) | 5 (2, 6) | 5 (1, 9) | 2 (0, 10) | 2 (0, 10) |

[Ref. 5.3.5.4: P003V1, P004V1, P006, P013V1]

## Concomitant Therapies

- Antibacterials 72.5%
- Analgesics 68.6%
- Anti-anemia preparations 44.8%

## Prior Therapy Compared to Concomitant Therapy

An increase in some treatments was observed when comparing prior therapy with concomitant therapy

- **Anti-diarrheals** use increased from 2 of 87 (2.3%) in prior therapy to 35 (40.2%) in concomitant therapies
- **Anti-anemics** increased from 17 (19.5%) to 39 (44.8%)
  - Darbepoetin-alfa use was not reported in prior therapy but was reported in 4 (4.6%) patients in concomitant therapies
  - Epoetin-alfa use increased from 6 (6.9%) to 19 (21.8%)
- **Anti-hemorrhagics** use increased from 7 (8.0%) to 34 (39.1 %)
- **Anti-thrombotic** use increased from 6 (6.9%) in prior therapies to 9 (10.3%) in concomitant therapies

***Reviewer Comments:*** *Above uses of concomitant therapies reflect the manifestations of the underlying diseases and management of AEs of the treatments of the underlying diseases in this patient population*

**Vorinostat Combination Therapies**
Phase I studies with combination therapies are summarized in the table below

**Table 63. Summary of Phase I Combination Therapies with Vorinostat (Applicant's Table)**

| Protocol Number | Study Title | Treatment Schedule | | | |
|---|---|---|---|---|---|
| 012 | A Phase I Clinical Trial of Oral Suberoylanilide Hydroxamic Acid in Combination with Pemetrexed and Cisplatin in Patients with Advanced Cancer | Cohort A: Vorinostat twice daily + pemetrexed and cisplatin<br>Dose Level 1 - 300 mg twice daily x 3/7 days for first week, followed by two weeks off<br>Dose Level 2 - 300 mg twice daily x 3/7 days for first 2 weeks, followed by one week off<br>Dose Level 3 - 300 mg twice daily x 3/7 days repeated weekly for 3 weeks<br>Cohort B: Vorinostat once daily + pemetrexed and cisplatin<br>Dose Level 1 - 400 mg daily x 7 days<br>Dose Level 2 - 500 mg daily x 7 days<br>Dose Level 3 - 600 mg daily x 7 days<br>Second Phase I study at MTD: vorinostat + pemetrexed<br>Starting vorinostat dose will be one dose above the MTD. | | | |
| 015 | Phase I Clinical Trial of Oral Suberoylanilide Hydroxamic Acid (L-001079038) in Combination With Bortezomib in Patients With Advanced Multiple Myeloma | Dose Level | Bortezomib Dose ($mg/m^2$) On Days 4, 8, 11, and 15 | Vorinostat Dose (mg) Twice Daily for 14 of 21 days | Vorinostat Total Daily Dose (mg) |
| | | 1 | 0.7 | 200 | 400 |
| | | 2 | 0.9 | 200 | 400 |
| | | 3 | 0.9 | 300 | 600 |
| | | 4 | 1.1 | 300 | 600 |
| | | 5 | 1.3 | 300 | 600 |
| 016 | Phase I Study in Combination with Bexarotene in Patients with Advanced CTCL | Starting dose at 200 mg once daily vorinostat + 150 $mg/m^2$ bexarotene once daily then escalating to 400 mg once daily vorinostat in 100 mg increments followed by escalating to 300 $mg/m^2$ bexarotene in 75 mg increments. No intrapatient dose escalation. | | | |

[Ref. 5.3.5.4: P012V1, P015V1, P016V1]

- Protocol 012 required a patient to have a histological and/or cytological confirmed diagnosis of a solid tumor including but not limited to malignant pleural mesothelioma and non-small-cell lung cancer (NSCLC) that has not been previously treated with systemic therapy or has failed standard first-line therapy and for which the approved chemotherapy regimen, pemetrexed, or pemetrexed/cisplatin, is acceptable treatment. Patients previously treated with cisplatinum or pemetrexed were ineligible.

- Protocol 015 required patients to have relapsed or refractory multiple myeloma. Patients must have quantifiable M protein in serum or urine. The use of complimentary or alternative medicines during the study was prohibited.

- Protocol 016 required a diagnosis of CTCL. Patients must be eligible for bexarotene therapy. Patients with bexarotene therapy within 3 months prior to enrollment were ineligible. Patients with other currently active malignancies were ineligible.

The demographic characteristics of Vorinostat Combination Therapy patients are shown in the table below.

**Table 64. Baseline Patient Characteristics (Vorinostat Combination Therapies) (Applicant's Table)**

| | | Combination Therapies (N = 10) | | Total (N = 10) | |
|---|---|---|---|---|---|
| | | n | (%) | n | (%) |
| Gender | Female | 2 | (20.0) | 2 | (20.0) |
| | Male | 8 | (80.0) | 8 | (80.0) |
| Age (years) | 25 And Under | 0 | (0.0) | 0 | (0.0) |
| | 26 to 35 | 0 | (0.0) | 0 | (0.0) |
| | 36 to 45 | 1 | (10.0) | 1 | (10.0) |
| | 46 to 55 | 1 | (10.0) | 1 | (10.0) |
| | 56 to 65 | 5 | (50.0) | 5 | (50.0) |
| | 66 to 75 | 2 | (20.0) | 2 | (20.0) |
| | Over 75 | 1 | (10.0) | 1 | (10.0) |
| | MEAN | | 62.0 | | 62.0 |
| | SD | | 12.29 | | 12.29 |
| | MEDIAN | | 63.0 | | 63.0 |
| | RANGE | | 39 - 81 | | 39 - 81 |
| Race | Hispanic American | 1 | (10.0) | 1 | (10.0) |
| | White | 9 | (90.0) | 9 | (90.0) |

[Ref. 5.3.5.4: P012V1, P015V1, P016V1]

- A total of 10 patients ≥ 36 years of age were enrolled.
- The **median age** of patients at enrollment was 63 years.
- Three (3) of 10 patients (30.0%) were 66 years of age or older.
- The study population was predominantly White (90.0%) and male (80.0%).
- The gender, age, and race distributions were consistent with the Vorinostat Monotherapy – CTCL population.

**Secondary Diagnoses for Vorinostat Combination Therapy Population**

- Hypertension 40%
- Insomnia 30%
- Back pain 30%

**Prior therapies for Vorinostat Combination Therapy Population**

- Anti-neoplastic agents 70%
- Blood forming agents 80%
- Analgesics 60%

**Concomitant therapies for Vorinostat Combination Therapy Population**

- Anti-emetics 70.0%
- Drugs for gastric acid related disorders, mineral supplements, serum lipid reducing agents, analgesics, and systemic corticosteroids 50.0%

**Prior Chemotherapy**

**Table 65. Summary of Prior Chemotherapy (Vorinostat Combination Therapies) (Applicant's Table)**

| Prior Therapies | Combination Therapies (N=10) |
|---|---|
| Number (%) of patients with | |
| no prior chemotherapy | 2 (20.0%) |
| one prior chemotherapy | 4 (40.0%) |
| two prior chemotherapies | 2 (20.0%) |
| three or more prior chemotherapies | 2 (20.0%) |
| Median (Range) | 1 (0, 11) |

[Ref. 5.3.5.4: P012V1, P015V1, P016V1]

## Adverse Experiences

### Analysis of Adverse Experiences (methodology for compilation, analysis and presentation of the safety data)

In this section, adverse experience data are presented for the following five safety populations:

1) Vorinostat Monotherapy – CTCL
2) Vorinostat Monotherapy – CTCL Stage IIB and Higher
3) Vorinostat Monotherapy – Solid Tumors
4) Vorinostat Monotherapy – Hematologic Malignancies
5) Vorinostat Combination Therapies

The table below summarizes the dose and schedule of Vorinostat studied within each population.

**Table 66. Summary of Vorinostat Dose and Schedule Studied in Each Population (Applicant's Table)**

| Population | Study Dose and Schedule | | |
|---|---|---|---|
| | MTD | Doses Above MTD | Doses Below MTD |
| Vorinostat Monotherapy – CTCL | 400 mg once daily,<br>300 mg twice daily 5 out of 7 days,<br>200 mg twice daily | 550 mg once daily | 400 mg once daily 5 out of 7 days |
| Vorinostat Monotherapy – CTCL Stage IIB and Higher | 400 mg once daily,<br>300 mg twice daily 3 out of 7 days,<br>200 mg twice daily | 550 mg once daily | 400 mg once daily 5 out of 7 days |
| Vorinostat Monotherapy – Solid Tumors | 400 mg once daily,<br>300 mg twice daily 5 out of 7 days,<br>200 mg twice daily,<br>200 mg twice daily 14 out of 21 days | 350 mg once daily,<br>300 mg twice daily,<br>600 mg once daily,<br>300 mg twice daily 14 out of 21 days,<br>400 mg twice daily,<br>400 mg twice daily 3 out of 7 days,<br>400 mg twice daily 14 out of 21 days | 300 mg once daily,<br>200 mg once daily,<br>200 mg twice daily 3 out of 7 days,<br>100 mg twice daily |

| Population | Study Dose and Schedule | | |
|---|---|---|---|
| | MTD | Doses Above MTD | Doses Below MTD |
| Vorinostat Monotherapy – Hematologic Malignancies | 400 mg once daily,<br>300 mg twice daily 5 out of 7 days,<br>200 mg twice daily,<br>200 mg twice daily 14 out of 21 days | 400 mg twice daily 3 out of 7 days,<br>200 mg three time daily 14 out of 21 days,<br>300 mg twice daily,<br>300 mg twice daily 14 out of 21 days,<br>250 mg three times daily 14 out of 21 days,<br>300 mg three times daily 14 out of 21 days,<br>250 mg twice daily 14 out of 21 days,<br>400 mg twice daily,<br>250 mg twice daily 5 out of 7 days,<br>150 mg three times daily 14 out of 21 days,<br>350 mg twice daily 4 out of 7 days,<br>600 mg once daily | 200 mg once daily,<br>200 mg twice daily 5 out of 7 days,<br>200 mg twice daily 3 out of 7 days,<br>100 mg three times daily 14 out of 21 days,<br>100 mg twice daily |
| Vorinostat Combination Therapies | 200 mg twice daily 14 out of 21 days | ---------- | 300 mg once daily 14 out of 21 days |

[Ref. 5.3.5.2: P008] [Ref. 5.3.5.2: P001, P005] [Ref. 5.3.5.4: P002, P003V1, P004V1, P006, P011V1, P012V1, P013V1, P014V1, P015V1, P016V1, P029V1, P030V1]

## Clinical Safety Assessments

Safety assessments in Vorinostat clinical studies were based on clinical and laboratory adverse experiences, laboratory abnormalities, electrocardiograms (ECGs), and vital signs. Serious adverse experiences, adverse experiences that led to discontinuation of study medication, and adverse experiences that led to dose modification were identified and summarized.

- Laboratory safety tests included blood chemistry, hematology, and urinalysis.
- Test abnormalities, irrespective of their clinical significance, were captured as laboratory abnormalities and assigned a grade in accordance with NCI CTCAE Version 3.0.
- Where appropriate (*i.e. clinically significant*), the investigators were instructed to follow a convention to code ***a laboratory abnormality as a clinical adverse experience*** *rather than* ***a laboratory adverse experience***. (For example, a decrease in platelet count that is *clinically significant* was to be reported as the *clinical* adverse experience of thrombocytopenia rather than the *laboratory* adverse experience of decreased platelets).
  - If an investigator did not follow the above convention, *laboratory abnormalities* would be coded as *laboratory adverse experiences*.
- Depending on the study timing, adverse experiences were evaluated using either the Common Toxicity Criteria (CTC) Version 2.0 or the Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0.
  - In Protocol 002, 003, 004, 005, and 006, adverse experiences were evaluated using CTC Version 2.0; in all other protocols (including protocol 001) adverse experiences were evaluated using CTCAE Version 3.0.
- To provide consistency when analyzing adverse experiences across protocols, the numeric grades from Protocol 002, 003, 004, 005, and 006 were converted to the CTCAE Version 3.0 values.

The table below summarizes the change from CTC Version 2.0 to CTCAE Version 3.0. The changes are related to the evaluation of decreased platelet count or thrombocytopenia (Grades 3 and 4); additionally, a classification of Grade 5 was included to capture adverse experiences resulting in death.

**Table 67. Summary of Changes from CTC Version 2.0 to CTCAE Version 3.0 (Applicant's Table)**

| Platelets | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 |
|---|---|---|---|---|---|
| CTC Version 2.0 | >LLN - 75,000/mm$^3$ | ≥50,000/mm$^3$ - <75,000/mm$^3$ | ≥10,000/mm$^3$ - <50,000/mm$^3$ | <10,000/mm$^3$ | ---------- |
| CTCAE Version 3.0 | >LLN to 75,000/mm$^3$ | <75,000 - 50,000/mm$^3$ | ≤50,000 - 25,000/mm$^3$ | <25,000/mm$^3$ | Death |
| LLN = Lower limit of normal | | | | | |

**Data Presentation in the Summary of Clinical Safety**

The primary focus in this Summary of Clinical Safety (SCS) is Vorinostat Monotherapy – CTCL, 400 mg once daily dosing, which is the clinically recommended dose and schedule.

The safety data is presented by individual study populations as follows:

- For each population a general summary of adverse experiences at *all doses* is provided. This is followed by a summary of overall adverse experiences observed at *each dose* that was studied within the population.
- Comparisons are performed across dosages within a population, and where appropriate, comparisons are also made to 400 mg once daily dosing in the Vorinostat Monotherapy – CTCL population.

- The summary of adverse experiences for each population is presented as follows:
  - Overall (all grades) clinical and laboratory adverse experiences
  - Overall (all grades) *drug-related* clinical and laboratory adverse experiences
  - Clinical and laboratory adverse experiences *Grades, 3, 4, and 5*
  - *Drug-related* clinical and laboratory adverse experiences *Grades, 3, 4, and 5*
  - Clinical adverse experiences resulting in *dose modification*
  - Clinical adverse experiences causing *discontinuation*

- Unless otherwise specified the most common adverse experiences were defined as those reported in at least 10% of patients in the overall population.
- Safety data are displayed by "treatment group" or by "dose level."
  - **Treatment group** is defined by the *initial* dosage and schedule to which a patient was assigned. Therefore, an individual patient listed on this table will appear once under a single dosage and schedule column.
  - **Dose level** is defined as the *actual* dosage and schedule that a patient received at any point during the study. Therefore, depending on the number of dose modifications a patient may have experienced, an individual patient listed on this table could appear under 2 or more dose and schedule columns.
- In the Vorinostat Monotherapy CTCL and CTCL stage IIB and Higher Populations, 4 patients in Protocol 005 were re-enrolled and participated in 2 dosing cohorts. In terms of the total number of assigned patients and the total number of patient exposures, safety data displays by treatment groups include the 4 re-enrolled patients; displays by dose level do not include these patients.

## Vorinostat Monotherapy – CTCL

A total of 107 patients with CTCL were enrolled in this population and the total patient exposure to Vorinostat was 111 patients. The table summarizes the total number of patients assigned to a dose and schedule and total number of patient exposures by dose and schedule.

**Table 68. Number of Patients and Number of Patient Exposures by Dose and Schedule (Applicant's Table)**

| | 400 mg QD continuous | 300 mg BID 3/7 | 200 mg BID continuous | Doses above MTD | Doses below MTD | Total |
|---|---|---|---|---|---|---|
| Total patients exposed to a dose and schedule[†] | 86 | 14 | 10 | 20 | 12 | 107[§] |
| Total patient assigned to a dose and schedule[‡] | 87 | 12 | -------- | 12 | -------- | 111[§] |

[†] Data displayed by dose level. A patient may be counted under 1 or more dose and schedules.
[‡] Data displayed by treatment group. A patient is counted only once under a dose and schedule.
[§] Four patients from Protocol 001 and Protocol 005 participated in 2 dosing cohorts.

[Ref. 5.3.5.2: P001, P005]

## Summary of Safety Outcomes – Clinical Adverse Experiences

The following table summarizes the outcomes of clinical adverse experience for 111 CTCL patients who received Vorinostat monotherapy.

- 106 (95.5%) patients had ≥ 1 clinical adverse experiences
  - 104 of these (98%) had adverse experiences considered *related to study drug* (by the Investigator)
- Eighteen (18) of 111 patients (16.2%) discontinued study medication due to adverse experiences
  - Thirteen (13) discontinued due to *drug-related* adverse experiences
- 30 of 111 patients (27.0%) reported serious adverse experiences
  - 17 patients reported serious *drug-related* adverse experiences
- Eleven (11) of 111 patients (9.9%) discontinued Vorinostat due to *serious* adverse experiences
  - Seven (7) patients (6.3%) discontinued Vorinostat due to *serious drug-related* adverse experiences

- The proportion of patients discontinuing due to clinical adverse experiences was lower in the cohort that received Vorinostat at a dose of 400 mg once daily (11.5%) compared to the other treatment cohorts (33.3%)
- Three (3) deaths were reported in patients who received Vorinostat at a dose of 400 mg once daily

**Table 69. Clinical Adverse Experience Summary (Vorinostat Monotherapy – CTCL) (Applicant's Table)**

| | 400mg QD continuous (N = 87) | | 300mg BID 3/7 (N = 12) | | Doses above MTD[3] (N = 12) | | Total (N = 111) | |
|---|---|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) | n | (%) |
| Number (%) of patients: | | | | | | | | |
| With one or more adverse experiences | 82 | (94.3) | 12 | (100) | 12 | (100) | 106 | (95.5) |
| With no adverse experience | 5 | (5.7) | 0 | (0.0) | 0 | (0.0) | 5 | (4.5) |
| With drug-related adverse experiences[2] | 80 | (92.0) | 12 | (100) | 12 | (100) | 104 | (93.7) |
| With serious adverse experiences | 19 | (21.8) | 6 | (50.0) | 5 | (41.7) | 30 | (27.0) |
| With serious drug-related adverse experiences[2] | 10 | (11.5) | 4 | (33.3) | 3 | (25.0) | 17 | (15.3) |
| Who died | 3 | (3.4) | 1 | (8.3) | 1 | (8.3) | 5 | (4.5) |
| Discontinued due to adverse experiences | 10 | (11.5) | 4 | (33.3) | 4 | (33.3) | 18 | (16.2) |
| Discontinued due to drug-related adverse experiences[2] | 8 | (9.2) | 3 | (25.0) | 2 | (16.7) | 13 | (11.7) |
| Discontinued due to serious adverse experiences | 7 | (8.0) | 1 | (8.3) | 3 | (25.0) | 11 | (9.9) |
| Discontinued due to serious drug-related adverse experiences[2] | 5 | (5.7) | 1 | (8.3) | 1 | (8.3) | 7 | (6.3) |

[1] Data are displayed by treatment group
[2] Determined by the Investigator to be possibly, probably or definitely drug-related.
[3] Maximum tolerated doses for CTCL patients were 400 mg once daily and 300 mg twice daily 3 out of 7 days.

[Ref. 5.3.5.2: P001, P005]

## Summary of Safety Outcomes – Laboratory Adverse Experiences

The following table summarizes the outcomes of laboratory adverse experiences in patients with CTCL who received Vorinostat monotherapy and who had at least 1 laboratory test post-baseline.

- Thirty-eight (38) of 111 patients (34%) had 1 or more laboratory adverse experience
  - Thirty (30) had laboratory adverse experiences which were considered *related* to study drug by the Investigator
- One serious laboratory adverse experience of Grade 3—an increase in blood creatinine—was considered by the Investigator to be related to the study therapy. (This laboratory adverse experience *met the serious criteria due to hospitalization* of the patient that was a part of a more complex clinical picture, and *not due to creatinine level itself*).
- No patients in this population were discontinued due to laboratory adverse experiences.
- In patients who received Vorinostat at a dose of 400 mg once daily, 27 of 87 patients (31%) had 1 or more laboratory adverse experience post-baseline
  - Twenty-two (22) had laboratory adverse experiences considered *related* to study drug by the Investigator. The serious drug-related laboratory experience described above being included in this treatment group.

**Table 70. Laboratory Adverse Experience Summary (Vorinostat Monotherapy – CTCL) (Applicant's Table)**

| | 400mg QD continuous (N = 87) | | 300mg BID 3/7 (N = 12) | | Doses above MTD[3] (N = 12) | | Total (N = 111) | |
|---|---|---|---|---|---|---|---|---|
| | n | (%)[4] | n | (%)[4] | n | (%)[4] | n | (%)[4] |
| Number (%) of patients: | | | | | | | | |
| With at least one lab test post-baseline | 87 | | 12 | | 12 | | 111 | |
| With one or more adverse experiences | 27 | (31.0) | 7 | (58.3) | 4 | (33.3) | 38 | (34.2) |
| With no adverse experience | 60 | (69.0) | 5 | (41.7) | 8 | (66.7) | 73 | (65.8) |
| With drug-related adverse experiences[2] | 22 | (25.3) | 5 | (41.7) | 3 | (25.0) | 30 | (27.0) |
| With serious adverse experiences | 2 | (2.3) | 0 | (0.0) | 0 | (0.0) | 2 | (1.8) |
| With serious drug-related adverse experiences[2] | 1 | (1.1) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| Who died | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| Discontinued due to adverse experiences | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| Discontinued due to drug-related adverse experiences[2] | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| Discontinued due to serious adverse experiences | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| Discontinued due to serious drug-related adverse experiences[2] | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |

[1] Data are displayed by treatment group.
[2] Determined by the Investigator to be possibly, probably or definitely drug-related
[3] The percent = number of patients within the laboratory adverse experience category / number of patients with one or more laboratory tests post-baseline.
[4] Maximum tolerated doses for CTCL patients were 400 mg once daily and 300 mg twice daily 3 out of 7 days

[Ref. 5.3.5.2: P001, P005]

**Summary Comparison of Adverse Experiences**

Clinical adverse experiences, *regardless of grade*, occurring in at least 20% of patients in the CTCL population on Vorinostat monotherapy:

- Fatigue 61.7%
- Diarrhea 53.3%
- Nausea 48.6%
- Dysgeusia 36.4%
- Thrombocytopenia 30.8%
- Anorexia 26.2%
- Weight decreased 23.4%
- Dry mouth 20.6%

**Dose Comparison within the CTCL Population**

87 patients were assigned to a dose of 400 mg once daily and 86 were exposed to this dose
14 patients received Vorinostat at a dose of 300 mg twice daily for 3 out of 7 days
10 patients received Vorinostat at a dose of 200 mg twice daily
20 patients received doses of Vorinostat above the MTD
12 patients received doses of Vorinostat below the MTD

- Overall, when compared to the 400 mg once daily dose, the safety profile was similar for all other doses of Vorinostat studied in this population
- Grade 1 and 2 clinical adverse experiences occurred most frequently

- Dysgeusia and fatigue adverse experiences were common to all doses
- Thrombocytopenia was observed in all doses of Vorinostat except 300 mg twice daily 3 out of 7 days
- Anemia was noted only in the 300 mg twice daily, 3 out of 7 days dose
- Dehydration was observed in the 200 mg twice daily dose and at doses above MTD

- No laboratory adverse experiences were noted in the 200 mg twice daily continuous dose
- Increased blood creatinine was observed in all other doses
- Prolonged prothrombin time was observed in the 300 mg twice daily 3 out of 7 days dose and at doses above the MTD
- The majority of these adverse experiences were considered by Investigators to be related to study therapy

- Similar Grade 3 and Grade 4 clinical adverse experiences, the majority of which were considered related to Vorinostat by the Investigators, occurred in all doses—although generally the incidence was lower.
- Grade 3 and 4 thromboembolic events occurred in patients who were receiving 400 mg once daily and 300 mg twice daily 3 out of 7 days
- Drug-related Grade 4 hepatic ischemia was reported in 1 patient at doses above the MTD.

- These adverse experiences were considered by the Investigators to be related to study drug and in most instances resulted in discontinuation of study therapy.
- Grade 3 and Grade 4 laboratory adverse experiences were observed only at doses above the MTD.
- The median time to onset of the first drug-related Grade 3, 4, or 5 clinical adverse experiences was 17 days and 28 days in the 300 mg twice daily 3 out of 7 days dose and doses above MTD, respectively, compared to 41 days in the 400 mg once daily dose.
- The duration of these adverse experiences was similar across all doses.
- Dose modification occurred in all doses as a result of adverse experiences. The frequency of dose modifications was similar across all doses. The time to the first adverse experience resulting in dose modification was similar in the 400 mg once daily dose and the 300 mg twice daily 3 out of 7 days dose; this was 41 and 46 days, respectively.
- In doses above the MTD the time to the first adverse experience resulting in dose modification was 17 days.

**Dose Analyses in the CTCL Population**

**400 mg Once Daily**

The following table summarizes the incidence of adverse experiences that occurred in the 86 patients who received Vorinostat at a dose of 400 mg once daily.
In the majority of patients, these adverse experiences were considered by the Investigators to be related to study drug.

The *most common clinical* adverse experiences at this dose, occurring in at least 20% of patients:

- Fatigue 52.3%
- Diarrhea 52.3%
- Nausea 40.7%
- Dysgeusia 27.9%
- Thrombocytopenia 24.4%
- Anorexia 24.4%

The *most common laboratory* adverse experience occurring in at least 10% of patients was an increased blood creatinine (14.0%)

*Grade 3 and Grade 4 clinical* adverse experiences occurring in at least 2% of patients at this dose were:

- Thrombocytopenia 4.7%
- Fatigue 3.5%
- Nausea 3.5%
- Anemia 2.3%
- Anorexia 2.3%
- Muscle spasms 2.3%

No *Grade 3 or Grade 4 laboratory* adverse experiences were reported in this dose.

**Table 71. Summary of Specific Clinical or Laboratory Adverse Experiences by Preferred Term (400 mg Once Daily; Incidence ≥10% in One or More Dose Levels) (Applicant's Table)**

| | 400mg QD continuous (N=86) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | All Experiences | | | | Related Experiences Only | | | |
| | All Grades | | Grade 3-5 | | All Grades | | Grade 3-5 | |
| | n | % | n | % | n | % | n | % |
| Fatigue | 45 | (52.3) | 3 | (3.5) | 39 | (45.3) | 2 | (2.3) |
| Diarrhoea | 45 | (52.3) | 0 | (0.0) | 40 | (46.5) | 0 | (0.0) |
| Nausea | 35 | (40.7) | 3 | (3.5) | 33 | (38.4) | 3 | (3.5) |
| Dysgeusia | 24 | (27.9) | 0 | (0.0) | 20 | (23.3) | 0 | (0.0) |
| Thrombocytopenia | 21 | (24.4) | 4 | (4.7) | 21 | (24.4) | 4 | (4.7) |
| Anorexia | 21 | (24.4) | 2 | (2.3) | 20 | (23.3) | 2 | (2.3) |
| Weight Decreased | 17 | (19.8) | 1 | (1.2) | 16 | (18.6) | 1 | (1.2) |
| Dry Mouth | 14 | (16.3) | 0 | (0.0) | 14 | (16.3) | 0 | (0.0) |
| Vomiting | 13 | (15.1) | 1 | (1.2) | 10 | (11.6) | 0 | (0.0) |
| Anaemia | 13 | (15.1) | 2 | (2.3) | 12 | (14.0) | 2 | (2.3) |
| Blood Creatinine Increased | 12 | (14.0) | 0 | (0.0) | 10 | (11.6) | 0 | (0.0) |
| Chills | 14 | (16.3) | 1 | (1.2) | 9 | (10.5) | 1 | (1.2) |
| Cough | 9 | (10.5) | 0 | (0.0) | 3 | (3.5) | 0 | (0.0) |
| Alopecia | 15 | (17.4) | 0 | (0.0) | 13 | (15.1) | 0 | (0.0) |
| Constipation | 13 | (15.1) | 0 | (0.0) | 9 | (10.5) | 0 | (0.0) |
| Decreased Appetite | 11 | (12.8) | 1 | (1.2) | 9 | (10.5) | 1 | (1.2) |
| Muscle Spasms | 15 | (17.4) | 2 | (2.3) | 14 | (16.3) | 2 | (2.3) |
| Dizziness | 12 | (14.0) | 1 | (1.2) | 5 | (5.8) | 1 | (1.2) |
| Oedema Peripheral | 9 | (10.5) | 0 | (0.0) | 2 | (2.3) | 0 | (0.0) |

| | 400mg QD continuous (N=86) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | All Experiences | | | | Related Experiences Only | | | |
| | All Grades | | Grade 3-5 | | All Grades | | Grade 3-5 | |
| | n | % | n | % | n | % | n | % |
| Upper Respiratory Tract Infection | 9 | (10.5) | 0 | (0.0) | 2 | (2.3) | 0 | (0.0) |
| Headache | 10 | (11.6) | 0 | (0.0) | 5 | (5.8) | 0 | (0.0) |
| Pruritus | 10 | (11.6) | 1 | (1.2) | 1 | (1.2) | 0 | (0.0) |

A patient is counted only once within a specific preferred term, even if more than one adverse experience with specific preferred term occurred.
Adverse experience terms are from MedDRA Version 8.1.

[Ref. 5.3.5.2: P001, P005]

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**300 mg Twice Daily 3 Out of 7 Days**

Fourteen (14) patients received Vorinostat at a dose of 300 mg twice daily for 3 out of 7 days.

The most common *clinical* adverse experiences at this dose, occurring in at least 20% of patients:

- Nausea 57.1%
- Fatigue 50.0%
- Diarrhea 42.9%
- Dysgeusia 42.9%
- Cough 42.9%
- Pyrexia 35.7%
- Additionally, anorexia, decreased weight, vomiting, anemia, decreased appetite, urinary tract infection, and deep vein thrombosis (each) were reported in 21.4%

The most common *laboratory* adverse experience:

- Increased blood creatinine 15.4%

In the majority of patients, these adverse experiences, with the exception of cough and pyrexia, were considered by the Investigators to be related to the study drug.

*Grade 3 and Grade 4* clinical adverse experiences that occurred at this dose:

- Deep vein thrombosis 21.4% (3/14)
- Pulmonary embolism 14.3% (2/14)
- Pyrexia 14.3%
- Additionally Grade 3 and 4 fatigue, anemia, chest pain, hypotension, neutropenia, diarrhea, drug eruption, febrile neutropenia, hallucination, and pain (each) occurred with frequency of 7.1% (1/14)

*Grade 3* laboratory adverse experiences:

- 2 patients had coagulation function tests performed: 1 patient (50.0%) had a Grade 3 decreased INR, and 1 patient (50.0%) reported a Grade 3 prolonged prothrombin time

In the majority of patients these clinical adverse experiences were considered by the Investigators to be related to study drug.

**200 mg Twice Daily**

Ten (10) patients received Vorinostat at a dose of 200 mg twice daily

The most common *clinical* adverse experiences in this dose group, occurring in at least 20% of patients:

- Thrombocytopenia 70.0%
- Fatigue 30.0%
- Dysgeusia 20.0%
- Dry mouth 20.0%
- Dehydration 20.0%

No *laboratory* adverse experiences were reported at this dose
In the majority of patients, these clinical adverse experiences were considered by the Investigators to be related to study drug.

*Grade 3 and 4* clinical adverse experiences that occurred at this dose:

- Thrombocytopenia 40.0% (4/10)
- Dehydration 20.0%
- Sepsis, syncope, polyneuropathy, and subdural hematoma (each) occurred at a frequency of 10%

In the majority of patients, these clinical adverse experiences were considered by Investigators to be related to study drug.

**Doses above the MTD**

Twenty (20) patients received Vorinostat at a dose above the MTD.

The *most common clinical* adverse experiences at this dose, occurring in at least 20% of patients, were:

- Fatigue 70.0%
- Thrombocytopenia 70.0%
- Nausea 60.0%
- Diarrhea 55.0%
- Dysgeusia 45.0%
- Dry mouth 40.0%
- Vomiting 35.0%
- Decreased weight, chills, asthenia, and dehydration (each) occurred at a frequency of 20%

*Laboratory* adverse experiences occurring in at least 10% of the patients at this dose:

- Increased blood creatinine 4 of 20 patients (20%)
- Increased alkaline phosphatase 2 of 20 patients (10%)
- Increased INR 1 patient (who had this test at this dose)

In the majority of patients, these adverse experiences were considered by the Investigators to be related to study drug.

*Grade 3 and 4 clinical* adverse experiences that occurred at this dose were:

- Thrombocytopenia 25% (5/20)
- Anemia, dehydration, nausea, pyrexia, sepsis, asthenia, hypotension, vomiting, dyspnea, erectile dysfunction, hepatic ischemia, hypertension, reduced oral intake, and wound infection (each) occurred at a frequency of 5% (1/20)

*Grade 3 and 4 laboratory* adverse experiences:

- Increased blood creatinine 1 of 20 patients (5%)
- Increased INR 1 patient who had this test at this dose

Adverse experiences considered by the Investigators to be *drug-related*:

- Grade 3 thrombocytopenia in 4 patients
- Grade 4 thrombocytopenia in 1 patient
- Grade 4 hepatic ischemia in 1 patient
- Grade 4 dehydration in 1 patient
- Grade 3 erectile dysfunction in 1 patient

**Onset and Duration of First Grade 3, 4, or 5 Clinical Adverse Experiences (by dose)**

The table below summarizes the onset and duration of the first Grade 3, 4, or 5 clinical adverse experiences in the patients on Vorinostat monotherapy for CTCL by dose

**400 mg once daily**

- 24 of 87 patients (27.6%) reported *drug-related* adverse experiences ≥ *Grade 3*
- The **median time to onset** for the first Grade 3, 4, or 5 clinical adverse experiences was 41 days (range, 1 to 185 days)
- The **median duration** was 14 days (range, 1 to 172 days)

**300 mg twice daily 3 days out of 7**

- 5 of 12 patients (41.7%) reported drug-related adverse experiences ≥ Grade 3

- The **median time to onset** for the first Grade 3, 4, or 5 clinical adverse experiences was 28 days (range, 5 to 58 days)
- The **median duration** was 12 days (range 2 to 32+ days)

**Doses above the MTD**

- 7 of 12 patients (58.3%) reported drug-related adverse experiences ≥ Grade 3
- The **median time to onset** for the first Grade 3, 4, or 5 clinical adverse experiences was 17 days (range, 10 to 109 days)
- The **median duration** was 8 days (range 1 to 30+ days)

**Table 72. Time to Onset and Duration of First Grade 3, 4 or 5 Clinical Adverse Experiences (Vorinostat Monotherapy – CTCL) (Applicant's Table)**

| | 400mg QD continuous (N=87) | | 300mg BID 3/7 (N=12) | | Doses above MTD[2] (N=12) | |
|---|---|---|---|---|---|---|
| | Drug-related | Overall[1] | Drug-related | Overall | Drug-related | Overall |
| Patients with Grade 3 or 4 Clinical Adverse Experience, n(%) | 24(27.6%) | 31(35.6%) | 5(41.7%) | 7(58.3%) | 7(58.3%) | 7(58.3%) |
| Patients with Grade 5 Clinical Adverse Experience, n(%) | 1(1.1%) | 2(2.3%) | 0(0.0%) | 0(0.0%) | 0(0.0%) | 0(0.0%) |
| Time to Onset of First Grade 3, 4 or 5 Clinical Adverse Experience (days) | | | | | | |
| Mean | 62.3 | 54.5 | 29.6 | 19.0 | 37.0 | 23.0 |
| SD | 55.34 | 48.86 | 23.75 | 20.67 | 35.46 | 16.65 |
| Median | 41.0 | 41.0 | 28.0 | 8.0 | 17.0 | 15.0 |
| Range | 1 - 185 | 1 - 185 | 5 - 58 | 2 - 58 | 10 - 109 | 10 - 50 |
| Duration of the First Grade 3 or 4 Clinical Adverse Experience (days)[1] | | | | | | |
| Median | 14.0 | 10.0 | 12.0 | 12.0 | 8.0 | 8.0 |
| Range | 1 - 172 | 1 - 114+ | 2 - 32+ | 1 - 43+ | 3 - 30+ | 1 - 128+ |

[1] Data are displayed by treatment group.
[2] Patients with ongoing adverse experiences are censored at date of last therapy + 30 days.
[3] Maximum tolerated doses for CTCL patients were 400 mg once daily and 300 mg twice daily 3 out of 7 days
SD = Standard Deviation
+: ongoing

[Ref. 5.3.5.2: P001, P005]

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**Adverse Experiences Resulting in Dose Modification**

The following table summarizes the number of adverse experiences resulted in dose modifications in the CTCL population in three dose categories. *(How many dose modifications in each dose category?)*

**Vorinostat monotherapy at a dose of 400 mg once daily**

- 76 of 87 patients (87.4%) **did not require** dose modification
- Two (2) patients (2.3%) **required** 2 or more dose modifications
- The median time to the first adverse experience resulting in dose modification was 41 days (range, 17 to 85 days)

**Vorinostat monotherapy at a dose of 300 mg twice daily 3 out of 7 days**

- 11 of 12 patients (91.7%) **did not require** dose modification
- One (1) patient at this dose **required** multiple dose modifications beginning on Study Day 46

**Vorinostat at doses above the MTD**

- Eleven (11) of 12 patients (91.7%) **did not require** dose modification
- One (1) of 12 patients (8.3%) **required** multiple dose modifications beginning on Study Day 17

**Table 73. Summary of Dose Modifications on Treatment with Vorinostat due to Adverse Experiences (Vorinostat Monotherapy – CTCL) (Applicant's Table)**

| Dose Modifications[1] | 400mg QD continuous (N=87) | 300mg BID 3/7 (N=12) | Doses above MTD[2] (N=12) |
|---|---|---|---|
| Number (%) of patients with | | | |
| one dose modification | 9 (10.3%) | 0 (0.0%) | 0 (0.0%) |
| two or more dose modifications | 2 (2.3%) | 1 (8.3%) | 1 (8.3%) |
| no dose modifications | 76 (87.4%) | 11 (91.7%) | 11 (91.7%) |
| Time to first AE resulting in a dose modification (days) | | | |
| Median (Range) | 41 (17, 85) | 46 (46, 46) | 17 (17, 17) |

[1] Data are displayed by treatment group.
[2] Maximum tolerated doses for CTCL patients were 400 mg once daily and 300 mg twice daily 3 out of 7 days.

[Ref. 5.3.5.2: P001, P005]

**Clinical and Laboratory Adverse Experiences Resulting in Vorinostat Dose Modifications**

The following two tables summarize the clinical and laboratory adverse experiences, respectively, in the CTCL population that resulted in dose modifications in the three dose categories. *(Tables show the name of the clinical or laboratory AE and its frequency in each dose category.)*

**Vorinostat at 400 mg once daily**

- In the 86 patients assigned to a dose of Vorinostat at 400 mg once daily, adverse experiences resulting in dose modification were **thrombocytopenia** in 3 patients (3.5%) and **nausea** in 2 patients (2.3%).
- In addition, **vomiting, decreased appetite, hypokalemia,** and **increased blood creatinine** resulted in dose modifications and were reported in 1.2% of patients
- Grades of AEs: All adverse experiences, with 2 exceptions, that resulted in dose modification were Grade 3. The 2 exceptions were Grade 2 thrombocytopenia in 1 patient and Grade 2 increased blood creatinine.

**Vorinostat at 300 mg twice daily 3 out of 7 days and 200 mg twice daily**

- In patients assigned to a dose of 300 mg twice daily 3 out of 7 days and 200 mg twice daily, no adverse experiences were reported that resulted in dose modification.

**Vorinostat at doses above the MTD**

- At doses above the MTD, the clinical adverse experience of Grade 2 **fatigue** was reported in 2 of 20 patients (10%)
- Adverse experiences occurring at an incidence of 5% were: Grade 4 **thrombocytopenia**, Grade 2 **gastrointestinal disorder**, Grade 1 **decreased weight**, and Grade 2 **dysgeusia**.
- No laboratory adverse experiences resulted in dose modifications in this group.

## Table 74. Number (%) of Patients with Specific Clinical Adverse Experiences by System Organ Class (Incidence > 0% in One or More Dose Levels) resulting in Dose Modification (Vorinostat Monotherapy – CTCL) (Applicant's Table)

| | 400mg QD continuous (N=86) | | 300mg BID 3/7 (N=14) | | 200mg BID continuous (N=10) | | doses above MTD (N=20) | | doses below MTD (N=12) | | Total Patients (N=107) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % | n | % | n | % |
| *Patients With One Or More Clinical Adverse Experiences* | 5 | (5.8) | 0 | (0.0) | 0 | (0.0) | 3 | (15.0) | 1 | (8.3) | 12 | (11.2) |
| *Patients With No Clinical Adverse Experiences* | 78 | (90.7) | 14 | (100) | 10 | (100) | 17 | (85.0) | 11 | (91.7) | 95 | (88.8) |
| **Blood And Lymphatic System Disorders** | **5** | **(5.8)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(5.0)** | **0** | **(0.0)** | **6** | **(5.6)** |
| Thrombocytopenia | 3 | (3.5) | 0 | (0.0) | 0 | (0.0) | 1 | (5.0) | 0 | (0.0) | 4 | (3.7) |
| *Grade 2* | 1 | (1.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| *Grade 3* | 2 | (2.3) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 2 | (1.9) |
| *Grade 4* | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (5.0) | 0 | (0.0) | 1 | (0.9) |
| Leukopenia | 1 | (1.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| *Grade 3* | 1 | (1.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| Neutropenia | 1 | (1.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| *Grade 4* | 1 | (1.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| **Gastrointestinal Disorders** | **2** | **(2.3)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(5.0)** | **0** | **(0.0)** | **3** | **(2.8)** |
| Nausea | 2 | (2.3) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 2 | (1.9) |
| *Grade 3* | 2 | (2.3) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 2 | (1.9) |
| Gastrointestinal Disorder | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (5.0) | 0 | (0.0) | 1 | (0.9) |
| *Grade 2* | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (5.0) | 0 | (0.0) | 1 | (0.9) |
| Vomiting | 1 | (1.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| *Grade 3* | 1 | (1.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| **General Disorders And Administration Site Conditions** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **2** | **(10.0)** | **0** | **(0.0)** | **2** | **(1.9)** |
| Fatigue | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 2 | (10.0) | 0 | (0.0) | 2 | (1.9) |
| *Grade 2* | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 2 | (10.0) | 0 | (0.0) | 2 | (1.9) |
| **Investigations** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(5.0)** | **0** | **(0.0)** | **1** | **(0.9)** |
| Weight Decreased | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (5.0) | 0 | (0.0) | 1 | (0.9) |
| *Grade 1* | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (5.0) | 0 | (0.0) | 1 | (0.9) |
| **Metabolism And Nutrition Disorders** | **2** | **(2.3)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **2** | **(1.9)** |
| Decreased Appetite | 1 | (1.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| *Grade 3* | 1 | (1.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| Hypokalaemia | 1 | (1.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| *Grade 3* | 1 | (1.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| **Nervous System Disorders** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(5.0)** | **1** | **(8.3)** | **2** | **(1.9)** |
| Dysgeusia | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (5.0) | 0 | (0.0) | 1 | (0.9) |
| *Grade 2* | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (5.0) | 0 | (0.0) | 1 | (0.9) |
| Lethargy | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (8.3) | 1 | (0.9) |
| *Grade 2* | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (8.3) | 1 | (0.9) |
| **Psychiatric Disorders** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(8.3)** | **1** | **(0.9)** |
| Confusional State | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (8.3) | 1 | (0.9) |
| *Grade 3* | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (8.3) | 1 | (0.9) |

A patient is counted only once within a System Organ Class category, even if more than one adverse experience with specific preferred terms occurred. Only the highest grade of a given adverse experience is counted per dose level for the individual patient.
Adverse experience terms are from MedDRA Version 8.1.

[Ref. 5.3.5.2: P001, P005]

**Table 75. Number (%) of Patients with Specific Laboratory Adverse Experiences by Laboratory Test Category (Incidence > 0% in One or More Dose Levels) resulting in Dose Modification (Vorinostat Monotherapy – CTCL) (Applicant's Table)**

| | 400mg QD continuous (N=86) | | 300mg BID 3/7 (N=14) | | 200mg BID continuous (N=10) | | doses above MTD (N=20) | | doses below MTD (N=12) | | Total Patients (N=107) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n/m | % | n/m | % | n/m | % | n/m | % | n/m | % | n/m | % |
| *Patients With One Or More Laboratory Adverse Experiences* | *1/86* | *(1.2)* | *0/13* | *(0.0)* | *0/10* | *(0.0)* | *0/20* | *(0.0)* | *0/12* | *(0.0)* | *1/107* | *(0.9)* |
| *Patients With No Laboratory Adverse Experiences* | *85/86* | *(98.8)* | *13/13* | *(100)* | *10/10* | *(100)* | *20/20* | *(100)* | *12/12* | *(100)* | *106/107* | *(99.1)* |
| Blood Chemistry Test | 1/86 | (1.2) | 0/13 | (0.0) | 0/10 | (0.0) | 0/20 | (0.0) | 0/12 | (0.0) | 1/107 | (0.9) |
| Blood Creatinine Increased | 1/86 | (1.2) | 0/13 | (0.0) | 0/10 | (0.0) | 0/20 | (0.0) | 0/12 | (0.0) | 1/107 | (0.9) |
| *Grade 2* | *1/86* | *(1.2)* | *0/13* | *(0.0)* | *0/10* | *(0.0)* | *0/20* | *(0.0)* | *0/12* | *(0.0)* | *1/107* | *(0.9)* |

n/m = number of patients with laboratory adverse experiences / number of patients for whom the laboratory test was recorded post-baseline.
A patient is counted only once within a Laboratory Test Type Category, even if more than one adverse experience with specific preferred terms occurred. Only the highest grade of a given adverse experience is counted per dose level for the individual patient.

[Ref. 5.3.5.2: P001, P005]

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**Adverse Experiences Resulting in Discontinuations**

The first of the following two tables shows the clinical adverse experiences that resulted in discontinuation of study medication and the second provides details of those patients who discontinued due to drug-related clinical adverse experiences. In addition, brief patient narratives are provided for those patients who discontinued due to non-serious adverse experiences.

**Vorinostat 400 mg once daily (n = 86)**

- Eight (8) patients (9.3%) discontinued study medication due to adverse experiences
- 6 (75.0%) of these discontinued Vorinostat for *drug-related* clinical adverse experiences

The *drug-related* clinical adverse experiences resulting in study drug discontinuation:

- Grade 4 deep vein thrombosis
- Grade 2 chest pain
- Grade 5 death
- Grade 2 angioneurotic edema
- Grade 4 pulmonary embolism
- Grade 3 anemia
- One (1) patient, AN1008 (Protocol 001), was discontinued due to a Grade 4 ischemic stroke while receiving Vorinostat 300 mg once daily. The patient initially received 59 days of Vorinostat at a dose of 400 mg once daily prior to requiring dose reduction for Grade 3 thrombocytopenia.

**Vorinostat 300 mg twice daily 3 out of 7 days (n = 14)**

- 4 of 14 patients (28.6%) discontinued study medication due to adverse experiences
- 3 of these 4 (75.0%) discontinued for *drug-related* clinical adverse experiences

The drug-related clinical adverse experiences resulting in study drug discontinuation:

- Grade 3 pulmonary embolism
- Grade 2 fatigue
- Grade 3 drug eruption

**Vorinostat 200 mg twice daily (n = 10)**

- 3 of 10 patients (30.0%) discontinued study medication due to adverse experiences
- 2 of these 3 (67.0%) discontinued for drug-related clinical adverse experiences

The drug-related clinical adverse experiences resulting in study drug discontinuation:

- Grade 3 polyneuropathy
- Grade 3 thrombocytopenia

**Vorinostat at doses above MTD**

- No patients discontinued due to clinical adverse experiences

**Table 76. Number (%) of Patients who Discontinued Vorinostat (Monotherapy in CTCL) due to Specific Clinical Adverse Experiences by System Organ Class (Incidence >0% in One or More Dose Levels) (Applicant's Table)**

| | 400mg QD continuous (N=86) | | 300mg BID 3/7 (N=14) | | 200mg BID continuous (N=10) | | doses above MTD (N=20) | | doses below MTD (N=12) | | Total Patients (N=107) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % | n | % | n | % |
| *Patients With One Or More Clinical Adverse Experiences* | 8 | (9.3) | 4 | (28.6) | 3 | (30.0) | 0 | (0.0) | 3 | (25.0) | 17 | (15.9) |
| *Patients With No Clinical Adverse Experiences* | 78 | (90.7) | 10 | (71.4) | 7 | (70.0) | 20 | (100) | 9 | (75.0) | 90 | (84.1) |
| **Blood And Lymphatic System Disorders** | 1 | (1.2) | 0 | (0.0) | 1 | (10.0) | 0 | (0.0) | 0 | (0.0) | 2 | (1.9) |
| Anaemia | 1 | (1.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| *Grade 3* | 1 | (1.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| Thrombocytopenia | 0 | (0.0) | 0 | (0.0) | 1 | (10.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| *Grade 3* | 0 | (0.0) | 0 | (0.0) | 1 | (10.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| **General Disorders And Administration Site Conditions** | 1 | (1.2) | 2 | (14.3) | 2 | (20.0) | 0 | (0.0) | 1 | (8.3) | 5 | (4.7) |
| Asthenia | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (8.3) | 1 | (0.9) |
| *Grade 3* | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (8.3) | 1 | (0.9) |
| Chest Pain | 1 | (1.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| *Grade 2* | 1 | (1.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| Death | 1 | (1.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| *Grade 5* | 1 | (1.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| Fatigue | 0 | (0.0) | 1 | (7.1) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| *Grade 3* | 0 | (0.0) | 1 | (7.1) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| Pyrexia | 0 | (0.0) | 1 | (7.1) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| *Grade 1* | 0 | (0.0) | 1 | (7.1) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |

| | 400mg QD continuous (N=86) | | 300mg BID 3/7 (N=14) | | 200mg BID continuous (N=10) | | doses above MTD (N=20) | | doses below MTD (N=12) | | Total Patients (N=107) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % | n | % | n | % |
| **Injury, Poisoning And Procedural Complications** | 1 | (1.2) | 0 | (0.0) | 1 | (10.0) | 0 | (0.0) | 0 | (0.0) | 2 | (1.9) |
| Spinal Cord Injury | 1 | (1.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| *Grade 3* | 1 | (1.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| Subdural Hematoma | 0 | (0.0) | 0 | (0.0) | 1 | (10.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| *Grade 3* | 0 | (0.0) | 0 | (0.0) | 1 | (10.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| **Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)** | 0 | (0.0) | 0 | (0.0) | 1 | (10.0) | 0 | (0.0) | 1 | (8.3) | 2 | (1.9) |
| T-Cell Lymphoma | 0 | (0.0) | 0 | (0.0) | 1 | (10.0) | 0 | (0.0) | 1 | (8.3) | 2 | (1.9) |
| *Grade 2* | 0 | (0.0) | 0 | (0.0) | 1 | (10.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| *Grade 4* | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (8.3) | 1 | (0.9) |
| **Nervous System Disorders** | 0 | (0.0) | 0 | (0.0) | 1 | (10.0) | 0 | (0.0) | 2 | (16.7) | 3 | (2.8) |
| Ischaemic Stroke | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (8.3) | 1 | (0.9) |
| *Grade 4* | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (8.3) | 1 | (0.9) |
| Lethargy | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (8.3) | 1 | (0.9) |
| *Grade 3* | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (8.3) | 1 | (0.9) |
| Polyneuropathy | 0 | (0.0) | 0 | (0.0) | 1 | (10.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| *Grade 3* | 0 | (0.0) | 0 | (0.0) | 1 | (10.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| **Respiratory, Thoracic And Mediastinal Disorders** | 1 | (1.2) | 1 | (7.1) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 2 | (1.9) |
| Pulmonary Embolism | 1 | (1.2) | 1 | (7.1) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 2 | (1.9) |
| *Grade 3* | 0 | (0.0) | 1 | (7.1) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| *Grade 4* | 1 | (1.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |

| | 400mg QD continuous (N=86) | | 300mg BID 3/7 (N=14) | | 200mg BID continuous (N=10) | | doses above MTD (N=20) | | doses below MTD (N=12) | | Total Patients (N=107) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % | n | % | n | % |
| **Skin And Subcutaneous Tissue Disorders** | 2 | (2.3) | 1 | (7.1) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 3 | (2.8) |
| Angioneurotic Oedema | 1 | (1.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| *Grade 2* | 1 | (1.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| Dermatitis Exfoliative | 1 | (1.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| *Grade 3* | 1 | (1.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| Drug Eruption | 0 | (0.0) | 1 | (7.1) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| *Grade 3* | 0 | (0.0) | 1 | (7.1) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| **Vascular Disorders** | 1 | (1.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| Deep Vein Thrombosis | 1 | (1.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| *Grade 4* | 1 | (1.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |

A patient is counted only once within a System Organ Class category, even if more than one adverse experience with specific preferred terms occurred. Only the highest grade of a given adverse experience is counted per dose level for the individual patient.
Adverse experience terms are from MedDRA Version 8.1

[Ref. 5.3.5.2: P001, P005]

- No patients discontinued due to clinical adverse experiences

**Table 76. Number (%) of Patients who Discontinued Vorinostat (Monotherapy in CTCL) due to Specific Clinical Adverse Experiences by System Organ Class (Incidence >0% in One or More Dose Levels) (Applicant's Table)**

| | 400mg QD continuous (N=86) | | 300mg BID 3/7 (N=14) | | 200mg BID continuous (N=10) | | doses above MTD (N=20) | | doses below MTD (N=12) | | Total Patients (N=107) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % | n | % | n | % |
| *Patients With One Or More Clinical Adverse Experiences* | 8 | (9.3) | 4 | (28.6) | 3 | (30.0) | 0 | (0.0) | 3 | (25.0) | 17 | (15.9) |
| *Patients With No Clinical Adverse Experiences* | 78 | (90.7) | 10 | (71.4) | 7 | (70.0) | 20 | (100) | 9 | (75.0) | 90 | (84.1) |
| **Blood And Lymphatic System Disorders** | 1 | (1.2) | 0 | (0.0) | 1 | (10.0) | 0 | (0.0) | 0 | (0.0) | 2 | (1.9) |
| Anaemia | 1 | (1.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| *Grade 3* | 1 | (1.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| Thrombocytopenia | 0 | (0.0) | 0 | (0.0) | 1 | (10.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| *Grade 2* | 0 | (0.0) | 0 | (0.0) | 1 | (10.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| **General Disorders And Administration Site Conditions** | 2 | (2.3) | 2 | (14.3) | 0 | (0.0) | 0 | (0.0) | 1 | (8.3) | 5 | (4.7) |
| Asthenia | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (8.3) | 1 | (0.9) |
| *Grade 3* | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (8.3) | 1 | (0.9) |
| Chest Pain | 1 | (1.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| *Grade 2* | 1 | (1.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| Death | 1 | (1.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| *Grade 5* | 1 | (1.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| Fatigue | 0 | (0.0) | 1 | (7.1) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| *Grade 2* | 0 | (0.0) | 1 | (7.1) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| Pyrexia | 0 | (0.0) | 1 | (7.1) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| *Grade 3* | 0 | (0.0) | 1 | (7.1) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |

| | 400mg QD continuous (N=86) | | 300mg BID 3/7 (N=14) | | 200mg BID continuous (N=10) | | doses above MTD (N=20) | | doses below MTD (N=12) | | Total Patients (N=107) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % | n | % | n | % |
| **Injury, Poisoning And Procedural Complications** | 1 | (1.2) | 0 | (0.0) | 1 | (10.0) | 0 | (0.0) | 1 | (8.3) | 2 | (1.9) |
| Spinal Cord Injury | 1 | (1.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| *Grade 3* | 1 | (1.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| Subdural Haematoma | 0 | (0.0) | 0 | (0.0) | 1 | (10.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| *Grade 3* | 0 | (0.0) | 0 | (0.0) | 1 | (10.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| **Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)** | 0 | (0.0) | 0 | (0.0) | 1 | (10.0) | 0 | (0.0) | 1 | (8.3) | 2 | (1.9) |
| T-Cell Lymphoma | 0 | (0.0) | 0 | (0.0) | 1 | (10.0) | 0 | (0.0) | 1 | (8.3) | 2 | (1.9) |
| *Grade 2* | 0 | (0.0) | 0 | (0.0) | 1 | (10.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| *Grade 4* | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (8.3) | 1 | (0.9) |
| **Nervous System Disorders** | 0 | (0.0) | 0 | (0.0) | 1 | (10.0) | 0 | (0.0) | 2 | (16.7) | 3 | (2.8) |
| Ischaemic Stroke | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (8.3) | 1 | (0.9) |
| *Grade 4* | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (8.3) | 1 | (0.9) |
| Lethargy | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (8.3) | 1 | (0.9) |
| *Grade 3* | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (8.3) | 1 | (0.9) |
| Polyneuropathy | 0 | (0.0) | 0 | (0.0) | 1 | (10.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| *Grade 3* | 0 | (0.0) | 0 | (0.0) | 1 | (10.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| **Respiratory, Thoracic And Mediastinal Disorders** | 1 | (1.2) | 1 | (7.1) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 2 | (1.9) |
| Pulmonary Embolism | 1 | (1.2) | 1 | (7.1) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 2 | (1.9) |
| *Grade 3* | 0 | (0.0) | 1 | (7.1) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| *Grade 4* | 1 | (1.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |

| | 400mg QD continuous (N=86) | | 300mg BID 3/7 (N=14) | | 200mg BID continuous (N=10) | | doses above MTD (N=20) | | doses below MTD (N=12) | | Total Patients (N=107) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % | n | % | n | % |
| **Skin And Subcutaneous Tissue Disorders** | 2 | (2.3) | 1 | (7.1) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 3 | (2.8) |
| Angioneurotic Oedema | 1 | (1.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| *Grade 2* | 1 | (1.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| Dermatitis Exfoliative | 1 | (1.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| *Grade 3* | 1 | (1.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| Drug Eruption | 0 | (0.0) | 1 | (7.1) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| *Grade 3* | 0 | (0.0) | 1 | (7.1) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| **Vascular Disorders** | 1 | (1.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| Deep Vein Thrombosis | 1 | (1.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| *Grade 4* | 1 | (1.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |

A patient is counted only once within a System Organ Class category, even if more than one adverse experience with specific preferred terms occurred. Only the highest grade of a given adverse experience is counted per dose level for the individual patient.
Adverse experience terms are from MedDRA Version 8.1

[Ref. 5.3.5.2: P001, P005]

**Table 77. Details of Patients who Discontinued Vorinostat Monotherapy due to Drug-Related Clinical Adverse Experiences by Dose Level (Applicant's Table)**

| Study Number | AN | Gender | Race | Age | Period | Rel Day of AE Onset | Adverse Experience | Duration of AE | Rel Day of Drug Discon | Toxicity Grade | Serious | Drug Relation | Action Taken | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **400mg QD continuous** | | | | | | | | | | | | | | |
| 683001 | 1035 | F | black | 42 | Treatment | 56 | Deep Vein Thrombosis | 15 days | 56 | 4 | Y | poss | discontinued PRx | recovered |
| | 1046 | M | white | 63 | Treatment | 29 | Chest Pain | 36 days | 43 | 2 | N | poss | discontinued PRx | recovered |
| | 1048 | F | black | 46 | Treatment | 2 | Death | 1 day | 2 | 5 | Y | poss | discontinued PRx | fatal |
| | 1057 | M | white | 67 | Treatment | 27 | Angioneurotic Oedema | 2 days | 27 | 2 | N | prob | discontinued PRx | recovered |
| | 1059 | M | white | 64 | Treatment | 185 | Pulmonary Embolism | | 185 | 4 | Y | poss | discontinued PRx | not recovered |
| 683005 | 1010 | F | white | 82 | Trt Cycle 2 | 43 | Anaemia | 1 day | 31 | 3 | Y | poss | discontinued PRx | recovered |
| **300mg BID 3/7** | | | | | | | | | | | | | | |
| 683005 | 1017 | F | white | 74 | Trt Cycle 3 | 50 | Pulmonary Embolism | 11 days | 50 | 5 | Y | poss | discontinued PRx | recovered |
| | 1020 | F | white | 69 | Trt Cycle 1 Wk 2 | 8 | Fatigue | | 58 | 2 | N | poss | discontinued PRx | not recovered |
| | 1025 | M | white | 58 | Trt Cycle 1 Wk 1 | 8 | Drug Eruption | 4 days | 8 | 3 | N | poss | discontinued PRx | recovered |
| **200mg BID continuous** | | | | | | | | | | | | | | |
| 683005 | 1032 | M | white | 49 | Trt Cycle 3 | 50 | Polyneuropathy | | 49 | 3 | N | poss | discontinued PRx | not recovered |
| | 1036 | F | white | 75 | Trt Cycle 2 | 26 | Thrombocytopenia | 2 days | 26 | 3 | Y | def | discontinued PRx | recovered |
| **doses below MTD** | | | | | | | | | | | | | | |
| 683001 | 1008 | F | white | 71 | Treatment | 227 | Ischaemic Stroke | 30 days | 227 | 4 | Y | poss | discontinued PRx | fatal |
| | 1044 | M | white | 82 | Treatment | 187 | Asthenia | | 189 | 3 | N | poss | discontinued PRx | not recovered |

| Study Number | AN | Gender | Race | Age | Period | Rel Day of AE Onset | Adverse Experience | Duration of AE | Rel Day of Drug Discon | Toxicity Grade | Serious | Drug Relation | Action Taken | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **doses below MTD** | | | | | | | | | | | | | | |
| 683001 | 1044 | M | white | 83 | Treatment | 187 | Lethargy | | 189 | 3 | N | poss | discontinued PRx | not recovered |

AN = Allocation number
def = Definitely; def not = Definitely not; poss = Possibly; prob = Probably; prob not = Probably not
PRx = prime therapy
Adverse experience terms are from MedDRA Version 8.1.
[Ref. 5.3.5.2: P001, P005]

Three (3) patients in the Vorinostat Monotherapy – CTCL Population discontinued Vorinostat due to *non-serious* clinical adverse experiences:

- AN1046 (Protocol 001) began Vorinostat at 400 mg once daily. On Study Day 29 a non-serious adverse experience of Grade 2 chest pain was reported. This adverse experience was considered by the Investigator to be possible related to the study drug. The patient discontinued study medication on Study Day 43. The adverse experience was reported as resolved on Study Day 64.
- AN1020 (Protocol 005) began Vorinostat 300 mg twice daily for 3 out of 7 days. On Study Day 8 a non-serious adverse experience of Grade 2 fatigue was reported. This episode persisted and as a result study medication was discontinued on Study Day 58. The adverse experience was considered by the Investigator to be possible related to study drug. A post-study visit occurred on Study Day 86 at which time the patient continued to report Grade 2 fatigue.
- AN1032 (Protocol 005) began Vorinostat 300 mg twice daily for 14 out of 21 days. On Study Day 22, the patient's dose was changed, per protocol, to 200 mg twice daily. A non-serious adverse experience of Grade 3 polyneuropathy was reported on Study Day 50 and the patient discontinued study medication at that time. This adverse experience was considered by the Investigator to be possible related to study therapy. A post-study visit occurred on Study Day 64 at which time the patient continued to report Grade 3 polyneuropathy. ***(Reviewer Comments:*** *Because grade 3 polyneuropathy interferes with activities of daily living, and is persistent in the above case, the reviewer believes that makes this a SAE rather than non-serious AE)*

## Vorinostat Monotherapy – CTCL Stage IIB and Higher

A total of 93 patients with CTCL Stage IIB and higher were in this population. As this population is a subset of the Vorinostat Monotherapy – CTCL Population.

## Summary of Safety Outcomes – Clinical and Laboratory Adverse Experiences

The following table summarizes the *clinical* adverse experience outcomes for 93 patients in this population.

- Ninety (90) of 93 patients (96.8%) had 1 or more clinical adverse experiences.
  - 88 patients had adverse experiences that were considered by the Investigator to be *related* to the study drug.
  - Twenty-eight (28) adverse experiences were considered to be *serious*
    - Sixteen (16) were considered by the Investigator to be both serious and drug-related

- Sixteen (16) of 93 patients (17.2%) were *discontinued* from the study due to clinical adverse experiences
- Twelve (12) of these adverse experiences were considered by the Investigator to be *drug-related*
- Seven (7) patients discontinued due to *serious drug-related* adverse experiences

- Five (5) deaths were reported in this population

- The proportion of patients with clinical adverse experiences was slightly less in those who received Vorinostat at 400mg once daily (95.8%) compared to the other treatment groups (100.0%)
- Three (3) deaths were reported in patients who received Vorinostat at a dose of 400 mg once daily.

**Table 78. Clinical Adverse Experience Summary (Vorinostat Monotherapy – CTCL Stage IIB and Higher) (Applicant's Table)**

| | 400mg QD continuous (N = 72) | | 300mg BID 3/7 (N = 11) | | Doses above MTD[3] (N = 10) | | Total (N = 93) | |
|---|---|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) | n | (%) |
| Number (%) of patients: | | | | | | | | |
| With one or more adverse experiences | 69 | (95.8) | 11 | (100) | 10 | (100) | 90 | (96.8) |
| With no adverse experience | 3 | (4.2) | 0 | (0.0) | 0 | (0.0) | 3 | (3.2) |
| With drug-related adverse experiences[1] | 67 | (93.1) | 11 | (100) | 10 | (100) | 88 | (94.6) |
| With serious adverse experiences | 18 | (25.0) | 6 | (54.5) | 4 | (40.0) | 28 | (30.1) |
| With serious drug-related adverse experiences[1] | 10 | (13.8) | 4 | (36.4) | 2 | (20.0) | 16 | (17.2) |
| Who died | 3 | (4.2) | 1 | (9.1) | 1 | (10.0) | 5 | (5.4) |
| Discontinued due to adverse experiences | 9 | (12.5) | 3 | (27.3) | 4 | (40.0) | 16 | (17.2) |
| Discontinued due to drug-related adverse experiences[1] | 8 | (11.1) | 2 | (18.2) | 2 | (20.0) | 12 | (12.9) |
| Discontinued due to serious adverse experiences | 6 | (8.3) | 1 | (9.1) | 3 | (30.0) | 10 | (10.8) |
| Discontinued due to serious drug-related adverse experiences[1] | 5 | (6.9) | 1 | (9.1) | 1 | (10.0) | 7 | (7.5) |

[2] Data are displayed by treatment group.
[1] Determined by the Investigator to be possibly, probably or definitely drug-related.
[3] Maximum tolerated doses for CTCL Stage IIB and higher patients were 400 mg once daily, continuously and 300 mg twice daily 3 of 7 days.

[Ref. 5.3.5.2: P001, P005]

**Laboratory adverse experiences**

The table below summarizes the *laboratory* adverse experience outcomes in the patients with CTCL Stage IIB and higher who received Vorinostat monotherapy and who had at least 1 laboratory test performed post-baseline.

- Thirty-three (33) patients (35.5%) had at least 1 or more laboratory adverse experiences and 26 (28.0%) had laboratory adverse experiences considered by the Investigator to be *related* to the study drug. One (1) laboratory adverse experience was considered by the Investigator to be both *serious and drug-related.*
- No patients discontinued study medication due to laboratory adverse experiences.

- In patients administered **Vorinostat 400 mg once daily**, 22 of 72 patients (30.6%) had at least 1 or more laboratory adverse experiences and 18 patients (25.0%) had laboratory adverse experiences considered by the Investigator to be related to study drug.

**Table 79. Laboratory Adverse Experience Summary (Vorinostat Monotherapy – CTCL Stage IIB and Higher) (Applicant's Table)**

| | 400mg QD continuous[1] (N = 72) | | 300mg BID 3/7[1] (N = 11) | | Doses above MTD[1] (N = 10) | | Total (N = 93) | |
|---|---|---|---|---|---|---|---|---|
| | n | (%)[2] | n | (%)[2] | n | (%)[2] | n | (%)[2] |
| Number (%) of patients | | | | | | | | |
| With at least one lab test post-baseline | 72 | | 11 | | 10 | | 93 | |
| With one or more adverse experiences | 22 | (30.6) | 7 | (63.6) | 4 | (40.0) | 33 | (35.5) |
| With no adverse experience | 50 | (69.4) | 4 | (36.4) | 6 | (60.0) | 60 | (64.5) |
| With drug-related adverse experiences[3] | 18 | (25.0) | 5 | (45.5) | 3 | (30.0) | 26 | (28.0) |
| With serious adverse experiences | 2 | (2.8) | 0 | (0.0) | 0 | (0.0) | 2 | (2.2) |
| With serious drug-related adverse experiences[3] | 1 | (1.4) | 0 | (0.0) | 0 | (0.0) | 1 | (1.1) |
| Who died | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| Discontinued due to adverse experiences | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| Discontinued due to drug-related adverse experiences[3] | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| Discontinued due to serious adverse experiences | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| Discontinued due to serious drug-related adverse experiences[3] | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |

[1] Data are displayed by treatment group.
[2] Determined by the Investigator to be possibly, probably or definitely drug-related
[3] The percent = number of patients within the laboratory adverse experience category / number of patients with one or more laboratory tests post-baseline.
[4] Maximum tolerated doses for CTCL Stage IIB and higher patients were 400 mg once daily, continuously and 300 mg twice daily 3 of 7 days.

[Ref. 5.3.5.2: P001, P005]

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**Summary Comparison of Adverse Experiences**

*Clinical* adverse experiences, regardless of grade, occurring in at least 20% of patients in the CTCL Stage IIB or Higher population who received Vorinostat monotherapy:

- Fatigue 65.2%
- Diarrhea 57.3%
- Nausea 50.6%
- Dysgeusia 38.2%
- Thrombocytopenia 29.2%
- Anorexia 25.8%
- Weight decreased 24.7%
- Vomiting 20.2%

- 72 patients were assigned to a dose of 400 mg once daily and 71 patients were exposed to Vorinostat at this dose
- 13 patients received 300 mg twice daily 3 out of 7 days
- 8 patients received 200 mg twice daily

- There were 17 patients exposures to the doses **above** the MTD and 12 exposures to the doses **below** the MTD

***Reviewer Comments:*** *No meaningful differences in the clinical or laboratory adverse experience profile were noted in this subset of patients with CTCL Stage IIB and Higher when compared to patients in the Vorinostat Monotherapy – CTCL Population*

**Dose Analyses in the CTCL Stage IIB and Higher Population**

**400 mg Once Daily (n = 72)**

The table below summarizes the incidence of adverse experiences that occurred in the 71 patients who received Vorinostat monotherapy at a dose of 400 mg once daily. The most common *clinical* adverse experiences (all grades) occurring in at least 20% of patients:

- Fatigue 57.7%
- Diarrhea 56.3%
- Nausea 40.8%
- Dysgeusia 31.0%
- Thrombocytopenia 22.5% (16)
- Anorexia 23.9%

The most common *laboratory* adverse experience (all grades) occurring in at least 10% of patients:

- Increased blood creatinine in 14.1% (10)

In the majority of patients, these adverse experiences were considered by the Investigators to be *related* to the study drug.

Grade 3 and 4 *clinical* adverse experiences occurring in at least 2% of patients:

- Thrombocytopenia 5.6% (4)
- Fatigue 4.2%
- Nausea 4.2%
- Anemia 2.8%
- Muscle Spasms 2.8%

No Grade 3 or Grade 4 *laboratory* adverse experiences were reported at this dose

In the majority of patients, these adverse experiences were considered by the Investigators to be related to the study drug.

**Table 80. Summary of Specific Clinical or Laboratory Adverse Experiences by Preferred Term at 400 mg Once Daily dose level (Incidence ≥10% in One or More Dose Levels) (Applicant's Table)**

| | 400mg QD continuous (N=71) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | All Experiences | | | | Related Experiences Only | | | |
| | All Grades | | Grade 3-5 | | All Grades | | Grade 3-5 | |
| | n | % | n | % | n | % | n | % |
| Fatigue | 41 | (57.7) | 3 | (4.2) | 35 | (49.3) | 2 | (2.8) |
| Diarrhoea | 40 | (56.3) | 0 | (0.0) | 35 | (49.3) | 0 | (0.0) |
| Nausea | 29 | (40.8) | 3 | (4.2) | 28 | (39.4) | 3 | (4.2) |
| Dysgeusia | 22 | (31.0) | 0 | (0.0) | 18 | (25.4) | 0 | (0.0) |
| Thrombocytopenia | 16 | (22.5) | 4 | (5.6) | 16 | (22.5) | 4 | (5.6) |
| Anorexia | 17 | (23.9) | 1 | (1.4) | 16 | (22.5) | 1 | (1.4) |
| Weight Decreased | 14 | (19.7) | 1 | (1.4) | 13 | (18.3) | 1 | (1.4) |
| Vomiting | 10 | (14.1) | 1 | (1.4) | 7 | (9.9) | 0 | (0.0) |
| Blood Creatinine Increased | 10 | (14.1) | 0 | (0.0) | 8 | (11.3) | 0 | (0.0) |
| Chills | 12 | (16.9) | 0 | (0.0) | 7 | (9.9) | 0 | (0.0) |
| Dry Mouth | 11 | (15.5) | 0 | (0.0) | 11 | (15.5) | 0 | (0.0) |
| Anaemia | 10 | (14.1) | 2 | (2.8) | 9 | (12.7) | 2 | (2.8) |
| Constipation | 12 | (16.9) | 0 | (0.0) | 9 | (12.7) | 0 | (0.0) |
| Alopecia | 11 | (15.5) | 0 | (0.0) | 9 | (12.7) | 0 | (0.0) |
| Muscle Spasms | 12 | (16.9) | 2 | (2.8) | 11 | (15.5) | 2 | (2.8) |
| Headache | 9 | (12.7) | 0 | (0.0) | 5 | (7.0) | 0 | (0.0) |
| Pruritus | 8 | (11.3) | 1 | (1.4) | 1 | (1.4) | 0 | (0.0) |

A patient is counted only once within a specific preferred term, even if more than one adverse experience with specific preferred term occurred
Adverse experience terms are from MedDRA Version 8.1.

[Ref. 5.3.5.2: P001, P005]

## Onset and Duration of the First Grade 3, 4, or 5 Clinical Adverse Experiences

The table below summarizes the onset and duration of the first Grade 3, 4, or 5 *clinical* adverse experiences in patients in the Vorinostat monotherapy CTCL Stage IIB and Higher population.

- No meaningful differences were noted when compared to the Vorinostat Monotherapy – CTCL population.

### Table 81. Onset and Duration of First Grade 3, 4 or 5 Clinical Adverse Experiences (Vorinostat Monotherapy – CTCL Stage IIB and Higher) (Applicant's Table)

| | 400mg QD continuous (N=72) | | 300mg BID 3/7 (N=11) | | Doses above MTD[3] (N=10) | |
|---|---|---|---|---|---|---|
| | Drug Related | Overall | Drug Related | Overall | Drug Related | Overall |
| Patients with Grade 3 or 4 Clinical Adverse Experience, n(%) | 21(29.2%) | 28(38.9%) | 5(45.5%) | 7(63.6%) | 7(70.0%) | 7(70.0%) |
| Patients with Grade 5 Clinical Adverse Experience, n(%) | 1(1.4%) | 2(2.8%) | 0(0.0%) | 0(0.0%) | 0(0.0%) | 0(0.0%) |
| Time to Onset of First Grade 3, 4 or 5 Clinical Adverse Experience (days) | | | | | | |
| Mean | 62.8 | 54.2 | 29.6 | 19.0 | 37.0 | 23.0 |
| SD | 55.21 | 48.03 | 25.75 | 20.67 | 35.46 | 16.65 |
| Median | 42.0 | 42.0 | 28.0 | 8.0 | 17.0 | 15.0 |
| Range | 1 - 185 | 1 - 185 | 5 - 58 | 2 - 58 | 10 - 109 | 10 - 50 |
| Duration of the First Grade 3 or 4 Clinical Adverse Experience (days) [1] | | | | | | |
| Median | 18.0 | 14.0 | 12.0 | 12.0 | 8.0 | 8.0 |
| Range | 1 - 372 | 1 - 114+ | 2 - 32+ | 1 - 43+ | 1 - 30+ | 1 - 128+ |

[1] Data are displayed by treatment group.
[2] Patients with ongoing adverse experiences are censored at date of last therapy + 30 days.
[3] Maximum tolerated doses for CTCL Stage IIB and higher patients were 400 mg once daily and 300 mg twice daily 3 out of 7 days.
SD = Standard Deviation
+: ongoing

[Ref. 5.3.5.2: P001, P005]

## Adverse Experiences Resulting in Dose Modification

The next three tables summarize the adverse experiences that resulted in dose modifications. No meaningful differences were noted when compared to the Vorinostat Monotherapy – CTCL population.

**Table 82. Summary of Dose Modifications Due to Adverse Experiences on Vorinostat Monotherapy for CTCL Stage IIB and Higher (Applicant's Table)**

| Dose Modifications | 400mg QD continuous (N=72) | 300mg BID 3/7 (N=11) | Doses above MTD[2] (N=10) |
|---|---|---|---|
| Number (%) of patients with | | | |
| one dose modification | 9 (12.5%) | 0 (0.0%) | 0 (0.0%) |
| two or more dose modifications | 2 (2.8%) | 1 (9.1%) | 1 (10.0%) |
| no dose modifications | 61 (84.7%) | 10 (90.9%) | 9 (90.0%) |
| Time to first AE resulting in a dose modification (days) | | | |
| Median (Range) | 41 (17, 85) | 46 (46, 46) | 17 (17, 17) |

[1] Data are displayed by treatment group.
[2] Maximum tolerated doses for CTCL Stage IIB and higher patients were 400 mg once daily and 300 mg twice daily 3 out of 7 days.

[Ref. 5.3.5.2: P001, P005]

**Table 83. Number (%) of Patients with Specific *Clinical* Adverse Experiences by System Organ Class (Incidence >0% in One or More Dose Levels) resulting in Dose Modification of Vorinostat Monotherapy – CTCL Stage IIB and Higher (Applicant's Table)**

| | 400mg QD continuous (N=71) | | 300mg BID 3/7 (N=13) | | 200mg BID continuous (N=8) | | doses above MTD (N=17) | | doses below MTD (N=13) | | Total Patients (N=88) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % | n | % | n | % |
| *Patients With One Or More Clinical Adverse Experiences* | 5 | (11.3) | 0 | (0.0) | 0 | (0.0) | 3 | (17.6) | 1 | (5.3) | 12 | (13.5) |
| *Patients With No Clinical Adverse Experiences* | 63 | (88.7) | 13 | (100) | 8 | (100) | 14 | (82.4) | 11 | (91.7) | 77 | (86.5) |
| **Blood And Lymphatic System Disorders** | 5 | (7.0) | 0 | (0.0) | 0 | (0.0) | 1 | (5.9) | 0 | (0.0) | 6 | (6.7) |
| Thrombocytopenia | 3 | (4.2) | 0 | (0.0) | 0 | (0.0) | 1 | (5.9) | 0 | (0.0) | 4 | (4.5) |
| *Grade 2* | 1 | (1.4) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.1) |
| *Grade 3* | 2 | (2.8) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 2 | (2.2) |
| *Grade 4* | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (5.9) | 0 | (0.0) | 1 | (1.1) |
| Leukopenia | 1 | (1.4) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.1) |
| *Grade 3* | 1 | (1.4) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.1) |
| Neutropenia | 1 | (1.4) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.1) |
| *Grade 4* | 1 | (1.4) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.1) |
| **Gastrointestinal Disorders** | 2 | (2.8) | 0 | (0.0) | 0 | (0.0) | 1 | (5.9) | 0 | (0.0) | 3 | (3.4) |
| Nausea | 2 | (2.8) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 2 | (2.2) |
| *Grade 3* | 2 | (2.8) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 2 | (2.2) |
| Gastrointestinal Disorder | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (5.9) | 0 | (0.0) | 1 | (1.1) |
| *Grade 2* | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (5.9) | 0 | (0.0) | 1 | (1.1) |
| Vomiting | 1 | (1.4) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.1) |
| *Grade 3* | 1 | (1.4) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.1) |
| **General Disorders And Administration Site Conditions** | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 2 | (11.8) | 0 | (0.0) | 2 | (2.2) |
| Fatigue | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 2 | (11.8) | 0 | (0.0) | 2 | (2.2) |

Table continued …

| | 400mg QD continuous (N=71) | | 300mg BID 3/7 (N=13) | | 200mg BID continuous (N=8) | | doses above MTD (N=17) | | doses below MTD (N=12) | | Total Patients (N=89) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % | n | % | n | % |
| *Grade 2* | *0* | *(0.0)* | *0* | *(0.0)* | *0* | *(0.0)* | *2* | *(11.8)* | *0* | *(0.0)* | *2* | *(2.2)* |
| **Investigations** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(5.9)** | **0** | **(0.0)** | **1** | **(1.1)** |
| Weight Decreased | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (5.9) | 0 | (0.0) | 1 | (1.1) |
| *Grade 1* | *0* | *(0.0)* | *0* | *(0.0)* | *0* | *(0.0)* | *1* | *(5.9)* | *0* | *(0.0)* | *1* | *(1.1)* |
| **Metabolism And Nutrition Disorders** | **2** | **(2.8)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **2** | **(2.2)** |
| Decreased Appetite | 1 | (1.4) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.1) |
| *Grade 3* | *1* | *(1.4)* | *0* | *(0.0)* | *0* | *(0.0)* | *0* | *(0.0)* | *0* | *(0.0)* | *1* | *(1.1)* |
| Hypokalaemia | 1 | (1.4) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.1) |
| *Grade 3* | *1* | *(1.4)* | *0* | *(0.0)* | *0* | *(0.0)* | *0* | *(0.0)* | *0* | *(0.0)* | *1* | *(1.1)* |
| **Nervous System Disorders** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(5.9)** | **1** | **(8.3)** | **2** | **(2.2)** |
| Dysgeusia | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (5.9) | 0 | (0.0) | 1 | (1.1) |
| *Grade 2* | *0* | *(0.0)* | *0* | *(0.0)* | *0* | *(0.0)* | *1* | *(5.9)* | *0* | *(0.0)* | *1* | *(1.1)* |
| Lethargy | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (8.3) | 1 | (1.1) |
| *Grade 2* | *0* | *(0.0)* | *0* | *(0.0)* | *0* | *(0.0)* | *0* | *(0.0)* | *1* | *(8.3)* | *1* | *(1.1)* |
| **Psychiatric Disorders** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(8.3)** | **1** | **(1.1)** |
| Confusional State | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (8.3) | 1 | (1.1) |
| *Grade 3* | *0* | *(0.0)* | *0* | *(0.0)* | *0* | *(0.0)* | *0* | *(0.0)* | *1* | *(8.3)* | *1* | *(1.1)* |

A patient is counted only once within a System Organ Class category, even if more than one adverse experience with specific preferred terms occurred. Only the highest grade of a given adverse experience is counted per dose level for the individual patient.
Adverse experience terms are from MedDRA Version 8.1

[Ref. 5.3.5.2: P001, P005]

**Table 84. Number (%) of Patients with Specific *Laboratory* Adverse Experiences by Laboratory Test Category (Incidence >0% at One or More Dose Levels) resulting in Dose Modification of Vorinostat Monotherapy – CTCL Stage IIB and Higher (Applicant's Table)**

| | 400mg QD continuous (N=71) | | 300mg BID 3/7 (N=13) | | 200mg BID continuous (N=8) | | doses above MTD (N=17) | | doses below MTD (N=12) | | Total Patients (N=89) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n/m | % | n/m | % | n/m | % | n/m | % | n/m | % | n/m | % |
| *Patients With One Or More Laboratory Adverse Experiences* | *1/71* | *(1.4)* | *0/12* | *(0.0)* | *0/8* | *(0.0)* | *0/17* | *(0.0)* | *0/12* | *(0.0)* | *1/89* | *(1.1)* |
| *Patients With No Laboratory Adverse Experiences* | *70/71* | *(98.6)* | *12/12* | *(100)* | *8/8* | *(100)* | *17/17* | *(100)* | *12/12* | *(100)* | *88/89* | *(98.9)* |
| **Blood Chemistry Test** | **1/71** | **(1.4)** | **0/12** | **(0.0)** | **0/8** | **(0.0)** | **0/17** | **(0.0)** | **0/12** | **(0.0)** | **1/89** | **(1.1)** |
| Blood Creatinine Increased | 1/71 | (1.4) | 0/12 | (0.0) | 0/8 | (0.0) | 0/17 | (0.0) | 0/12 | (0.0) | 1/89 | (1.1) |
| *Grade 3* | *1/71* | *(1.4)* | *0/12* | *(0.0)* | *0/8* | *(0.0)* | *0/17* | *(0.0)* | *0/12* | *(0.0)* | *1/89* | *(1.1)* |

n/m = number of patients with laboratory adverse experiences / number of patients for whom the laboratory test was recorded post baseline.
A patient is counted only once within a Laboratory Test Type Category, even if more than one adverse experience with specific preferred terms occurred. Only the highest grade of a given adverse experience is counted per dose level for the individual patient.

[Ref. 5.3.5.2: P001, P005]

## Adverse Experiences Resulting in Discontinuation

The following table provides the details of the patients with CTCL (stages IIB or higher) who discontinued study medication due to *clinical* adverse experiences.

**Table 85. Details of Patients who Discontinued Vorinostat Monotherapy (CTCL Stage IIB or Higher) due to Drug-related Clinical Adverse Experiences by Dose Level (Applicant's Table)**

| Study Number | AN | Gender | Race | Age | Period | Rel Day of AE Onset | Adverse Experience | Duration of AE | Rel Day of Drug Discon | Toxicity Grade | Serious | Drug Relation | Action Taken | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **400mg QD continuous** | | | | | | | | | | | | | | |
| 683001 | 1015 | F | black | 42 | Treatment | 56 | Deep Vein Thrombosis | 15 days | 56 | 4 | Y | poss | discontinued PRx | recovered |
| | 1046 | M | white | 53 | Treatment | 29 | Chest Pain | 36 days | 45 | 2 | N | poss | discontinued PRx | recovered |
| | 1048 | F | black | 46 | Treatment | 2 | Death | 1 day | 2 | 5 | Y | poss | discontinued PRx | fatal |
| | 1057 | M | white | 67 | Treatment | 27 | Angioneurotic Oedema | 2 days | 27 | 2 | N | prob | discontinued PRx | recovered |
| | 1059 | M | white | 64 | Treatment | 185 | Pulmonary Embolism | | 185 | 4 | Y | poss | discontinued PRx | not recovered |
| 683005 | 1010 | F | white | 82 | Trt Cycle 2 | 43 | Anaemia | 1 day | 31 | 3 | Y | poss | discontinued PRx | recovered |
| **300mg BID 3/7** | | | | | | | | | | | | | | |
| 683006 | 1017 | F | white | 74 | Trt Cycle 3 | 50 | Pulmonary Embolism | 11 days | 50 | 3 | Y | poss | discontinued PRx | recovered |
| | 1025 | M | white | 58 | Trt Cycle 1 Wk 1 | 8 | Drug Eruption | 4 days | 8 | 3 | N | poss | discontinued PRx | recovered |
| **200mg BID continuous** | | | | | | | | | | | | | | |
| 683005 | 1032 | M | white | 49 | Trt Cycle 3 | 58 | Polyneuropathy | | 49 | 3 | N | poss | discontinued PRx | not recovered |
| | 1036 | F | white | 75 | Trt Cycle 2 | 26 | Thrombocytopenia | 2 days | 26 | 3 | Y | def | discontinued PRx | recovered |

| Study Number | AN | Gender | Race | Age | Period | Rel Day of AE Onset | Adverse Experience | Duration of AE | Rel Day of Drug Discon | Toxicity Grade | Serious | Drug Relation | Action Taken | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **doses below MTD** | | | | | | | | | | | | | | |
| 683001 | 1008 | F | white | 71 | Treatment | 227 | Ischaemic Stroke | 30 days | 227 | 4 | Y | poss | discontinued PRx | fatal |
| | 1044 | M | white | 83 | Treatment | 187 | Asthenia | | 189 | 3 | N | poss | discontinued PRx | not recovered |
| | | | | | | | Lethargy | | 189 | 3 | N | poss | discontinued PRx | not recovered |

AN = Allocation number
def = Definitely, def not = Definitely not, poss = Possibly, prob = Probably, prob not = Probably not
PRx = prime therapy
Adverse experience terms are from MedDRA Version 8.1.

[Ref. 5.3.5.2: P001, P005]

**Vorinostat Monotherapy – Solid Tumors**

- Patient population = 101
- Exposures = 101

The following table summarizes the total number of patients and total number of patient exposures by dose and schedule.

**Table 86. Number of Patients and Number of Patient Exposures by Dose and Schedule (Applicant's Table)**

| | 400 mg QD continuous | 300 mg BID 3/7 | 200 mg BID continuous | 200 mg BID 14/21 | Doses above MTD | Doses below MTD | Total |
|---|---|---|---|---|---|---|---|
| Total patients exposed to a dose and schedule[1] | 45 | 16 | 8 | 6 | 38 | 15 | 101 |
| Total patients assigned to a dose and schedule[2] | 40 | 13 | 4 | -------- | 38 | 6 | 101 |

[1] Data displayed by dose level. A patient may be counted under 1 or more dose and schedules.
[2] Data displayed by treatment group. A patient is counted only once under a dose and schedule.

[Ref. 5.3.3.2: P008] [Ref. 5.3.5.4: P002, P006, P011V1]

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## Summary of Safety Outcomes—Clinical Adverse Experiences

The following table summarizes *clinical* adverse experience outcomes for 101 patients who received Vorinostat monotherapy in this population (solid tumors).

- All patients (100.0%) had at least 1 or more clinical adverse experiences.
- 97 (96.0%) patients had clinical adverse experiences considered by the Investigator to be related to study drug, including 17 patients (16.8%) who had *serious* adverse experiences.
- Ten (10) deaths were reported in this population.

### Table 87. Clinical Adverse Experience Summary (Vorinostat Monotherapy – Solid Tumors) (Applicant's Table)

| | Total (N = 101) | |
|---|---|---|
| | n | (%) |
| Number (%) of patients: | | |
| With one or more adverse experiences | 101 | (100.0) |
| With no adverse experience | 0 | ( 0.0) |
| With drug-related adverse experiences[2] | 97 | ( 96.0) |
| With serious adverse experiences | 47 | ( 46.5) |
| With serious drug-related adverse experiences [2] | 17 | ( 16.8) |
| Who died | 10 | ( 9.9) |
| Discontinued due to adverse experiences | 19 | ( 18.8) |
| Discontinued due to drug-related adverse experiences[2] | 13 | ( 12.9) |
| Discontinued due to serious adverse experiences | 10 | ( 9.9) |
| Discontinued due to serious drug-related adverse experiences[2] | 6 | ( 5.9) |

[1] Data are displayed by treatment group.
[2] Determined by the investigator to be possibly, probably or definitely drug related
[3] Maximum tolerated doses for solid tumor patients were 400 mg once daily, 300 mg twice daily 3 out of 7 days, and 200 mg twice daily.

[Ref. 5.3.3.2: P008] [Ref. 5.3.5.4: P002, P006, P011V1]

| | 400mg QD continuous (N = 40) | | 300mg BID 3/7 (N = 13) | | 200mg BID continuous (N = 4) | | doses above MTD[3] (N = 38) | | doses below MTD (N = 6) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) |
| Number (%) of patients: | | | | | | | | | | |
| With one or more adverse experiences | 40 | ( 100) | 13 | ( 100) | 4 | ( 100) | 38 | ( 100) | 6 | ( 100) |
| With no adverse experience | 0 | ( 0.0) | 0 | ( 0.0) | 0 | ( 0.0) | 0 | ( 0.0) | 0 | ( 0.0) |
| With drug-related adverse experiences[2] | 37 | (92.5) | 12 | ( 100) | 4 | ( 100) | 37 | (97.4) | 6 | ( 100) |
| With serious adverse experiences | 10 | (25.0) | 7 | (53.8) | 0 | ( 0.0) | 25 | (65.8) | 5 | (83.3) |
| With serious drug-related adverse experiences[2] | 4 | (10.0) | 0 | ( 0.0) | 0 | ( 0.0) | 13 | (34.2) | 0 | ( 0.0) |
| Who died | 1 | ( 2.5) | 1 | ( 7.7) | 0 | ( 0.0) | 7 | (18.4) | 1 | (16.7) |
| Discontinued due to adverse experiences | 5 | (12.5) | 0 | ( 0.0) | 0 | ( 0.0) | 14 | (36.8) | 0 | ( 0.0) |
| Discontinued due to drug-related adverse experiences[2] | 4 | (10.0) | 0 | ( 0.0) | 0 | ( 0.0) | 9 | (23.7) | 0 | ( 0.0) |
| Discontinued due to serious adverse experiences | 1 | ( 2.5) | 0 | ( 0.0) | 0 | ( 0.0) | 9 | (23.7) | 0 | ( 0.0) |
| Discontinued due to serious drug-related adverse experiences[2] | 1 | ( 2.5) | 0 | ( 0.0) | 0 | ( 0.0) | 5 | (13.2) | 0 | ( 0.0) |

### 400 mg once daily cohort (n = 40)

- Incidence of serious drug-related adverse experiences = 4 (10%)
- Discontinued due to drug-related adverse experiences = 4 (10%)
- Discontinued due to a serious drug-related adverse experiences = 1 (2.5%)
- Death = 1 (2.5%)

## Summary of Safety Outcomes—Laboratory Adverse Experiences

The following table summarizes *laboratory* adverse experiences outcomes in patients with solid tumors who received Vorinostat monotherapy and who had at least 1 post-baseline laboratory test.

- 69 of these 101 patients (68.3%) had at least one laboratory adverse experience
  - 65 had a laboratory adverse experience that was considered by the Investigator to be related to study drug. (A majority of clinical and laboratory adverse experiences in patients with solid tumor were considered by the Investigator to be related to study drug).
- 38 of 101 patients (37.6%) in this population were treated at doses above the MTD
- The proportion of patients with drug-related laboratory adverse experiences was similar for those administered 400 mg once daily compared to those administered doses that exceeded the MTD

**Table 88. Laboratory Adverse Experience Summary (Vorinostat Monotherapy – Solid Tumor) (Applicant's Table)**

| | 400mg QD continuous (N = 40) | | 300mg BID 3/7 (N = 13) | | 200mg BID continuous (N = 4) | | doses above MTD[4] (N = 38) | | doses below MTD (N = 6) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n | (%)[1] | n | (%)[1] | n | (%)[1] | n | (%)[1] | n | (%)[1] |
| Number (%) of patients: | | | | | | | | | | |
| With at least one lab test post baseline | 40 | | 13 | | 4 | | 38 | | 6 | |
| With one or more adverse experiences | 25 | (62.5) | 13 | (100.0) | 4 | (100.0) | 21 | (55.3) | 6 | (100.0) |
| With no adverse experience | 15 | (37.5) | 0 | (0.0) | 0 | (0.0) | 17 | (44.7) | 0 | (0.0) |
| With drug-related adverse experiences[2] | 23 | (57.5) | 12 | (92.3) | 4 | (100.0) | 21 | (55.3) | 5 | (83.3) |
| With serious adverse experiences | 1 | (2.5) | 0 | (0.0) | 0 | (0.0) | 2 | (5.3) | 0 | (0.0) |
| With serious drug-related adverse experiences[2] | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 2 | (5.3) | 0 | (0.0) |
| Who died | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| Discontinued due to adverse experiences | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.6) | 0 | (0.0) |
| Discontinued due to drug-related adverse experiences[2] | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.6) | 0 | (0.0) |
| Discontinued due to serious adverse experiences | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| Discontinued due to serious drug-related adverse experiences[2] | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |

| | Total (N = 101) | |
|---|---|---|
| | n | (%)[1] |
| Number (%) of patients: | | |
| With at least one lab test post baseline | 101 | |
| With one or more adverse experiences | 69 | (68.3) |
| With no adverse experience | 32 | (31.7) |
| With drug-related adverse experiences[2] | 65 | (64.4) |
| With serious adverse experiences | 3 | (3.0) |
| With serious drug-related adverse experiences[2] | 2 | (2.0) |
| Who died | 0 | (0.0) |
| Discontinued due to adverse experiences | 1 | (1.0) |
| Discontinued due to drug-related adverse experiences[2] | 1 | (1.0) |
| Discontinued due to serious adverse experiences | 0 | (0.0) |
| Discontinued due to serious drug-related adverse experiences[2] | 0 | (0.0) |

[1] Data are displayed by treatment group.
[2] Determined by the investigator to be possibly, probably or definitely drug related.
[4] Maximum tolerated doses for solid tumor patients were 400 mg once daily, 300 mg twice daily 3 out of 7 days, and 200 mg twice daily.

[Ref. 5.3.3.2: P008] [Ref. 5.3.5.4: P002, P006, P011V1]

**Summary Comparison of Adverse Experiences**

Clinical adverse experiences, *regardless of grade*, occurring in at least 20% of patients in the solid tumor population who received Vorinostat monotherapy:

- Fatigue 81.2%
- Nausea 70.3%
- Anorexia 64.4%
- Vomiting 53.5%
- Hyperglycemia 52.5%
- Increased creatinine 40.6%
- Diarrhea 40.6%
- Constipation 39.6%
- Decreased hemoglobin 38.6%
- Dyspnea 37.6%
- Decreased weight 37.6%
- Abdominal pain 23.8%
- Cough 23.8%
- Thrombocytopenia 23.8%
- Increased AST 22.8%
- Increased alk-phosphatase 22.8%
- Hyponatremia 22.8%
- Back pain 20.8%
- Decreased platelet count 20.8%

**Population Comparison (CTCL vs. Solid Tumor Population)**

- Compared to the CTCL population, a higher proportion of patients in the solid tumor population reported gastrointestinal, constitutional, and metabolic adverse experiences
- Laboratory adverse experiences of decreased hemoglobin, increased blood creatinine, increased AST, and increased alkaline phosphatase were also observed in a higher proportion of patients with solid tumors.
- The incidence of thrombocytopenia was similar in the CTCL and the solid tumor populations
- In the solid tumor population 9 patients experienced thromboembolic events and 2 patients experienced cerebrovascular events

**Dose Comparisons in the Solid Tumor Population**

- Small numbers of patients in dose groups (other than the 400 mg once daily dose group) do not allow a precise comparison across all the doses studied in the solid tumor population; however, the overall safety profile is consistent across doses studied.
- Adverse experiences of fatigue, nausea, vomiting, diarrhea, dehydration, anemia, thrombocytopenia, hyperglycemia, increased blood creatinine were observed at all doses.

- These adverse experiences were noted in a higher proportion of patients who received Vorinostat at doses of 300 mg twice daily, 3 out of 7 days; 200 mg twice daily; and at doses above the MTD.
- Thromboembolic events occurred in patients who received Vorinostat at doses of 400 mg once daily, 300 mg twice daily 3 out of 7 days, at doses above the MTD, and at doses below the MTD.
- No laboratory adverse experiences occurred at a dose of 200 mg twice daily 14 out of 21 days.

- The median time to onset of the first drug-related Grade 3, 4, or 5 clinical adverse experiences was similar for patients who received Vorinostat at doses of 400 mg once daily and for patients who received doses above the MTD. A notably longer time to onset was observed in patients who received Vorinostat at doses of 300 mg twice daily 3 out of 7 days.

- The duration of these adverse experiences after onset was similar across all doses studied.

- The proportion of patients who required dose modification was similar in patients administered Vorinostat at doses of 400 mg once daily, 300 mg twice daily 3 out of 7 days and at doses of 200 mg twice daily.
- Compared to the other doses studied in this population, a lower proportion of patients who received Vorinostat at doses above the MTD required dose modifications.
- The time to the first adverse experience requiring dose modifications was similar across all doses studied.

**Dose Analyses in the Solid Tumor Population**

**400 mg Once Daily (n = 45)**

- In the majority of patients these adverse experiences were considered by the Investigators to be related to study drug.

The following table summarizes the incidence of adverse experiences (all grades) that occurred in the 45 patients who received Vorinostat monotherapy at a dose of 400 mg once daily. The most common *clinical* adverse experiences, occurring in at least 20% of patients in this dose:

- Fatigue 73.3%
- Anorexia 62.2%
- Nausea 57.8%
- Vomiting 42.2%
- Hyperglycemia 42.2%
- Diarrhea 35.6%
- Decreased weight 31.1%
- Thrombocytopenia 28.9%
- Dyspnea 26.7%
- Anemia 26.7%
- Constipation 24.4%

The most common *laboratory* adverse experiences (all grades), occurring in at least 10% of patients at this dose:

- Increased blood creatinine 37.8%
- Increased AST 22.2%
- Decreased hemoglobin 17.8%
- Increased alkaline phosphatase 15.6%
- Increased blood bilirubin 15.6%
- Increased BUN 15.6%
- Decreased platelet count 13.3%
- Increased ALT 11.1%

The most common *Grade 3 and 4 clinical* adverse experiences, occurring in at least 5% of patients in this dose:

- Fatigue 13.3%
- Thrombocytopenia 13.3%
- Anorexia 13.3%
- Hyperglycemia 8.9%
- Nausea 6.7%
- Hyponatremia 6.7%

The most common *Grade 3 and 4 laboratory* adverse experiences, occurring in at least 2% of patients at this dose:

- Increased AST = 2.2%
- Increased alkaline phosphatase = 2.2%
- Increased blood creatinine = 2.2%
- Decreased hemoglobin = 2.2%
- Decreased platelet count = 2.2%

- In the majority of patients these adverse experiences were considered by the Investigators to be related to study drug.

**Table 89. Summary of Specific Clinical or Laboratory Adverse Experiences by Preferred Term—400 mg Once Daily Dose (Incidence ≥10% in One or More Dose Levels) (Applicant's Table)**

| | 400mg QD continuous (N=45) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | All Experiences | | | | Related Experiences Only | | | |
| | All Grades | | Grade 3-5 | | All Grades | | Grade 3-5 | |
| | n | % | n | % | n | % | n | % |
| Fatigue | 33 | (73.3) | 6 | (13.3) | 25 | (55.6) | 5 | (11.1) |
| Nausea | 26 | (57.8) | 3 | (6.7) | 23 | (51.1) | 2 | (4.4) |
| Anorexia | 28 | (62.2) | 6 | (13.3) | 26 | (57.8) | 5 | (11.1) |
| Vomiting | 19 | (42.2) | 1 | (2.2) | 14 | (31.1) | 0 | (0.0) |
| Hyperglycaemia | 19 | (42.2) | 4 | (8.9) | 17 | (37.8) | 4 | (8.9) |
| Blood Creatinine Increased | 17 | (37.8) | 1 | (2.2) | 17 | (37.8) | 1 | (2.2) |
| Diarrhoea | 16 | (35.6) | 0 | (0.0) | 11 | (24.4) | 0 | (0.0) |
| Constipation | 11 | (24.4) | 1 | (2.2) | 7 | (15.6) | 1 | (2.2) |
| Haemoglobin Decreased | 8 | (17.8) | 1 | (2.2) | 8 | (17.8) | 1 | (2.2) |
| Dyspnoea | 12 | (26.7) | 0 | (0.0) | 6 | (13.3) | 0 | (0.0) |
| Weight Decreased | 14 | (31.1) | 1 | (2.2) | 10 | (22.2) | 1 | (2.2) |
| Abdominal Pain | 6 | (13.3) | 2 | (4.4) | 2 | (4.4) | 0 | (0.0) |
| Cough | 7 | (15.6) | 0 | (0.0) | 1 | (2.2) | 0 | (0.0) |
| Thrombocytopenia | 13 | (28.9) | 6 | (13.3) | 13 | (28.9) | 6 | (13.3) |
| Aspartate Aminotransferase Increased | 10 | (22.2) | 1 | (2.2) | 9 | (20.0) | 0 | (0.0) |
| Blood Alkaline Phosphatase Increased | 7 | (15.6) | 1 | (2.2) | 5 | (11.1) | 1 | (2.2) |
| Hyponatraemia | 7 | (15.6) | 3 | (6.7) | 6 | (13.3) | 2 | (4.4) |
| Back Pain | 5 | (11.1) | 2 | (4.4) | 0 | (0.0) | 0 | (0.0) |
| Platelet Count Decreased | 6 | (13.3) | 1 | (2.2) | 5 | (11.1) | 1 | (2.2) |
| Hypokalaemia | 7 | (15.6) | 1 | (2.2) | 5 | (11.1) | 1 | (2.2) |
| Anaemia | 12 | (26.7) | 1 | (2.2) | 12 | (26.7) | 1 | (2.2) |

| | 400mg QD continuous (N=45) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | All Experiences | | | | Related Experiences Only | | | |
| | All Grades | | Grade 3-5 | | All Grades | | Grade 3-5 | |
| | n | % | n | % | n | % | n | % |
| Alanine Aminotransferase Increased | 5 | (11.1) | 0 | (0.0) | 5 | (11.1) | 0 | (0.0) |
| Blood Bilirubin Increased | 7 | (15.6) | 0 | (0.0) | 6 | (13.3) | 0 | (0.0) |
| Dehydration | 5 | (11.1) | 2 | (4.4) | 3 | (6.7) | 2 | (4.4) |
| Alopecia | 6 | (13.3) | 0 | (0.0) | 6 | (13.3) | 0 | (0.0) |
| Dysgeusia | 8 | (17.8) | 0 | (0.0) | 7 | (15.6) | 0 | (0.0) |
| Oedema Peripheral | 5 | (11.1) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| Stomatitis | 6 | (13.3) | 0 | (0.0) | 6 | (13.3) | 0 | (0.0) |
| Blood Urea Increased | 7 | (15.6) | 0 | (0.0) | 7 | (15.6) | 0 | (0.0) |
| Depression | 5 | (11.1) | 0 | (0.0) | 1 | (2.2) | 0 | (0.0) |

A patient is counted only once within a specific preferred term, even if more than one adverse experience with specific preferred term occurred.
Adverse experience terms are from MedDRA Version 8.1.

[Ref. 5.3.3.2: P008] [Ref. 5.3.5.4: P002, P006, P011V1]

**300 mg Twice Daily 3 Out of 7 Days (n = 16)**

The most common *clinical* adverse experiences (all grades) occurring in at least 20% of patients on this dose:

- Fatigue 100.0%
- Hyperglycemia 81.3%
- Nausea 75.0%
- Anorexia 56.3%
- Vomiting 56.3%
- Dyspnea 56.3%
- Hypo-albuminemia 50.0%
- Hypocalcemia 50.0%
- Diarrhea 43.8%
- Constipation 43.8%
- Abdominal pain 43.8%
- Cough 37.5%
- Hyponatremia 31.3%
- Chest pain 31.3%
- Back pain 31.3%
- Hyperkalemia 31.3%
- Decreased weight 25.0%
- Peripheral sensory neuropathy 25.0%
- Upper respiratory tract infection 25.0%

*Laboratory* adverse experiences (all grades) occurring in at least 10% of patients at this dose:

- Decreased hemoglobin 100.0%
- Increased AST 37.5%
- Increased blood creatinine 31.3%
- Increased alkaline phosphatase 31.3%
- Increased ALT 31.3%
- Increased blood bilirubin 25.0%
- Decreased platelet count 25.0%
- Decreased white blood cell count 18.8%
- Prolonged prothrombin time 50.0%
- Prolonged activated partial thromboplastin time 25.0%

With the exceptions of abdominal pain, back pain, chest pain, cough, and increased alkaline phosphatase, the majority of these adverse experiences were considered by the Investigators to be related to study drug.

*Grade 3 and 4 clinical* adverse experiences, occurring in at least 5% of patients in this dose:

- Dyspnea = 25.0%

- Fatigue, hyperglycemia, abdominal pain, constipation, thrombosis, embolism, hyperkalemia, hypoxia, and non-cardiac chest pain (each) = 12.5%
- Dehydration, anorexia, nausea, back pain, cancer pain, vomiting, deep vein thrombosis, chest pain, flank pain, lung disorder, muscle spasms, and myalgia (each) = 6.3%

*Grade 3 laboratory* adverse experience:

- Increased AST = 6.3%

Adverse experiences considered by the Investigators to be related to study drug were fatigue, hyperglycemia, anorexia, nausea, constipation, hyperkalemia, myalgia, and increased AST.

**200 mg Twice Daily (n = 8)**

The most common *clinical* adverse experiences (all grades) occurring in at least 20% of patients at this dose:

- Fatigue = 75.0%
- Nausea, hyperglycemia, and hypo-albuminemia = 62.5%
- Anorexia, diarrhea, decreased weight, and hyperkalemia = 50.0%
- Dyspnea, abdominal pain, cough, hypocalcemia, hyponatremia, pollakiuria, peripheral sensory neuropathy, and alopecia = 37.5%
- Vomiting, pyrexia, back pain, dehydration, muscle spasms, hypernatremia = 25%

*Laboratory* adverse experiences (all grades) occurring in at least 10% of patients at this dose:

- Increased blood creatinine 75.0%
- Decreased platelet count 62.5%
- Decreased hemoglobin 37.5%
- Increased AST 37.5%
- Increased alkaline phosphatase 31.3%
- Increased blood bilirubin 25.0%
- Decreased carbon dioxide 25.0%
- Prolonged prothrombin time 25.0%
- Decreased white blood cell count 18.8%
- Decreased neutrophil count 12.5%
- Increased ALT 12.5%
- Prolonged activated partial thromboplastin time 12.5%

With the exceptions of cough and hyperkalemia, the majority of these adverse experiences were considered by the Investigators to be related to study drug.

*Grade 3 and 4 clinical* adverse experiences occurring in at least 5% of patients at this dose were fatigue, dehydration, hyperglycemia, infection, cough, and muscular weakness, each reported in 12.5% of patients.

*Grade 3 and 4 laboratory* adverse experiences, occurring in at least 5% of patients at this dose, were decreased hemoglobin and decreased platelet count reported in 12.5% of patients.

With the exceptions of dehydration and hyperglycemia, the majority of these adverse experiences were considered by the Investigators to be related to study drug.

**200 mg Twice Daily 14 Out of 21 Days (n = 6)**

*Clinical* adverse experiences (all grades) occurring in at least 20% of patients at this dose:

- Anorexia, anemia, and cancer pain = 66.7%
- Fatigue and nausea = 50.0%
- Vomiting, diarrhea, constipation, dyspnea, decreased weight, thrombocytopenia, pyrexia, headache, asthenia, and general physical health deterioration = 33.3%

No *laboratory* adverse experiences were reported at this dose.

With the exceptions of constipation, dyspnea, pyrexia, headache, cancer pain, and general physical health deterioration, the majority of clinical adverse experiences were considered by the Investigators to be related to study drug.

The most common *Grade 3 and 4 clinical* adverse experiences occurring in at least 5% of patients:

- Anemia = 33.3%
- Asthenia = 33.3%
- Thrombocytopenia, dyspnea, cancer pain, constipation, cerebrovascular accident, general health deterioration, anxiety, neoplasm progression, tumor hemorrhage = 16.7%

With the exceptions of dyspnea, cancer pain, cerebrovascular accident, general physical health deterioration, anxiety, and neoplasm progression the majority of these adverse experiences were considered by the Investigators to be related to study drug.

**Doses above the MTD (n = 38)**

- 28 of 38 patients (73.7%) reported *drug-related* adverse experiences ≥ *Grade 3* and the median time to onset for the first Grade 3, 4, or 5 clinical adverse experiences was 12 days (range, 2 to 467 days)

## Onset and Duration of First Grade 3, 4, and 5 Clinical Adverse Experiences

The following table summarizes the onset and the duration of the first Grade 3, 4, or 5 *clinical* adverse experiences in the patients in the Vorinostat Monotherapy Solid Tumor population.

### 400 mg once daily dose

- Seventeen (17) of 40 patients (42.5%) reported drug related adverse experiences ≥ Grade 3.
- The **median time to onset** for the first Grade 3, 4, or 5 clinical adverse experiences was 19 days (range, 8 to 56 days)
- The **median duration** was 8 days (range, 2 to 58+ days).

### 300 mg twice daily 3 out of 7 days

- Four (4) of 13 patients (30.8%) reported drug-related adverse experiences ≥ Grade 3.
- The **median time to onset** for the first Grade 3, 4, or 5 clinical adverse experiences was 50 days range, 37 to 198 days).
- The **median duration** was 8.5 days (range, 5 to 107 days).

### Above the MTD dose

- 28 of 38 patients (73.7%) reported drug-related adverse experiences ≥ Grade 3.
- The **median time to onset** for the first Grade 3, 4, or 5 clinical adverse experiences was 12 days (range, 2 to 467 days).
- The **median duration** was 8 days (range, 1 to 34+ days).

**Table 90. Time to Onset and Duration of First Grade 3, 4 or 5 Clinical Adverse Experiences (Vorinostat Monotherapy – Solid Tumors) (Applicant's Table)**

| | 400mg QD continuous (N=40) | | 300mg BID 3/7 (N=13) | | 200mg BID continuous (N=4) | | Doses above MTD[3] (N=38) | | Doses below MTD (N=6) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Drug-related | Overall | Drug-related | Overall | Drug-related | Overall | Drug-related | Overall | Drug-related | Overall |
| Patients with Grade 3 or 4 Clinical Adverse Experience, n(%) | 17(42.5%) | 20(50.0%) | 4(30.8%) | 8(61.5%) | 0(0.0%) | 0(0.0%) | 28(73.7%) | 32(84.2%) | 1(16.7%) | 3(50.0%) |
| Patients with Grade 5 Clinical Adverse Experience, n(%) | 0(0.0%) | 1(2.5%) | 0(0.0%) | 1(7.7%) | 0(0.0%) | 0(0.0%) | 0(0.0%) | 1(2.6%) | 0(0.0%) | 1(16.7%) |
| Time to Onset of First Grade 3, 4 or 5 Clinical Adverse Experience (days) | | | | | | | | | | |
| Mean | 25.3 | 20.9 | 83.8 | 54.1 | N/A | N/A | 36.3 | 34.3 | 618.0 | 174.0 |
| SD | 14.38 | 15.08 | 76.41 | 56.21 | N/A | N/A | 92.31 | 85.55 | N/A | 292.94 |
| Median | 19.0 | 16.0 | 50.0 | 50.0 | N/A | N/A | 12.0 | 10.0 | 618.0 | 38.0 |
| Range | 8 - 56 | 1 - 56 | 37 - 198 | 10 - 198 | N/A | N/A | 2 - 467 | 2 - 467 | 618 - 618 | 8 - 612 |
| Duration of the First Grade 3 or 4 Clinical Adverse Experience (days)[1] | | | | | | | | | | |
| Median | 8.0 | 9.5 | 8.5 | 8.5 | N/A | N/A | 8.0 | 8.0 | N/A | 11.0 |
| Range | 2 - 58+ | 2 - 58+ | 5 - 107 | 4 - 107 | N/A | N/A | 1 - 34+ | 1 - 63+ | 30+ - 30+ | 10 - 13 |

[1] Data are displayed by treatment group.
[2] Patients with ongoing adverse experiences are censored at date of last therapy + 30 days.
[3] Maximum tolerated doses for solid tumor patients were 400 mg once daily, 300 mg twice daily 3 out of 7 days, and 200 mg twice daily.
SD = Standard Deviation
+: ongoing

[Ref. 5.3.3.2: P008] [Ref. 5.3.5.4: P002, P006, P011V1]

**Adverse Experiences Resulting in Dose Modification**

The following table summarizes the adverse experiences resulting in **dose modifications** in the Vorinostat monotherapy solid tumor population.

- On **400 mg once daily dose**, 33 of 40 patients (82.5%) did not require dose modification. Seven (7) patients (17.5%) required 1 dose modification. The median time to the first adverse experience resulting in dose modification was 22 days (range, 14 to 75 days).
- On **300 mg twice daily 3 out of 7 days dose**, 12 of 13 patients (92.3%) required no dose modification. One (1) patient at this dose required multiple dose modifications beginning on Study Day 14.
- On **200 mg twice daily dose**, none required dose modification.
- **At doses above the MTD**, twenty-six (26) of 38 patients (68.4%) who received Vorinostat monotherapy required no dose modification. Eleven (11) patients (28.9%) required 1 dose modification and 1 patient (2.6%) required multiple dose modifications. The median time to the first adverse experience resulting in dose modification was 16 days (range, 3 to 625 days).

**Table 91. Summary of Dose Modifications Due to Adverse Experiences after Treatment with Vorinostat (Vorinostat Monotherapy – Solid Tumors) (Applicant's Table)**

| Dose Modifications | 400mg QD continuous (N=40) | 300mg BID 3/7 (N=13) | 200mg BID continuous (N=4) | Doses above MTD‡ (N=38) | Doses below MTD (N=6) |
|---|---|---|---|---|---|
| Number (%) of patients with | | | | | |
| one dose modification | 7 (17.5%) | 0 (0.0%) | 0 (0.0%) | 11 (28.9%) | 0 (0.0%) |
| two or more dose modifications | 0 (0.0%) | 1 (7.7%) | 0 (0.0%) | 1 (2.6%) | 0 (0.0%) |
| no dose modifications | 33 (82.5%) | 12 (92.3%) | 4 (100.0%) | 26 (68.4%) | 6 (100.0%) |
| Time to first AE resulting in a dose modification (days) | | | | | |
| Median (Range) | 22 (14, 75) | 14 (14, 14) | N/A | 16 (3, 625) | N/A |

† Data are displayed by treatment group.
‡ Maximum tolerated doses for solid tumor patients were 400 mg once daily, 300 mg twice daily 3 out of 7 days, and 200 mg twice daily.

[Ref. 5.3.3.2: P008] [Ref. 5.3.5.4: P002, P006, P011V1]

The following two tables summarize clinical and laboratory adverse experiences, respectively, in the solid tumor population that resulted in **dose modifications**.

- In the 45 patients who received **Vorinostat 400 mg once daily**, adverse experiences resulting in dose modification were Grade 3 **thrombocytopenia** in 4 (8.9%), Grade 3 **nausea** in 1 (2.2%), Grade 3 **fatigue** in 1 (2.2%), and Grade 1 and Grade 3 **anorexia** in 1 patient each (2.2%).
- In patients who received **Vorinostat 300 mg twice daily 3 out of 7 days**, adverse experiences resulting in dose modification were Grade 2 **vomiting**, Grade 2 **fatigue**, and

Grade 2 **dehydration**. These adverse experiences occurred in 1 patient each at an incidence of 6.3%.

- In patients who received **200 mg twice daily** and **200 mg twice daily 14 out of 21 days**, no adverse experiences were reported that resulted in dose modification.
- At doses **above the MTD**, adverse experiences resulting in dose modification were Grade 3 **thrombocytopenia** in 1 (2.6%), Grade 2 **vomiting** in 2 (5.3%), Grade 2 **nausea** in 1 (2.6%), and Grade 2 and Grade 3 **fatigue** in 1 (2.6%) and 5 patients (13.2%), respectively. In addition 1 patient each (2.6%) require dose modification for adverse experiences of Grade 2 **anorexia**, Grade 3 **hemoptysis**, and Grade 3 **vasculitis**.
- A *laboratory* adverse experience of Grade 2 **increased blood creatinine** resulted in dose modification in 1 patient (2.3%) who received Vorinostat monotherapy at a dose of 400 mg once daily and in another who received doses above the MTD. Additionally 1 patient who received Vorinostat monotherapy at a dose of 200 mg twice daily, required dose modification for Grade 1 **increased ALT**.

**Table 92. Number (%) Of Patients with Specific Clinical Adverse Experiences by System Organ Class (Incidence > 0% in One or More Dose Levels) Resulting in Dose Modification (Vorinostat Monotherapy – Solid Tumor) (Applicant's Table)**

| | 400mg QD continuous (N=45) | | 300mg BID 3/7 (N=16) | | 200mg BID continuous (N=8) | | 200mg BID 14/21 (N=6) | | doses above MTD (N=38) | | cases below MTD (N=15) | | Total Patients (N=101) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % | n | % | n | % | n | % |
| *Patients With One Or More Clinical Adverse Experiences* | 7 | (15.6) | 1 | (6.3) | 0 | (0.0) | 0 | (0.0) | 9 | (23.7) | 0 | (0.0) | 17 | (16.8) |
| *Patients With No Clinical Adverse Experiences* | 38 | (84.4) | 15 | (93.8) | 8 | (100) | 6 | (100) | 29 | (76.3) | 15 | (100) | 84 | (83.2) |
| **Blood And Lymphatic System Disorders** | **4** | **(8.9)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(2.6)** | **0** | **(0.0)** | **5** | **(5.0)** |
| Thrombocytopenia | 4 | (8.9) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.6) | 0 | (0.0) | 5 | (5.0) |
| *Grade 3* | 4 | (8.9) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.6) | 0 | (0.0) | 5 | (5.0) |
| **Gastrointestinal Disorders** | **1** | **(2.2)** | **1** | **(6.3)** | **0** | **(0.0)** | **0** | **(0.0)** | **2** | **(5.3)** | **0** | **(0.0)** | **4** | **(4.0)** |
| Vomiting | 0 | (0.0) | 1 | (6.3) | 0 | (0.0) | 0 | (0.0) | 2 | (5.3) | 0 | (0.0) | 3 | (3.0) |
| *Grade 2* | 0 | (0.0) | 1 | (6.3) | 0 | (0.0) | 0 | (0.0) | 2 | (5.3) | 0 | (0.0) | 3 | (3.0) |
| Nausea | 1 | (2.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.6) | 0 | (0.0) | 2 | (2.0) |
| *Grade 2* | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.6) | 0 | (0.0) | 1 | (1.0) |
| *Grade 3* | 1 | (2.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.0) |
| **General Disorders And Administration Site Conditions** | **1** | **(2.2)** | **1** | **(6.3)** | **0** | **(0.0)** | **0** | **(0.0)** | **6** | **(15.8)** | **0** | **(0.0)** | **8** | **(7.9)** |
| Fatigue | 1 | (2.2) | 1 | (6.3) | 0 | (0.0) | 0 | (0.0) | 6 | (15.8) | 0 | (0.0) | 8 | (7.9) |
| *Grade 2* | 0 | (0.0) | 1 | (6.3) | 0 | (0.0) | 0 | (0.0) | 1 | (2.6) | 0 | (0.0) | 2 | (2.0) |
| *Grade 3* | 1 | (2.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 5 | (13.2) | 0 | (0.0) | 6 | (5.9) |
| **Metabolism And Nutrition Disorders** | **2** | **(4.4)** | **1** | **(6.3)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(2.6)** | **0** | **(0.0)** | **4** | **(4.0)** |
| Anorexia | 2 | (4.4) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.6) | 0 | (0.0) | 3 | (3.0) |
| *Grade 1* | 1 | (2.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.0) |
| *Grade 2* | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.6) | 0 | (0.0) | 1 | (1.0) |
| *Grade 3* | 1 | (2.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.0) |
| Dehydration | 0 | (0.0) | 1 | (6.3) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.0) |
| *Grade 2* | 0 | (0.0) | 1 | (6.3) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.0) |
| **Respiratory, Thoracic And Mediastinal Disorders** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(2.6)** | **0** | **(0.0)** | **1** | **(1.0)** |
| Haemoptysis | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.6) | 0 | (0.0) | 1 | (1.0) |
| *Grade 3* | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.6) | 0 | (0.0) | 1 | (1.0) |
| **Vascular Disorders** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(2.6)** | **0** | **(0.0)** | **1** | **(1.0)** |
| Vasculitis | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.6) | 0 | (0.0) | 1 | (1.0) |
| *Grade 3* | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.6) | 0 | (0.0) | 1 | (1.0) |

A patient is counted only once within a System Organ Class category, even if more than one adverse experience with specific preferred terms occurred. Only the highest grade of a given adverse experience is counted per dose level for the individual patient.
Adverse experience terms are from MedDRA Version 8.1.

[Ref. 5.3.5.2: P008] [Ref. 5.3.5.4: P002, P006, P011V1]

**Table 93. Number (%) Of Patients with Specific Laboratory Adverse Experiences by Laboratory Test Category (Incidence > 0% in One or More Dose Levels) Resulting in Dose Modification (Vorinostat Monotherapy – Solid Tumor) (Applicant's Table)**

| | 400mg QD continuous (N=45) | | 300mg BID 3/7 (N=16) | | 200mg BID continuous (N=8) | | 200mg BID 14/21 (N=6) | | doses above MTD (N=38) | | doses below MTD (N=15) | | Total Patients (N=101) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n/m | % | n/m | % | n/m | % | n/m | % | n/m | % | n/m | % | n/m | % |
| *Patients With One Or More Laboratory Adverse Experiences* | *1/45* | *(2.2)* | *0/16* | *(0.0)* | *1/8* | *(12.5)* | *0/6* | *(0.0)* | *1/37* | *(2.7)* | *0/15* | *(0.0)* | *3/101* | *(3.0)* |
| *Patients With No Laboratory Adverse Experiences* | *44/45* | *(97.8)* | *16/16* | *(100)* | *7/8* | *(87.5)* | *6/6* | *(100)* | *36/37* | *(97.3)* | *15/15* | *(100)* | *98/101* | *(97.0)* |
| **Blood Chemistry Test** | 1/44 | (2.3) | 0/16 | (0.0) | 1/8 | (12.5) | 0/6 | (0.0) | 1/37 | (2.7) | 0/14 | (0.0) | 3/100 | (3.0) |
| Blood Creatinine Increased | 1/44 | (2.3) | 0/16 | (0.0) | 0/8 | (0.0) | 0/6 | (0.0) | 1/37 | (2.7) | 0/14 | (0.0) | 2/100 | (2.0) |
| *Grade 2* | *1/44* | *(2.3)* | *0/16* | *(0.0)* | *0/8* | *(0.0)* | *0/6* | *(0.0)* | *1/37* | *(2.7)* | *0/14* | *(0.0)* | *2/100* | *(2.0)* |
| Alanine Aminotransferase Increased | 0/44 | (0.0) | 0/16 | (0.0) | 1/8 | (12.5) | 0/6 | (0.0) | 0/37 | (0.0) | 0/14 | (0.0) | 1/100 | (1.0) |
| *Grade 1* | *0/44* | *(0.0)* | *0/16* | *(0.0)* | *1/8* | *(12.5)* | *0/6* | *(0.0)* | *0/37* | *(0.0)* | *0/14* | *(0.0)* | *1/100* | *(1.0)* |

n/m = number of patients with laboratory adverse experiences / number of patients for whom the laboratory test was recorded post-baseline.
A patient is counted only once within a Laboratory Test Type Category, even if more than one adverse experience with specific preferred terms occurred. Only the highest grade of a given adverse experience is counted per dose level for the individual patient.

*[Ref. 5.3.3.2: P008] [Ref. 5.3.5.4: P002, P006, P011V1]*



## Adverse Experiences Resulting in Discontinuation

The following two tables summarize the *clinical* adverse experiences that resulted in **discontinuation** of study medication and the details of patients who discontinued Vorinostat due to drug-related clinical adverse experiences. In addition, brief patient narratives are provided for those patients who discontinued due to non-serious adverse experiences.

- In the 45 patients who received Vorinostat **400 mg once daily**, 4 (8.9%) discontinued study medication due to adverse experiences; 3 of these 4 discontinued due to drug-related clinical adverse experiences. The drug-related clinical adverse experiences resulting in study drug discontinuation were Grade 2 **dehydration**, Grade 3 **thrombosis**, and Grade 2 **anorexia**.
- In the 16 patients who received Vorinostat **300 mg twice daily 3 out of 7 days** dose, 1 (6.3%) discontinued study medication due to adverse experiences. This patient discontinued study medication secondary to Grade 2 **fatigue**.
- In the 6 patients who received Vorinostat **200 mg twice daily 14 out of 21 days** dose, 4 (66.7%) discontinued study medication due to adverse experiences. 2 of these 4 discontinued for drug-related clinical adverse experiences. The drug-related clinical adverse experiences resulting in study drug discontinuation were Grade 3 **tumor hemorrhage** and Grade 2 **thrombocytopenia**.
- At the **doses above the MTD**, 8 of 38 patients (21.1%) discontinued study medication due to adverse experiences. Five (5) of these 8 patients discontinued for drug-related clinical adverse experiences. The drug-related clinical adverse experiences resulting in study drug discontinuation were Grade 3 **thrombocytopenia**, Grade 2 **fatigue**, Grade 2 **asthenia**, and Grade 2 **vomiting**.

**Table 94. Number (%) of Patients who Discontinued due to Specific Clinical Adverse Experiences by System Organ Class; Incidence > 0% in One or More Dose Levels (Vorinostat Monotherapy – Solid Tumor) (Applicant's Table)**

| | 400mg QD continuous (N=45) | | 300mg BID 3/7 (N=16) | | 200mg BID continuous (N=8) | | 200mg BID 14/21 (N=6) | | doses above MTD (N=38) | | doses below MTD (N=15) | | Total Patients (N=101) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % | n | % | n | % | n | % |
| *Patients With One Or More Clinical Adverse Experiences* | 4 | (8.9) | 1 | (6.3) | 0 | (0.0) | 4 | (66.7) | 5 | (21.1) | 2 | (13.3) | 19 | (18.8) |
| *Patients With No Clinical Adverse Experiences* | 41 | (91.1) | 15 | (93.8) | 8 | (100) | 2 | (33.3) | 30 | (78.9) | 13 | (86.7) | 82 | (81.2) |
| **Blood And Lymphatic System Disorders** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(16.7)** | **1** | **(2.6)** | **0** | **(0.0)** | **2** | **(2.0)** |
| Thrombocytopenia | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (16.7) | 1 | (2.6) | 0 | (0.0) | 2 | (2.0) |
| *Grade 2* | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (16.7) | 0 | (0.0) | 0 | (0.0) | 1 | (1.0) |
| *Grade 3* | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.6) | 0 | (0.0) | 1 | (1.0) |
| **Gastrointestinal Disorders** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **2** | **(5.3)** | **1** | **(6.7)** | **3** | **(3.0)** |
| Vomiting | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 2 | (5.3) | 0 | (0.0) | 2 | (2.0) |
| *Grade 2* | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 2 | (5.3) | 0 | (0.0) | 2 | (2.0) |
| Abdominal Pain | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.6) | 0 | (0.0) | 1 | (1.0) |
| *Grade 2* | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.6) | 0 | (0.0) | 1 | (1.0) |
| Nausea | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (6.7) | 1 | (1.0) |
| *Grade 3* | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (6.7) | 1 | (1.0) |
| **General Disorders And Administration Site Conditions** | **1** | **(2.2)** | **1** | **(6.3)** | **0** | **(0.0)** | **1** | **(16.7)** | **4** | **(10.5)** | **1** | **(6.7)** | **8** | **(7.9)** |
| Fatigue | 0 | (0.0) | 1 | (6.3) | 0 | (0.0) | 0 | (0.0) | 1 | (2.6) | 1 | (6.7) | 3 | (3.0) |
| *Grade 2* | 0 | (0.0) | 1 | (6.3) | 0 | (0.0) | 0 | (0.0) | 1 | (2.6) | 0 | (0.0) | 2 | (2.0) |
| *Grade 3* | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (6.7) | 1 | (1.0) |
| Asthenia | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 2 | (5.3) | 0 | (0.0) | 2 | (2.0) |
| *Grade 2* | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 2 | (5.3) | 0 | (0.0) | 2 | (2.0) |
| General Physical Health Deterioration | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (16.7) | 1 | (2.6) | 0 | (0.0) | 2 | (2.0) |
| *Grade 3* | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (16.7) | 1 | (2.6) | 0 | (0.0) | 2 | (2.0) |
| Performance Status Decreased | 1 | (2.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.0) |
| *Grade 3* | 1 | (2.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.0) |
| **Metabolism And Nutrition Disorders** | **2** | **(4.4)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(6.7)** | **3** | **(3.0)** |
| Anorexia | 1 | (2.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (6.7) | 2 | (2.0) |
| *Grade 2* | 1 | (2.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.0) |
| *Grade 3* | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (6.7) | 1 | (1.0) |
| Dehydration | 1 | (2.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.0) |
| *Grade 2* | 1 | (2.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.0) |
| **Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **2** | **(33.3)** | **1** | **(2.6)** | **0** | **(0.0)** | **3** | **(3.0)** |
| Cancer Pain | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.6) | 0 | (0.0) | 1 | (1.0) |
| *Grade 3* | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.6) | 0 | (0.0) | 1 | (1.0) |
| Neoplasm Progression | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (16.7) | 0 | (0.0) | 0 | (0.0) | 1 | (1.0) |
| *Grade 5* | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (16.7) | 0 | (0.0) | 0 | (0.0) | 1 | (1.0) |
| Tumour Haemorrhage | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (16.7) | 0 | (0.0) | 0 | (0.0) | 1 | (1.0) |
| *Grade 3* | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (16.7) | 0 | (0.0) | 0 | (0.0) | 1 | (1.0) |
| **Respiratory, Thoracic And Mediastinal Disorders** | **1** | **(2.2)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(1.0)** |
| Cough | 1 | (2.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.0) |
| *Grade 2* | 1 | (2.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.0) |
| **Vascular Disorders** | **1** | **(2.2)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(2.6)** | **0** | **(0.0)** | **2** | **(2.0)** |
| Thrombosis | 1 | (2.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.6) | 0 | (0.0) | 2 | (2.0) |
| *Grade 3* | 1 | (2.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.6) | 0 | (0.0) | 2 | (2.0) |

A patient is counted only once within a System Organ Class category, even if more than one adverse experience with specific preferred terms occurred. Only the highest grade of a given adverse experience is counted per dose level for the individual patient.
Adverse experience terms are from MedDRA Version 8.1.

[Ref. 5.3.3.2: P008] [Ref. 5.3.5.4: P002, P006, P011V1]

**Table 95. Details of Patients who Discontinued due to Drug-Related Clinical Adverse Experiences by Dose Level (Vorinostat Monotherapy – Solid Tumor) (Applicant's Table)**

| Study Number | AN | Gender | Race | Age | Period | Rel Day of AE Onset | Adverse Experience | Duration of AE | Rel Day of Drug Discon | Toxicity Grade | Serious | Drug Relation | Action Taken | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **400mg QD continuous** | | | | | | | | | | | | | | |
| 683002 | 1011 | F | white | 40 | Trt Cycle 2 | 42 | Dehydration | 7 days | 41 | 3 | Y | poss | discontinued PRx | recovered |
| 683006 | 1020 | M | white | 72 | Trt Cycle 34 | 960 | Thrombosis | 4 days | 959 | 3 | Y | poss | discontinued PRx | recovered |
| 683005 | 1 | F | white | 65 | Part 1 | 63 | Anorexia | | 67 | 2 | N | poss | discontinued PRx | not recovered |
| **300mg BID 3/7** | | | | | | | | | | | | | | |
| 683006 | 1063 | M | white | 49 | Trt Cycle 2 | 37 | Fatigue | | 30 | 2 | N | poss | discontinued PRx | not recovered |
| **200mg BID 14/21** | | | | | | | | | | | | | | |
| 683011 | 5 | F | white | 39 | Cycle 2 | 34 | Tumour Haemorrhage | 8 days | 40 | 3 | Y | prob | discontinued PRx | fatal |
| | 37 | F | white | 65 | Cycle 3+5 | 44 | Thrombocytopenia | 8 days | 44 | 2 | Y | def | discontinued PRx | recovered |
| **doses above MTD** | | | | | | | | | | | | | | |
| 683021 | 1 | F | white | 63 | Rept 1 Cycle 1 | 29 | Thrombocytopenia | 5 days | 28 | 3 | N | def | discontinued PRx | recovered |
| | 17 | M | white | 72 | Cycle 2 | 49 | Fatigue | | 35 | 2 | Y | poss | discontinued PRx | not recovered |
| | 31 | M | white | 48 | Rept 1 Day 1 Predose | 28 | Asthenia | 8 days | 26 | 2 | N | prob | discontinued PRx | recovered |
| | 33 | M | white | 58 | Cycle 1 | 2 | Vomiting | 20 days | 20 | 2 | Y | prob | discontinued PRx | recovered |
| | 36 | M | white | 64 | Cycle 1 | 22 | Asthenia | | 14 | 2 | N | prob | discontinued PRx | not recovered |
| **doses below MTD** | | | | | | | | | | | | | | |
| 683006 | 1026 | M | white | 72 | Trt Cycle 5 | 120 | Fatigue | 15 days | 115 | 3 | N | poss | discontinued PRx | recovered |
| 683005 | 20 | F | white | 51 | Part 1 | 31 | Anorexia | | 30 | 3 | N | poss | discontinued PRx | not recovered |
| | | | | | | | Nausea | | 30 | 3 | N | poss | discontinued PRx | not recovered |

AN = Allocation number
def = Definitely; def not = Definitely not; poss = Possibly; prob = Probably; prob not = Probably not
PRx = prime therapy
Adverse experience terms are from MedDRA Version 8.1.
[Ref. 5.3.3.2: P008] [Ref. 5.3.5.4: P002, P006, P011V1]

Narratives of 6 patients in the Vorinostat Monotherapy – Solid Tumors population who **discontinued** Vorinostat due to *non-serious* clinical and laboratory adverse experiences:

AN1026 (Protocol 006) began study therapy with Vorinostat 400 mg once daily. On Study Day 38, study drug therapy was interrupted for non-serious grade 3 fatigue considered by the Investigator to be possibly related to Vorinostat. This fatigue resolved on Study Day 43 and the Vorinostat was resumed at 200 mg daily. Grade 2 fatigue was reported from Study Day 92 to Day 119. On Day 120, Grade 3 fatigue was reported again and was considered by the Investigator to be possibly related to study drug and the patient was discontinued from the study. The patient recovered from the adverse experience of Grade 3 fatigue by Study Day 134.

AN1063 (Protocol 006) began study therapy with 400 mg twice daily 3 out of 7 days. On Study Day 18 the patient experienced a non-serious Grade 3 fatigue that was considered by the Investigator to be possibly related to study drug. The fatigue lessened to Grade 2 on Study Day 21 and resolved by Study Day 23. The patient resumed therapy at the reduced dose of 300 mg twice daily 3 out of 7 days until Study Day 30 when study drug was interrupted for non-serious adverse experiences of Grade 1 nausea, vomiting and fatigue. The patient recovered from nausea and vomiting on Study Day 36; however, the fatigue increased to Grade 2 on Study Day 37. The patient discontinued study medication. The adverse experience of Grade 2 fatigue remained unresolved.

AN1065 (Protocol 006) began study therapy with 400 mg twice daily 3 out of 7 days. On Study Day 10 the patient experienced a non-serious adverse experience of Grade 3 fatigue. This was considered by the Investigator possibly related to Vorinostat. The fatigue lessened to Grade 2 Study Day 16 and resolved by Study Day 23. The patient resumed therapy at a reduced dose of 300 mg twice daily, but Vorinostat was discontinued for non-serious adverse experience of

Grade 3 increased AST, later that same day (Study Day 23). The Investigator considered this adverse experience to be possible related to the study drug. Post-treatment, an additional adverse experience of Grade 2 increased AST was reported on Study Day 29.

AN001 (Protocol 008) began study therapy with 400 mg daily. On the Study Day 13 the patient experienced a non-serious adverse experience of Grade 2 cough which the Investigator did not consider to be related to study therapy. On Study Day 29 the patient experienced Grade 1 anorexia which was considered by the Investigator to be non-serious and not related to study drug. On Study Day 63, however, the anorexia worsened to Grade 2 and the Investigator determined that the anorexia may possibly be related to the study drug. The patient discontinued study medication due to non-serious adverse experiences of cough and worsening anorexia. The patient had not recovered from either adverse experience at time of the post-study visit on Study Day 75.

AN003 (Protocol 008) began study therapy with 400 mg daily. On Study Day 16 the study drug was interrupted for non-serious adverse experiences of Grade 3 asthenia and Grade 3 thrombocytopenia, considered related to the study drug by the Investigator. On Study Day 26 the patient discontinued study medication for a non-serious adverse experience of Grade 3 decreased performance status which the Investigator did not consider to be related to study therapy. While the thrombocytopenia resolved by Study Day 34, asthenia and decreased performance status had continued at the post-treatment visit on Study Day 47.

AN001 (Protocol 011) began study therapy with 400 mg twice daily 14 out of 21 days. On Study Day 8, the study drug was interrupted for non-serious adverse experiences of Grade 2 nausea, Grade 2 vomiting, and Grade 2 thrombocytopenia. The Investigator considered all 3 of these adverse experiences to be related to the study drug. On Study Day 15, the study drug was reduced to 300 mg twice daily 14 out of 21 days. The patient discontinued study therapy on Study Day 22 for a non-serious adverse experience of Grade 3 thrombocytopenia which the Investigator considered to be definitely related to the study drug. The thrombocytopenia resolved on Study Day 29.

## Vorinostat Monotherapy – Hematologic Malignancies

- A total of 87 patients with hematologic malignancies were enrolled in this population

## Summary of Safety Outcomes—Clinical Adverse Experiences

The following table summarizes the *clinical* adverse experience outcomes for 87 patients in this population.

- All 87 patients had at least 1 or more clinical adverse experience
- 85 (97.7%) had at least 1 adverse experience that was considered by the Investigator to be *related* to Vorinostat and 4 (4.6%) patients *discontinued* due to a drug-related adverse experience
- The incidence of *serious drug-related* adverse experiences was 18.4% (16) and 1 patient (1.1%) discontinued Vorinostat due to a *serious* drug-related adverse experience

- All of the 11 patients who were administered **400 mg once daily** reported 1 or more *clinical adverse experience*.
- Ten (10) patients (90.9%) had *clinical adverse experiences* that were considered by the Investigator to be *related to the study drug*, with 5 of the 11 patients (45.5%) reporting *serious drug-related* clinical adverse experiences.
- One (1) of 11 patients (9.1%) was *discontinued* from the study due to a clinical adverse experience which was considered by the Investigator to be serious and related to study drug.

**Table 96. Clinical Adverse Experience Summary (Vorinostat Monotherapy – Hematologic Malignancies) (Applicant's Table)**

| | 400mg QD continuous (N = 11) | | 300mg BID 3/7 (N = 3) | | 200mg BID Continuous (N = 6) | | 200mg BID 14/21 (N = 10) | | Doses above MTD[3] (N = 51) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) |
| Number (%) of patients: | | | | | | | | | | |
| With one or more adverse experiences | 11 | (100) | 3 | (100) | 6 | (100) | 10 | (100) | 51 | (100) |
| With no adverse experience | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| With drug-related adverse experiences[2] | 10 | (90.9) | 3 | (100) | 6 | (100) | 9 | (90.0) | 51 | (100) |
| With serious adverse experiences | 6 | (54.5) | 1 | (33.3) | 4 | (66.7) | 4 | (40.0) | 31 | (60.8) |
| With serious drug-related adverse experiences[2] | 5 | (45.5) | 1 | (33.3) | 3 | (50.0) | 0 | (0.0) | 7 | (13.7) |
| Who died | 0 | (0.0) | 1 | (33.3) | 1 | (16.7) | 0 | (0.0) | 2 | (3.9) |
| Discontinued due to adverse experiences | 1 | (9.1) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 4 | (7.8) |
| Discontinued due to drug-related adverse experiences [2] | 1 | (9.1) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 3 | (5.9) |
| Discontinued due to serious adverse experiences | 1 | (9.1) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.0) |
| Discontinued due to serious drug-related adverse experiences[2] | 1 | (9.1) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |

| | Doses below MTD (N = 6) | | Total (N = 87) | |
|---|---|---|---|---|
| | n | (%) | n | (%) |
| Number (%) of patients: | | | | |
| With one or more adverse experiences | 6 | (100) | 87 | (100.0) |
| With no adverse experience | 0 | (0.0) | 0 | (0.0) |
| With drug-related adverse experiences[2] | 6 | (100) | 85 | (97.7) |
| With serious adverse experiences | 2 | (33.3) | 48 | (55.2) |
| With serious drug-related adverse experiences[2] | 0 | (0.0) | 16 | (18.4) |
| Who died | 0 | (0.0) | 4 | (4.6) |
| Discontinued due to adverse experiences | 0 | (0.0) | 5 | (5.7) |
| Discontinued due to drug-related adverse experiences[2] | 0 | (0.0) | 4 | (4.6) |
| Discontinued due to serious adverse experiences | 0 | (0.0) | 2 | (2.3) |
| Discontinued due to serious drug-related adverse experiences[2] | 0 | (0.0) | 1 | (1.1) |

[1] Data are displayed by treatment group.
[2] Determined by the investigator to be possibly, probably or definitely drug related.
[3] Maximum tolerated doses for solid tumor patients were 400 mg once daily, 300 mg twice daily 3 out of 7 days, 200 mg twice daily, and 200 mg twice daily 14 out of 21 days.

[Ref. 5.3.5.4; P003V1, P004V1, P006, P013V1]

## Summary of Safety Outcomes—Laboratory Adverse Experiences

The following table summarizes the *laboratory* adverse experiences in patients with hematologic malignancies. All 87 patients with hematologic malignancies had at least one post-baseline laboratory test.

- 64 (73.6%) patients had at least 1 or more *laboratory* adverse experience, including 50 patients (57.5%) who had at least 1 *laboratory* adverse experience that was considered by the Investigator to *be related* to the study drug.
- 51 patients received Vorinostat at **doses above the MTD**, 27 of these patients (52.9%) had *drug-related* adverse experiences.
- *Serious* laboratory adverse experiences were reported in 2 patients (2.3%). Both of the serious laboratory adverse experiences occurred in patients treated at doses above the MTD.
- Of the 11 patients who were administered **400 mg once daily**, all reported 1 or more laboratory adverse experience post-baseline—all considered by the Investigator to be related to the study drug. There were no serious laboratory adverse experiences at this dose and no patients were discontinued due to a laboratory adverse experience.

**Table 97. Laboratory Adverse Experiences Summary (Vorinostat Monotherapy—Hematologic Malignancies) (Applicant's Table)**

| | 400mg QD continuous (N = 11) | | 300mg BID 3/7 (N = 3) | | 200mg BID Continuous (N = 6) | | 200mg BID 14/21 (N = 10) | | Doses above MTD[2] (N = 51) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n | (%)‡ | n | (%)‡ | n | (%)‡ | n | (%)‡ | n | (%)‡ |
| Number (%) of patients: | | | | | | | | | | |
| With at least one lab test postbaseline | 11 | | 3 | | 6 | | 10 | | 51 | |
| With one or more adverse experiences | 11 | (100.0) | 1 | (33.3) | 6 | (100.0) | 7 | (70.0) | 35 | (68.6) |
| With no adverse experience | 0 | (0.0) | 2 | (66.7) | 0 | (0.0) | 3 | (30.0) | 16 | (31.4) |
| With drug-related adverse experiences[1] | 11 | (100.0) | 1 | (33.3) | 6 | (100.0) | 4 | (40.0) | 27 | (52.9) |
| With serious adverse experiences | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 2 | (3.9) |
| With serious drug-related adverse experiences[1] | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 2 | (3.9) |
| Who died | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| Discontinued due to adverse experiences | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| Discontinued due to drug-related adverse experiences[1] | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| Discontinued due to serious adverse experiences | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| Discontinued due to serious drug-related adverse experiences[1] | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |

| | Doses below MTD (N = 6) | | Total (N = 87) | |
|---|---|---|---|---|
| | n | (%)‡ | n | (%)‡ |
| Number (%) of patients: | | | | |
| With at least one lab test postbaseline | 6 | | 87 | |
| With one or more adverse experiences | 4 | (66.7) | 64 | (73.6) |
| With no adverse experience | 2 | (33.3) | 23 | (26.4) |
| With drug-related adverse experiences[1] | 1 | (16.7) | 50 | (57.5) |
| With serious adverse experiences | 0 | (0.0) | 2 | (2.3) |
| With serious drug-related adverse experiences[1] | 0 | (0.0) | 2 | (2.3) |
| Who died | 0 | (0.0) | 0 | (0.0) |
| Discontinued due to adverse experiences | 0 | (0.0) | 0 | (0.0) |
| Discontinued due to drug-related adverse experiences[1] | 0 | (0.0) | 0 | (0.0) |
| Discontinued due to serious adverse experiences | 0 | (0.0) | 0 | (0.0) |
| Discontinued due to serious drug-related adverse experiences[1] | 0 | (0.0) | 0 | (0.0) |

[1] Data are displayed by treatment group.
[1] Determined by the investigator to be possibly, probably or definitely drug related.
[2] Maximum tolerated doses for solid tumor patients were 400 mg once daily, 300 mg twice daily 3 out of 7 days, 200 mg twice daily, and 200 mg twice daily 14 out of 21 days.

[Ref. 5.3.5.4: P003V1, P004V1, P006, P013V1]

**Summary Comparison of Adverse Experiences in the Hematologic Malignancies Population (Vorinostat Monotherapy)**

Clinical and laboratory adverse experiences, *regardless of the grade*, occurring in at least 20% of the patients:

| | |
|---|---|
| o Diarrhea | 75.9% |
| o Fatigue | 65.5% |
| o Nausea | 63.2% |
| o Hyperglycemia | 60.9% |
| o Anorexia | 57.5% |
| o Vomiting | 40.2% |
| o Dyspnea | 37.9% |
| o Hypocalcemia | 35.6% |
| o Increased blood creatinine | 34.5% |
| o Hypo-albuminemia | 32.2% |
| o Cough | 29.9% |
| o Hypokalemia | 29.9% |
| o Constipation | 28.7% |
| o Dehydration | 27.6% |
| o Decreased hemoglobin | 26.4% |
| o Decreased platelet count | 26.4% |
| o Increased alkaline phosphatase | 24.1% |
| o Hypophosphatemia | 24.1% |
| o Hyponatremia | 23.0% |
| o Dizziness | 21.8% |
| o Pyrexia | 21.8% |
| o Increased ALT | 20.7% |
| o Prolonged PT | 20.7% |
| o Decreased white blood cell count | 20.7% |

- 11 patients were *assigned* to 400 mg once daily dose and 16 patients *received* Vorinostat at this dose
- Three (3) patients *received* Vorinostat at a dose of 300 mg twice daily 3 out of 7 days
- 6 patients *received* Vorinostat at a dose of 200 mg twice daily
- 14 patients *received* Vorinostat at a dose of 200 mg twice daily 14 out of 21 days
- 51 patients *received* doses of Vorinostat above the MTD
- 13 patients *received* doses of Vorinostat below the MTD

**Population Comparison**

- The overall safety profile observed in patients with hematologic malignancies is similar to that in the overall CTCL population; however, patients with hematologic malignancies had a higher incidence of gastrointestinal, constitutional, and metabolic adverse experiences.

**Dose Comparison in the Hematologic Malignancies Population**

- The overall safety profile is consistent across the doses studied.
- The adverse experiences of fatigue, nausea, vomiting, diarrhea, dehydration, anemia, thrombocytopenia, hyperglycemia, increased blood creatinine were observed at all doses.
- These adverse experiences were noted in a higher proportion of the patients who received Vorinostat at doses of 200 mg twice daily and at doses above the MTD compared to 400 mg once daily dose.
- A thromboembolic event occurred in 1 patient who received Vorinostat at a dose of 400 mg once daily.
- The median time to onset and the duration of the first drug-related Grade 3, 4, or 5 clinical adverse experiences were similar for patients across all doses.
- A higher proportion of the patients who received Vorinostat at doses above the MTD required dose modifications.
- The time to the first adverse experience requiring dose modifications was longer for patients who were being treated with Vorinostat 400 mg once daily.

**Dose Analyses in the Hematologic Malignancies Population**

**400 mg Once Daily**

The following table summarizes the incidence of adverse experiences that occurred in the 16 patients who received Vorinostat monotherapy at a dose of 400 mg once daily continuously. The most common *clinical* adverse experiences (all grades) occurring in at least 20% of patients at this dose:

| | |
|---|---|
| o Hyperglycemia | 93.8% |
| o Fatigue | 68.8% |
| o Diarrhea | 56.3% |
| o Dyspnea | 56.3% |
| o Hypocalcemia | 43.8% |
| o Nausea | 37.5% |
| o Hypo-albuminemia | 37.5% |
| o Cough | 37.5% |
| o Constipation | 31.3% |
| o Dehydration | 31.3% |
| o Hypophosphatemia | 31.3% |
| o Hyponatremia | 31.3% |
| o Pyrexia | 31.3% |
| o Anorexia | 25.0% |
| o Dizziness | 25.0% |
| o Peripheral sensory neuropathy | 25.0% |

*Laboratory* adverse experiences (all grades) occurring in at least 10% of patients at this dose:

- Decreased platelet count 81.3%
- Increased blood creatinine 75.0%
- Prolonged prothrombin time 68.8%
- Decreased hemoglobin 68.8%
- Decreased white blood cell count 50.0%
- Increased ALT 43.8%
- Increased AST 37.5%
- Increased alkaline phosphatase 25.0%
- Increased bilirubin 25.0%
- Prolonged aPTT 25.0%
- Decreased blood carbon dioxide 18.8%
- Decreased neutrophil count 18.8%

- In majority of the patients these adverse experiences were considered by the Investigators to be *related* to study drug.

*Grade 3 and Grade 4 clinical* adverse experiences were:

- Dehydration = 31.3%
- Diarrhea = 25.0%
- Staphylococcal infection = 12.5%
- Fatigue, hypokalemia, hypophosphatemia, hyperglycemia, anorexia, dyspnea, peripheral edema, and upper respiratory tract infection (each) = 6.3%

*Grade 3 and Grade 4 laboratory* adverse experiences:

- Decreased platelet count 37.5%
- Decreased hemoglobin 31.3%
- Decreased white blood cell count 12.5%
- Decreased neutrophil count 12.5%
- Increased blood bilirubin 6.3%

- In majority of the patients these adverse experiences were considered by the Investigators to be *related* to the study drug.

**Table 98. Summary of Specific Clinical or Laboratory Adverse Experiences by Preferred Terms—400 mg Once Daily Dose (Incidence ≥ 10% in One or More Dose Levels) (Applicant's Table)**

| | 400mg QD continuous (N=16) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | All Experiences | | | | Related Experiences Only | | | |
| | All Grades | | Grade 3-5 | | All Grades | | Grade 3-5 | |
| | n | % | n | % | n | % | n | % |
| Diarrhoea | 9 | (56.3) | 4 | (25.0) | 8 | (50.0) | 4 | (25.0) |
| Fatigue | 11 | (68.8) | 1 | (6.3) | 11 | (68.8) | 1 | (6.3) |
| Nausea | 6 | (37.5) | 0 | (0.0) | 6 | (37.5) | 0 | (0.0) |
| Hyperglycaemia | 15 | (93.8) | 1 | (6.3) | 14 | (87.5) | 1 | (6.3) |
| Anorexia | 4 | (25.0) | 1 | (6.3) | 4 | (25.0) | 1 | (6.3) |
| Vomiting | 3 | (18.8) | 0 | (0.0) | 3 | (18.8) | 0 | (0.0) |
| Dyspnoea | 9 | (56.3) | 1 | (6.3) | 7 | (43.8) | 0 | (0.0) |
| Hypocalcaemia | 7 | (43.8) | 0 | (0.0) | 7 | (43.8) | 0 | (0.0) |
| Blood Creatinine Increased | 12 | (75.0) | 0 | (0.0) | 10 | (62.5) | 0 | (0.0) |
| Hypoalbuminaemia | 6 | (37.5) | 0 | (0.0) | 5 | (31.3) | 0 | (0.0) |
| Cough | 6 | (37.5) | 0 | (0.0) | 2 | (12.5) | 0 | (0.0) |
| Hypokalaemia | 2 | (12.5) | 1 | (6.3) | 2 | (12.5) | 1 | (6.3) |
| Constipation | 5 | (31.3) | 0 | (0.0) | 4 | (25.0) | 0 | (0.0) |
| Dehydration | 5 | (31.3) | 5 | (31.3) | 5 | (31.3) | 5 | (31.3) |
| Haemoglobin Decreased | 11 | (68.8) | 5 | (31.3) | 11 | (68.8) | 5 | (31.3) |
| Platelet Count Decreased | 13 | (81.3) | 6 | (37.5) | 13 | (81.3) | 6 | (37.5) |
| Blood Alkaline Phosphatase Increased | 4 | (25.0) | 0 | (0.0) | 4 | (25.0) | 0 | (0.0) |
| Hypophosphataemia | 5 | (31.3) | 1 | (6.3) | 5 | (31.3) | 1 | (6.3) |
| Hyponatraemia | 5 | (31.3) | 0 | (0.0) | 5 | (31.3) | 0 | (0.0) |
| Dizziness | 4 | (25.0) | 0 | (0.0) | 3 | (18.8) | 0 | (0.0) |
| Pyrexia | 5 | (31.3) | 0 | (0.0) | 2 | (12.5) | 0 | (0.0) |
| Alanine Aminotransferase Increased | 7 | (43.8) | 0 | (0.0) | 5 | (31.3) | 0 | (0.0) |
| Prothrombin Time Prolonged | 11 | (68.8) | 0 | (0.0) | 7 | (43.8) | 0 | (0.0) |
| White Blood Cell Count Decreased | 8 | (50.0) | 2 | (12.5) | 8 | (50.0) | 2 | (12.5) |
| Aspartate Aminotransferase Increased | 6 | (37.5) | 0 | (0.0) | 4 | (25.0) | 0 | (0.0) |
| Oedema Peripheral | 3 | (18.8) | 1 | (6.3) | 2 | (12.5) | 1 | (6.3) |
| Upper Respiratory Tract Infection | 3 | (18.8) | 1 | (6.3) | 0 | (0.0) | 0 | (0.0) |
| Blood Bilirubin Increased | 4 | (25.0) | 1 | (6.3) | 4 | (25.0) | 1 | (6.3) |
| Activated Partial Thromboplastin Time Prolonged | 4 | (25.0) | 0 | (0.0) | 4 | (25.0) | 0 | (0.0) |
| Neutrophil Count Decreased | 3 | (18.8) | 2 | (12.5) | 3 | (18.8) | 2 | (12.5) |
| Exfoliative Rash | 3 | (18.8) | 0 | (0.0) | 1 | (6.3) | 0 | (0.0) |
| Hypermagnesaemia | 3 | (18.8) | 0 | (0.0) | 3 | (18.8) | 0 | (0.0) |
| Peripheral Sensory Neuropathy | 4 | (25.0) | 0 | (0.0) | 4 | (25.0) | 0 | (0.0) |
| Muscular Weakness | 2 | (12.5) | 0 | (0.0) | 2 | (12.5) | 0 | (0.0) |
| Carbon Dioxide Decreased | 3 | (18.8) | 0 | (0.0) | 3 | (18.8) | 0 | (0.0) |
| Hypoglycaemia | 2 | (12.5) | 0 | (0.0) | 2 | (12.5) | 0 | (0.0) |
| Staphylococcal Infection | 2 | (12.5) | 2 | (12.5) | 0 | (0.0) | 0 | (0.0) |
| Wound Infection | 2 | (12.5) | 0 | (0.0) | 2 | (12.5) | 0 | (0.0) |

A patient is counted only once within a specific preferred term, even if more than one adverse experience with specific preferred term occurred.
Adverse experience terms are from MedDRA Version 8.1.

[Ref. 5.3.5.4: P003V1, P004V1, P006, P013V1]

**300 mg Twice Daily 3 Out of 7 Days**

N = 3

*Clinical* adverse experiences occurring in at least 20% of patients at this dose:

- Diarrhea, fatigue, nausea, anorexia, vomiting, dyspnea, anemia, hyponatremia, asthenia, hypotension, gastro-esophageal reflux disease, gastrointestinal hemorrhage, chest discomfort, upper abdominal pain, worsening of diffuse large B-cell lymphoma, ischemia, general physical health deterioration, and hemorrhagic shock reported in 33.3% of patients.

*Laboratory* adverse experience:

- Anemia in 1 of 3 patients (33.3%)

A majority of these adverse experiences were considered by the Investigators to be related to study drug with the exception of gastrointestinal hemorrhage and worsening of diffuse large B-cell lymphoma.

*Grade 3 and Grade 4 clinical* adverse experiences, occurring in at least 5% of patients:

- Dyspnea, gastrointestinal hemorrhage, hyponatremia, diffuse large B-cell lymphoma, and general health deterioration reported in 33.3% of patients.

No Grade 3 or 4 laboratory adverse experiences were observed at this dose.

Dyspnea, hyponatremia, and general health deterioration were considered by the Investigators to be *related* to study drug.

**200 mg Twice Daily**

N = 6

*Clinical* adverse experiences (all grades) occurring in at least 20% of patients at this dose:

- Diarrhea 100.0%
- Fatigue 100.0%
- Anorexia 83.3%
- Nausea 83.3%
- Hyperglycemia 66.7%
- Hypermagnesemia 66.7%
- Decreased weight 50.0%
- Dyspnea 50.0%
- Dehydration 50.0%
- Exfoliative rash 50.0%

- Abdominal pain 33.3%
- Back pain 33.3%
- Dyspepsia 33.3%
- Flatulence 33.3%
- Hypocalcemia 33.3%
- Hypokalemia 33.3%
- Pyrexia 33.3%
- Stomatitis 33.3%
- Vomiting 33.3%

*Laboratory* adverse experiences occurring in at least 10% of patients at this dose:

- Decreased hemoglobin 83.3%
- Decreased platelet count 83.3%
- Decreased white blood cell count 66.7%
- Increased blood creatinine 66.7%
- Decreased neutrophil count 50.0%
- Prolonged prothrombin time 50.0%
- Increased AST 33.3%
- Increased alkaline phosphatase 16.7%
- Increased blood bilirubin 16.7%
- Decreased blood carbon dioxide 16.7%
- Prolonged aPTT 16.7%

In the majority of patients, these clinical adverse experiences were considered by the Investigators to be *related* to study drug.

*Grade 3 and Grade 4 clinical* adverse experiences occurring in at least 5% of patients at this dose:

- Fatigue = 50.0%
- Dehydration = 50.0%
- Anorexia, back pain, diarrhea, hypotension, and recurrent diffuse large B-cell lymphoma (each) = 16.7%

*Grade 3 and 4 laboratory* adverse experiences occurring in at least 2% of patients at this dose:

- Decreased hemoglobin, decreased neutrophil count, and decreased platelet count (each) reported in 16.7% of patients.

In the majority of patients these laboratory adverse experiences were considered by the Investigators to be *related* to the study drug.

**200 mg Twice Daily for 14 Out of 21 Days**

N = 14

The most common *clinical* adverse experiences (all grades) occurring in at least 20% of patients at this dose:

- Fatigue 57.1%
- Nausea 57.1%
- Anorexia 50.0%
- Vomiting 42.9%
- Diarrhea 28.6%
- Thrombocytopenia 28.6%
- Anemia, asthenia, cough, headache, hyperglycemia, hyponatremia, pyrexia (each) 21.4%

*Laboratory* adverse experiences occurring in at least 10% of patients at this dose:

- Decreased blood calcium 21.4%
- Increased blood glucose 21.4%
- Decreased hemoglobin 21.4%
- Decreased platelet count 21.4%
- Decreased white blood cell count 21.4%
- Increased metamyelocyte count 20%
- Decreased blood magnesium 16.7%
- Increased blood creatinine, increased alkaline phosphatase, increased ALT, increased AST, decreased blood albumin, increased blood phosphorus 14.3%

In the majority of patients these clinical adverse experiences were considered by the Investigators to be *related* to study drug. All of the experiences of fatigue, nausea, vomiting thrombocytopenia, asthenia, and, hyperglycemia were considered by the Investigator to be drug-related, and the majority of the experiences of anemia, anorexia, cough and diarrhea were also considered to be drug-related.

*Grade 3 and Grade 4 clinical* adverse experiences occurring in at least 5% of patients:

- Fatigue 35.7%
- Thrombocytopenia 21.4%
- Acute myeloid leukemia, asthenia, back pain, cellulitis, chest pain, cholecystitis, confusional state, febrile neutropenia, headache, hepato-biliary infection, hyperglycemia, incoherence, neutropenia, syncope, transfusion reaction, urinary tract infection 7.1%

*Grade 3 and Grade 4 laboratory* adverse experiences occurring in at least 2% of patients:

- Decreased hemoglobin 21.4%
- Increased metamyelocyte count 20%

- Decreased platelet count 14.3%
- Decreased white blood cell count 14.3%
- Decreased absolute neutrophil count 8.3%
- Decreased neutrophil count, increased monocyte count 7.1%

In the majority of patients these laboratory adverse experiences were considered by the Investigators to be related to study drug.

**Doses above the MTD**

N = 51

*Clinical* adverse experiences (all grades) occurring in at least 20% of patients at this dose:

- Diarrhea 82.4%
- Nausea 66.7%
- Hyperglycemia 64.7%
- Fatigue 58.8%
- Anorexia 56.9%
- Thrombocytopenia 43.1%
- Vomiting 41.2%
- Dyspnea 35.3%
- Hypocalcemia 35.3%
- Hypokalemia 35.3%
- Anemia 33.3%
- Hypo-albuminemia 33.3%
- Hypophosphatemia 31.4%
- Constipation 29.4%
- Dehydration 29.4%
- Cough 27.5%
- Asthenia 25.5%
- Dizziness 23.5%
- Hyponatremia 23.5%
- Decreased weight 21.6%

*Laboratory* adverse experiences (all grades) occurring in at least 10% of the patients:

- Increased alkaline phosphatase 27.5%
- Decreased platelet count 13.7%
- Decreased hemoglobin 17.6%
- Increased ALT 17.6%
- Increased mean cell hemoglobin concentrations 16.7%
- Increased blood creatinine 15.7%
- Increased AST 12%
- Decreased blood magnesium 11.8%

- Prolonged prothrombin time 11.8%

In the majority of the patients, these clinical adverse experiences were considered by the Investigators to be *related* to the study drug.

*Grade 3 and Grade 4 clinical* adverse experiences occurring in at least 5% of patients:

- Thrombocytopenia 33.3%
- Fatigue 23.5%
- Anemia 21.6%
- Hypophosphatemia 21.6%
- Febrile neutropenia 19.6%
- Hypokalemia 19.6%
- Neutropenia 13.7%
- Dehydration 11.8%
- Diarrhea 11.8%
- Nausea 11.8%
- Leucopenia 9.8%
- Hyperglycemia 7.8%
- Acute myeloid leukemia 5.9%
- Vomiting 5.9%

*Grade 3 and Grade 4 laboratory* adverse experiences occurring in at least 2% of patients:

- Decreased hemoglobin 9.8%
- Decreased platelet count 7.8%
- Decreased white blood cell count 5.9%
- Positive urine white blood cells 2.3%
- Prolonged activated partial thromboplastin time 2.3%
- Decreased blood phosphorus, decreased blood potassium, decreased monocyte count, decreased neutrophil count, increased AST, increased lactate dehydrogenase 2.0%

In the majority of patients these laboratory adverse experiences were considered by the Investigators to be related to study drug.

**Onset and Duration of First Grade 3, 4, and 5 Clinical Adverse Experiences**

The following table summarizes the onset and duration of the first Grade 3, 4, or 5 clinical adverse experiences in patients in the Vorinostat Monotherapy (Hematologic Malignancies Population)

**400 mg once daily**

- Six (6) of 11 patients (54.5%) reported drug-related adverse experiences ≥ Grade 3.
- The median time to onset for the first Grade 3, 4, or 5 clinical adverse experiences was 26 days (range, 8 to 57 days).
- The median duration was 7 days (range, 2 to 55 days).

**300 mg twice daily 3 out of 7 days**

- One (1) of 3 patients (33.3%) reported drug-related adverse experiences ≥ Grade 3.
- The median time to onset for the first Grade 3, 4, or 5 clinical adverse experiences was 15 days (range, 15 – 15 days).
- Median time of duration could not be assessed.

**200 mg twice daily**

- Four (4) of 6 patients (66.7%) reported drug-related adverse experiences ≥ Grade 3.
- The median time to onset for the first Grade 3, 4, or 5 clinical adverse experiences was 23.5 days (range, 4 to 35 days).
- The median duration was 4.5 days (range, 2 to 11 days)

**200 mg twice daily 14 out of 21 days**

- Five of (5) of 10 patients (50.0%) reported drug-related adverse experiences ≥ Grade 3.
- The median time to onset for the first Grade 3, 4, or 5 clinical adverse experiences was 13 days (range, 6 to 35 days).
- The median time of duration was 57 days (range, 8 to 99+ days)

**Doses above the MTD**

- 31 of 51 patients (60.8%) reported drug-related adverse experiences ≥ Grade 3.
- The median time to onset for the first Grade 3, 4, or 5 clinical adverse experiences was 13 days (range, 1 to 59 days).
- The median time of duration was 11 days (range, 1 to 108 days).

**Table 99. Onset and Duration of First Grade 3, 4 or 5 Clinical Adverse Experiences (Vorinostat Monotherapy – Hematologic Malignancies) (Applicant's Table)**

| | 400mg QD continuous (N=11) | | 300mg BID 3/7 (N=3) | | 200mg BID continuous (N=6) | | 200mg BID 14/21 (N=10) | | Doses above MTD[2] (N=51) | | Doses below MTD (N=6) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Drug Related | Overall | Drug Related | Overall | Drug Related | Overall | Drug Related | Overall | Drug Related | Overall | Drug Related | Overall |
| Patients with Grade 3 or 4 Clinical Adverse Experience, n(%) | 6(54.5%) | 8(72.7%) | 1(33.3%) | 1(33.3%) | 4(66.7%) | 5(83.3%) | 5(50.0%) | 7(70.0%) | 31(60.8%) | 46(90.2%) | 0(0.0%) | 3(50.0%) |
| Patients with Grade 5 Clinical Adverse Experience, n(%) | 0(0.0%) | 0(0.0%) | 0(0.0%) | 0(0.0%) | 0(0.0%) | 0(0.0%) | 0(0.0%) | 0(0.0%) | 0(0.0%) | 0(0.0%) | 0(0.0%) | 0(0.0%) |
| Time to Onset of First Grade 3, 4 or 5 Clinical Adverse Experience (days) | | | | | | | | | | | | |
| Mean | 31.2 | 56.5 | 15.0 | 15.0 | 21.5 | 19.6 | 15.2 | 14.7 | 14.9 | 9.7 | N/A | 6.0 |
| SD | 18.20 | 70.25 | N/A | N/A | 15.93 | 14.43 | 11.56 | 13.33 | 13.38 | 9.68 | N/A | 5.57 |
| Median | 26.0 | 34.5 | 15.0 | 15.0 | 23.5 | 12.0 | 13.0 | 12.0 | 15.0 | 7.0 | N/A | 5.0 |
| Range | 8 - 57 | 8 - 226 | 15 - 15 | 15 - 15 | 4 - 35 | 4 - 35 | 6 - 35 | 6 - 44 | 1 - 59 | 1 - 39 | N/A | 1 - 12 |
| Duration of the First Grade 3 or 4 Clinical Adverse Experience (days)[1] | | | | | | | | | | | | |
| Median | 7.0 | 10.0 | N/A | N/A | 4.5 | 5.0 | 52.0 | 10.0 | 11.0 | 13.0 | N/A | N/A |
| Range | 2 - 55 | 2 - 55 | 46+ - 46+ | 46+ - 46+ | 2 - 11 | 2 - 11 | 8 - 98+ | 3 - 99+ | 1 - 108 | 1 - 157+ | N/A | 3 - 140+ |

[1] Data are displayed by treatment group.
[2] Patients with ongoing adverse experiences are censored at date of last therapy + 30 days.
[3] Maximum tolerated doses for solid tumor patients were 400 mg once daily, 300 mg twice daily 3 out of 7 days, 200 mg twice daily, and . 200 mg twice daily 14 out of 21 days.
SD = Standard Deviation
+: ongoing

[Ref. 5.3.5.4: P003V1, P004V1, P006, P013V1]

**Frequency of Adverse Experiences Resulting In Dose Modification (Vorinostat Monotherapy in Hematological Malignancies)**

- At 400 mg once daily dose, 7 of 11 patients (63.6%) did not require dose modification. Four (4) patients (36.4%) required 1 dose modification. The median time to the first adverse experience resulting in dose modification was 39 days (range, 22 to 68 days)
- At 300 mg twice daily, 3 out of 7 days, dose no dose modifications were required.
- At 200 mg twice daily dose, 5 of 6 patients (83.3%) did not require dose modification. One (1) patient required a single dose modification on Study Day 12.
- At dose of 200 mg twice daily, 14 out of 21 days, no dose modifications were required.
- At doses above the MTD, 35 of 51 patients (68.6%) required no dose modification. Sixteen (16) patients (31.4%) required 1 dose modification. The median time to the first adverse experience resulting in dose modification was 16 days (range, 2 to 66 days)

**Table 100. Summary of Dose Modifications Due to Adverse Experiences (Applicant's Table)**

| Dose Modifications | 400mg QD continuous (N=11) | 300mg BID 3/7 (N=3) | 200mg BID continuous (N=6) | 200mg BID 14/21 (N=10) | Doses above MTD[2] (N=51) | Doses below MTD (N=6) |
|---|---|---|---|---|---|---|
| Number (%) of patients with | | | | | | |
| one dose modification | 4 (36.4%) | 0 (0.0%) | 1 (16.7%) | 0 (0.0%) | 16 (31.4%) | 0 (0.0%) |
| two or more dose modifications | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| no dose modifications | 7 (63.6%) | 3 (100.0%) | 5 (83.3%) | 10 (100.0%) | 35 (68.6%) | 6 (100.0%) |
| Time to first AE resulting in a dose modification (days) | | | | | | |
| Median (Range) | 39 (22, 68) | N/A | 12 (12, 12) | N/A | 16 (2, 66) | N/A |

[1] Data are displayed by treatment group.
[2] Maximum tolerated doses for solid tumor patients were 400 mg once daily, 300 mg twice daily 3 out of 7 days, 200 mg twice daily, and . 200 mg twice daily 14 out of 21 days.

[Ref. 5.3.5.4: P003V1, P004V1, P006, P013V1]

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**Clinical and Laboratory Adverse Experiences in the Hematologic Malignancies Population that Resulted in Dose Modifications (specific AE leading to dose modification)**

The following table summarizes the clinical and the laboratory adverse experiences in the hematologic malignancies population that resulted in dose modifications.

**400 mg once daily (n = 16)**

- Adverse experiences resulting in dose modification were Grade 3 **thrombocytopenia** in 1 patient (6.3%), Grade 3 **diarrhea** in 3 patients (18.8%), and Grade 3 **dehydration** in 1 patient (6.3%)

**200 mg twice daily (n = 6)**

- 1 patient each (16.7%) required dose modification for Grade 3 **fatigue** and Grade 3 **anorexia**

**At doses above MTD (n = 51)**

- 14 (27.5%) patients required dose modification due to *clinical* adverse experiences. Those adverse experiences were Grade 4 **thrombocytopenia** in 2 patients (3.9%), Grade 2 in 1 patient (2.0%), Grade 3 **diarrhea** in 1 patient (5.9%), Grade 2 and Grade 3 **vomiting** in 1 patient each (2.0%), Grade 3 **nausea** in 2 patients (3.9%), Grade 3 **fatigue** in 4 patients (7.8%), Grade 3 **dehydration** in 2 patients (3.9%), and Grade 3 **anorexia**, Grade 3 **hypophosphatemia**, and Grade 3 **muscle spasms** each in 1 patient (2.0%).
- *Laboratory* adverse experience of Grade 3 **decreased platelet count** resulted in dose modification in 2 patients (3.9%) who received Vorinostat monotherapy at a dose above the MTD.

***Reviewer Comments:*** *incidence of thrombocytopenia leading to dose modifications is 4/51 (8%).*

**Table 101. Number (%) Of Patients With Specific Clinical and Laboratory Adverse Experiences by System Organ Class (Incidence > 0% in One or More Dose Levels) Resulting in Dose Modification in Vorinostat Monotherapy – Hematologic Malignancies Population (Applicant's Table)**

| | 400mg QD continuous (N=16) | | 300mg BID 3/7 (N=3) | | 200mg BID continuous (N=6) | | 200mg BID 14/21 (N=14) | | doses above MTD (N=51) | | doses below MTD (N=13) | | Total Patients (N=87) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % | n | % | n | % | n | % |
| *Patients With One Or More Clinical Adverse Experiences* | 4 | (25.0) | 0 | (0.0) | 1 | (16.7) | 0 | (0.0) | 14 | (27.5) | 0 | (0.0) | 19 | (21.8) |
| *Patients With No Clinical Adverse Experiences* | 12 | (75.0) | 3 | (100) | 5 | (83.3) | 14 | (100) | 37 | (72.5) | 13 | (100) | 68 | (78.2) |
| **Blood And Lymphatic System Disorders** | **1** | **(6.3)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **2** | **(3.9)** | **0** | **(0.0)** | **3** | **(3.4)** |
| Thrombocytopenia | 1 | (6.3) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 2 | (3.9) | 0 | (0.0) | 3 | (3.4) |
| *Grade 3* | 1 | (6.3) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.1) |
| *Grade 4* | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 2 | (3.9) | 0 | (0.0) | 2 | (2.3) |
| **Gastrointestinal Disorders** | **3** | **(18.8)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **5** | **(9.8)** | **0** | **(0.0)** | **8** | **(9.2)** |
| Diarrhoea | 3 | (18.8) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 4 | (7.8) | 0 | (0.0) | 7 | (8.0) |
| *Grade 2* | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.0) | 0 | (0.0) | 1 | (1.1) |
| *Grade 3* | 3 | (18.8) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 3 | (5.9) | 0 | (0.0) | 6 | (6.9) |
| Nausea | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 2 | (3.9) | 0 | (0.0) | 2 | (2.3) |
| *Grade 3* | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 2 | (3.9) | 0 | (0.0) | 2 | (2.3) |
| Vomiting | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 2 | (3.9) | 0 | (0.0) | 2 | (2.3) |
| *Grade 2* | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.0) | 0 | (0.0) | 1 | (1.1) |
| *Grade 3* | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.0) | 0 | (0.0) | 1 | (1.1) |
| **General Disorders And Administration Site Conditions** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(16.7)** | **0** | **(0.0)** | **4** | **(7.8)** | **0** | **(0.0)** | **5** | **(5.7)** |
| Fatigue | 0 | (0.0) | 0 | (0.0) | 1 | (16.7) | 0 | (0.0) | 4 | (7.8) | 0 | (0.0) | 5 | (5.7) |
| *Grade 3* | 0 | (0.0) | 0 | (0.0) | 1 | (16.7) | 0 | (0.0) | 4 | (7.8) | 0 | (0.0) | 5 | (5.7) |
| **Metabolism And Nutrition Disorders** | **1** | **(6.3)** | **0** | **(0.0)** | **1** | **(16.7)** | **0** | **(0.0)** | **4** | **(7.8)** | **0** | **(0.0)** | **6** | **(6.9)** |
| Dehydration | 1 | (6.3) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 2 | (3.9) | 0 | (0.0) | 3 | (3.4) |
| *Grade 3* | 1 | (6.3) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 2 | (3.9) | 0 | (0.0) | 3 | (3.4) |
| Anorexia | 0 | (0.0) | 0 | (0.0) | 1 | (16.7) | 0 | (0.0) | 1 | (2.0) | 0 | (0.0) | 2 | (2.3) |
| *Grade 3* | 0 | (0.0) | 0 | (0.0) | 1 | (16.7) | 0 | (0.0) | 1 | (2.0) | 0 | (0.0) | 2 | (2.3) |
| Hypophosphataemia | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.0) | 0 | (0.0) | 1 | (1.1) |
| *Grade 3* | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.0) | 0 | (0.0) | 1 | (1.1) |
| **Musculoskeletal And Connective Tissue Disorders** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(2.0)** | **0** | **(0.0)** | **1** | **(1.1)** |
| Muscle Spasms | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.0) | 0 | (0.0) | 1 | (1.1) |
| *Grade 3* | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.0) | 0 | (0.0) | 1 | (1.1) |
| A patient is counted only once within a System Organ Class category, even if more than one adverse experience with specific preferred terms occurred. Only the highest grade of a given adverse experience is counted per dose level for the individual patient. Adverse experience terms are from MedDRA Version 8.1. | | | | | | | | | | | | | | |
| *Patients With One Or More Laboratory Adverse Experiences* | 0/16 | (0.0) | 0/3 | (0.0) | 0/6 | (0.0) | 0/14 | (0.0) | 2/51 | (3.9) | 0/13 | (0.0) | 2/87 | (2.3) |
| *Patients With No Laboratory Adverse Experiences* | 16/16 | (100) | 3/3 | (100) | 6/6 | (100) | 14/14 | (100) | 49/51 | (96.1) | 13/13 | (100) | 85/87 | (97.7) |
| **Hematology Laboratory Test** | **0/16** | **(0.0)** | **0/3** | **(0.0)** | **0/6** | **(0.0)** | **0/14** | **(0.0)** | **2/51** | **(3.9)** | **0/13** | **(0.0)** | **2/87** | **(2.3)** |
| Platelet Count Decreased | 0/16 | (0.0) | 0/3 | (0.0) | 0/6 | (0.0) | 0/14 | (0.0) | 2/51 | (3.9) | 0/13 | (0.0) | 2/87 | (2.3) |
| *Grade 3* | 0/16 | (0.0) | 0/3 | (0.0) | 0/6 | (0.0) | 0/14 | (0.0) | 2/51 | (3.9) | 0/13 | (0.0) | 2/87 | (2.3) |
| n/m = number of patients with laboratory adverse experiences / number of patients for whom the laboratory test was recorded post baseline. A patient is counted only once within a Laboratory Test Type Category, even if more than one adverse experience with specific preferred terms occurred. Only the highest grade of a given adverse experience is counted per dose level for the individual patient. | | | | | | | | | | | | | | |

[Ref. 5.3.5.4: P003V1, P004V1, P006, P015V1]

## Adverse Experiences Resulting in Discontinuation

The first of the two following tables summarizes the *clinical adverse experiences that resulted in discontinuation* of Vorinostat and the second table provides a detailed list of the *patients who discontinued* due to drug-related clinical adverse experiences.

- In the 16 patients administered Vorinostat 400 mg once daily, 2 patients (12.5%) discontinued study medication due to adverse experiences, in both patients the AEs were considered drug-related: Grade 3 **decreased weight** and Grade 4 **Guillain-Barré Syndrome**.
- Of the 14 patients administered Vorinostat 200 mg twice daily 14 out of 21 days, 1 patient (7.1%) discontinued study medication due to adverse experiences. This patient discontinued study medication due to Grade 3 **fatigue**.
- At the doses above the MTD, 2 of 51 patients (3.9%) discontinued study medication due to adverse experiences. Of these 2 patients, 1 discontinued for a *drug-related* clinical adverse experience. The drug-related clinical adverse experiences resulting in study drug discontinuation was Grade 3 **asthenia**.

**Table 102. Number (%) of Patients Discontinued due to Specific Clinical Adverse Experiences by System Organ Class (Incidence > 0% in One or More Dose Levels) (Applicant's Table)**

| | 400mg QD continuous (N=16) | | 300mg BID 3/7 (N=3) | | 200mg BID continuous (N=6) | | 200mg BID 14/21 (N=14) | | doses above MTD (N=51) | | doses below MTD (N=13) | | Total Patients (N=87) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % | n | % | n | % | n | % |
| *Patients With One Or More Clinical Adverse Experiences* | *2* | *(12.5)* | *0* | *(0.0)* | *0* | *(0.0)* | *1* | *(7.1)* | *2* | *(3.9)* | *0* | *(0.0)* | *5* | *(5.7)* |
| *Patients With No Clinical Adverse Experiences* | *14* | *(87.5)* | *3* | *(100)* | *6* | *(100)* | *13* | *(92.9)* | *49* | *(96.1)* | *13* | *(100)* | *82* | *(94.3)* |
| **Gastrointestinal Disorders** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(2.0)** | **0** | **(0.0)** | **1** | **(1.1)** |
| Intestinal Obstruction | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.0) | 0 | (0.0) | 1 | (1.1) |
| *Grade 3* | *0* | *(0.0)* | *0* | *(0.0)* | *0* | *(0.0)* | *0* | *(0.0)* | *1* | *(2.0)* | *0* | *(0.0)* | *1* | *(1.1)* |
| **General Disorders And Administration Site Conditions** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(7.1)** | **1** | **(2.0)** | **0** | **(0.0)** | **2** | **(2.3)** |
| Asthenia | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.0) | 0 | (0.0) | 1 | (1.1) |
| *Grade 3* | *0* | *(0.0)* | *0* | *(0.0)* | *0* | *(0.0)* | *0* | *(0.0)* | *1* | *(2.0)* | *0* | *(0.0)* | *1* | *(1.1)* |
| Fatigue | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (7.1) | 0 | (0.0) | 0 | (0.0) | 1 | (1.1) |
| *Grade 3* | *0* | *(0.0)* | *0* | *(0.0)* | *0* | *(0.0)* | *1* | *(7.1)* | *0* | *(0.0)* | *0* | *(0.0)* | *1* | *(1.1)* |
| **Investigations** | **1** | **(6.3)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(1.1)** |
| Weight Decreased | 1 | (6.3) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.1) |
| *Grade 3* | *1* | *(6.3)* | *0* | *(0.0)* | *0* | *(0.0)* | *0* | *(0.0)* | *0* | *(0.0)* | *0* | *(0.0)* | *1* | *(1.1)* |
| **Nervous System Disorders** | **1** | **(6.3)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(1.1)** |
| Guillain-Barré Syndrome | 1 | (6.3) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.1) |
| *Grade 4* | *1* | *(6.3)* | *0* | *(0.0)* | *0* | *(0.0)* | *0* | *(0.0)* | *0* | *(0.0)* | *0* | *(0.0)* | *1* | *(1.1)* |

A patient is counted only once within a System Organ Class category, even if more than one adverse experience with specific preferred terms occurred. Only the highest grade of a given adverse experience is counted per dose level for the individual patient.
Adverse experience terms are from MedDRA Version 8.1

**Table 103. Details of the Patients who Discontinued Vorinostat due to Drug-Related Clinical Adverse Experiences (By Dose Level; Vorinostat Monotherapy – Hematologic Malignancies) (Applicant's Table)**

| Study Number | AN | Gender | Race | Age | Period | Rel Day of AE Onset | Adverse Experience | Duration of AE | Rel Day of Drug Discon | Toxicity Grade | Serious | Drug Relation | Action Taken | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **400mg QD continuous** | | | | | | | | | | | | | | |
| 683006 | 1035 | F | white | 69 | Trt Cycle 11 | 302 | Weight Decreased | | 359 | 3 | N | poss | discontinued PRx | not recovered |
| | 1058 | M | white | 49 | Trt Cycle 1 | 22 | Guillain-Barre Syndrome | 55 days | 22 | 4 | Y | poss | discontinued PRx | recovered |
| **200mg BID 14/21** | | | | | | | | | | | | | | |
| 683005 | 1028 | M | white | 68 | Trt Cycle 2 | 31 | Fatigue | 13 days | 43 | 3 | N | poss | discontinued PRx | recovered |
| **doses above MTD** | | | | | | | | | | | | | | |
| 683003 | 1024 | M | white | 43 | Trt Cycle 3 | 47 | Asthenia | | 47 | 3 | N | poss | discontinued PRx | not recovered |

AN = Allocation number
def = Definitely, def not = Definitely not, poss = Possibly, prob = Probably, prob not = Probably not
PRx = prime therapy.
Adverse experience terms are from MedDRA Version 8.1.

[Ref. 5.3.5.4: P005V1, P004V1, P006, P013V1]

**Vorinostat Combination Therapies**

**Summary of Safety Outcomes (Clinical Adverse Experiences)**

10 patients diagnosed with advanced solid tumors or hematologic malignancies were enrolled in this population. The following table summarizes *clinical* adverse experiences outcomes for these patients.

- 9/10 (90.0%) had 1 or more *clinical* adverse experiences
- 8 clinical adverse experiences were determined by the Investigator to be *related* to the study drug.
- Three (3) patients had 1 or more *serious* adverse experience
- No *serious drug-related* adverse experiences were reported
- One (1) patient (10.0%) was *discontinued* due to a serious clinical adverse experience.

*In the absence of a randomized control group in the Phase I studies, it is not possible to separate which of the adverse experiences are attributable only to Vorinostat or to the other agents with which Vorinostat was combined.*

**200 mg Twice Daily 14 Out of 21 Days**

- Seven (7) of 7 patients had 1 or more *clinical* adverse experiences.
- Six (6) of 7 patients (85.7%) had clinical adverse experiences considered by the Investigator to be *related* to study drug.
- One (1) patient was discontinued due to **dehydration** which was not considered related to study drug.

**Doses below the MTD**

- Six (6) of 7 patients (85.7%) had 1 or more *clinical* adverse experiences.
- Six (6) patients had clinical adverse experiences considered by the Investigator to be *related* to study drug.
- No patients discontinued due clinical adverse experiences in this treatment group.

**Table 104. Clinical Adverse Experience Summary (Vorinostat Combination Therapies) (Applicant's Table)**

| | Combination Therapies (N = 10)* | |
|---|---|---|
| | n | (%) |
| Number (%) of patients: | | |
| With one or more adverse experiences | 9 | (90.0) |
| With no adverse experience | 1 | (10.0) |
| With drug-related adverse experiences‡ | 8 | (80.0) |
| With serious adverse experiences | 3 | (30.0) |
| With serious drug-related adverse experiences‡ | 0 | ( 0.0) |
| Who died | 0 | ( 0.0) |
| Discontinued due to adverse experiences | 1 | (10.0) |
| Discontinued due to drug-related adverse experiences‡ | 0 | ( 0.0) |
| Discontinued due to serious adverse experiences | 1 | (10.0) |
| Discontinued due to serious drug-related adverse experiences‡ | 0 | ( 0.0) |

* Data are displayed by treatment group.
‡ Determined by the Investigator to be possibly, probably or definitely drug-related.

[Ref. 5.3.5.4: P012V1, P015V1, P016V1]

**Summary of Safety Outcomes (Laboratory Adverse Experiences)**

The following table summarizes *laboratory* adverse experiences in patients diagnosed with advanced solid tumors or hematologic malignancies who received Vorinostat in combination with other chemotherapeutic agents.

- 5 (50.0%) had 1 or more adverse experience
- 4 (40.0%) had laboratory adverse experiences determined by the Investigator to be related to study drug
- No patient reported a serious laboratory adverse experience
- No patient discontinued from study therapy due to a laboratory adverse experience

**200 mg Twice Daily 14 Out of 21 Days**

- Two (2) of 7 patients (28.6%) had 1 or more *laboratory* adverse experiences
- These adverse experiences were considered related to study drug by the Investigator
- No patient was discontinued due to the laboratory adverse experiences.

**Doses below the MTD**

- Four (4) of 7 patients (57.1 %) had 1 or more *laboratory* adverse experiences
- Three (3) patients had *laboratory* adverse experiences considered related to study drug by the Investigator
- No patients in this treatment group discontinued due laboratory adverse experiences.

**Table 105. Laboratory Adverse Experience Summary (Vorinostat Combination Therapies) (Applicant's Table)**

| | Combination Therapies (N = 10) | |
|---|---|---|
| | n | (%)[§] |
| Number (%) of patients: | | |
| With at least one lab test post-baseline | 10 | |
| With one or more adverse experiences | 5 | (50.0) |
| With no adverse experience | 5 | (50.0) |
| With drug-related adverse experiences[‡] | 4 | (40.0) |
| With serious adverse experiences | 0 | (0.0) |
| With serious drug-related adverse experiences[‡] | 0 | (0.0) |
| Who died | 0 | (0.0) |
| Discontinued due to adverse experiences | 0 | (0.0) |
| Discontinued due to drug-related adverse experiences[‡] | 0 | (0.0) |
| Discontinued due to serious adverse experiences | 0 | (0.0) |
| Discontinued due to serious drug-related adverse experiences[‡] | 0 | (0.0) |

[†] Data are displayed by treatment group.
[‡] Determined by the Investigator to be possibly, probably or definitely drug-related.
[§] The percent = number of patients within the laboratory adverse experience category / number of patients with one or more laboratory tests post-baseline.

[Ref. 5.3.5.4: P012V1, P015V1, P016V1]

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### Grade 3, 4, and 5 Clinical and Laboratory Adverse Experiences

- Grade 3, 4, and 5 *clinical* adverse experiences observed at this dose and occurring in 10% of the patients were fatigue, anorexia, cancer pain, dehydration, dyspnea, hyperglycemia, hypoxia, nausea, peripheral edema, and T-cell lymphoma
- Grade 3, 4, and 5 *laboratory* adverse experiences observed at this dose were decreased blood calcium (20.0%), and in 10.0% of patients decreased blood glucose, decreased blood sodium, decreased neutrophil count, decreased INR, and prolonged activated partial thromboplastin time

### Onset and Duration of First Grade 3, 4, or 5 Clinical Adverse Experiences

The following table summarizes the *onset and duration* of the first Grade 3, 4, or 5 *clinical* adverse experiences in patients in the Vorinostat Combination Therapies population.

- Four (4) of 10 patients reported drug-related adverse experiences ≥ Grade 3
- Median time to onset for the first Grade 3, 4, or 5 clinical adverse experience was 5 days (range, 1 to 50 days)
- Median duration was 16 days (range, 13 to 80 days)

**Table 106. Time to Onset and Duration of the First Grade 3, 4 or 5 Clinical Adverse Experience (Applicant's Table)**

| | Combination Therapies (N=10) | |
|---|---|---|
| | Drug Related | Overall |
| Patients with Grade 3 or 4 Clinical Adverse Experience, n(%) | 4(40.0%) | 6(60.0%) |
| Patients with Grade 5 Clinical Adverse Experience, n(%) | 0(0.0%) | 0(0.0%) |
| Time to Onset of First Grade 3, 4 or 5 Clinical Adverse Experience (days) | | |
| Mean | 15.3 | 25.2 |
| SD | 23.37 | 26.06 |
| Median | 5.0 | 18.0 |
| Range | 1 - 50 | 1 - 62 |
| Duration of the First Grade 3 or 4 Clinical Adverse Experience (days)[1] | | |
| Median | 16.0 | 15.5 |
| Range | 13 - 80+ | 3 - 80+ |

[1] Data are displayed by treatment group.
[2] Patients with ongoing adverse experiences are censored at date of last therapy + 30 days.
SD = Standard Deviation
+: ongoing

[Ref. 5.3.5.4: P012V1, P015V1, P016V1]

**Adverse Experiences Resulting in Dose Modification**

The following table summarizes the adverse experiences resulting in a *dose modification* in this study population.

- Two (2) of 10 patients had *clinical* adverse experiences that resulted in 1 dose modification
- One (1) patient had adverse experiences that resulted in 2 or more dose modifications
- Median time to first adverse experience resulting in dose modification was 27 days (range, 5 to 29 days)

**Table 107. Summary of Dose Modifications Due to Adverse Experiences (Vorinostat Combination Therapies) (Applicant's Table)**

| Dose Modifications | Combination Therapies (N=10) |
|---|---|
| Number (%) of patients with | |
| one dose modification | 2 (20.0%) |
| two or more dose modifications | 1 (10.0%) |
| no dose modifications | 7 (70.0%) |
| Time to first AE resulting in a dose modification (days) | |
| Median (Range) | 27 (5, 29) |
| Data are displayed by treatment group. | |

[Ref. 5.3.5.4: P012V1, P015V1, P016V1]

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**Deaths and Other Serious Adverse Experiences**

**Deaths**

- A total of 24 deaths were reported in the CTCL, solid tumors, and hematological malignancies populations in different Vorinostat monotherapies and Vorinostat combination therapies studies. Six (6) additional deaths were reported in Protocol 014: an ongoing double-blind Phase III placebo controlled study in patients with advanced mesothelioma.

- 21/24 (87.5%) deaths were considered ***not drug-related*** by the Investigator
- 3 deaths—AN1008 (unknown cause) and AN1048 (ischemic stroke) in Protocol 001, and AN003 (tumor hemorrhage) in Protocol 011—were considered by the Investigators to be ***related*** to the study drug.
- 14 (58.3%) deaths were attributed to progression of the underlying disease.

- Three (3) deaths occurred on the 400 mg once daily dose, the clinically recommended dose and schedule.
- The only possibly drug related death at the 400 mg daily continuous dose was due to unknown cause in Protocol 001.

FOR FURTHER DETAILS ON DEATHS PLEASE SEE SECTION 7.1.1 Deaths

**Other Serious Adverse Experiences**

A serious adverse experience is defined as an untoward (unfavorable) medical occurrence at any dose that:

- Results in death, or
- Is life-threatening (the term "life-threatening" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe), or
- Requires inpatient hospitalization or prolongation of existing hospitalization, or
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect, or
- Jeopardizes the subject/patient and may require medical or surgical intervention to prevent one of the outcomes listed above, or
- Is an overdose (i.e. the patient, accidentally or intentionally, takes an amount of the study drug that exceeds the dose prescribed by the protocol or an amount of a marketed drug that exceeds the maximal daily dose recommended in the package circular), or
- Cancer (that is not the condition under study).

- All SAEs, regardless of relationship to the study drug, occurring after study drug administration to 30 days from the last dose of the study drug, or until the initiation of a new anticancer therapy, whichever came first, were to be reported to the sponsor via

telephone and by fax within 24 hours of the first knowledge of the occurrence of the event.

- Any SAE occurring at *any time after completion of the study* also must be promptly reported to the sponsor, *if a causal relationship to the study drug is suspected.*
- The Investigator is required to fill out the SAE form provided by the sponsor. Sufficient details are to be provided to allow a complete medical assessment of the adverse event and independent determination of possible causality.

FOR FURTHER DETAILS ON OTHER SERIOUS ADVERSE EXPERIENCES PLEASE SEE SECTION 7.1.2 Other Serious Adverse Events

**Other *Significant* Adverse Experiences**

Clinical and laboratory adverse experiences of special interest (eg clinical adverse experiences: **cardiovascular**, **cerebrovascular**, and **venous thromboembolic**; and laboratory adverse experiences: **hyperglycemia, increased serum creatinine,** and **thrombocytopenia)** are detailed in Section 7.1.3 Dropouts and Other Significant Adverse Events under Subsection 7.1.3.3 Other Significant Adverse Events.

## 7.1.1 Deaths

**Deaths**

The following table summarizes the deaths of all patients who received Vorinostat treatment. It includes the deaths that occurred within 30 days after treatment termination. Deaths are grouped in the table by *the last dose level* which the patient received in the study, not *the by the initial assigned dose*. The discussion of deaths in the Clinical Summary of Safety is based on the information recorded in the outcome section of the adverse experience page of the case report form (CRF).

- A total of 24 deaths were reported in the studies of CTCL, solid tumors, hematological malignancies, and combination therapies populations.
  - [Additional 6 deaths were reported in Protocol 014: an ongoing double-blind Phase III placebo controlled study (Protocol 014) in patients with advanced mesothelioma.]
- 21/24 (87.5%) deaths were considered ***not drug-related*** by the Investigator
- 3 deaths: AN1008 (unknown cause) and AN1048 (ischemic stroke) in Protocol 001, and AN003 (tumor hemorrhage) in Protocol 011 were considered by the Investigator to be ***related*** to the study drug.
- 14 (58.3%) deaths were attributed to progression of the underlying disease.

- Three (3) deaths occurred on the 400 mg once daily dose, the clinically recommended dose and schedule.
- The only possibly drug related death at the 400 mg daily continuous dose was due to unknown causes in Protocol 001.

**Protocol 014**

- As of 30-Nov-2005, the serious adverse experiences cut-off date, 6 deaths had occurred in an ongoing double-blind Phase III placebo controlled study (Protocol 014) in patients with **advanced mesothelioma**.

- **None** of the deaths on this study was considered by the Investigator as related to the study drug and all deaths were attributed to the underlying malignancy.
    - Since this is an ongoing blinded study, these deaths are not included in the 24 deaths summarized in the table below.

**Total number of deaths:**

- 24 deaths displayed in the first table below
- 6 deaths from Protocol 014 in the second table below



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## Table 108. Details of the Patients with Clinical Adverse Experiences resulting in Death by Dose Level (All Patients) (Applicant's Table)

| Study Number | AN | Gender | Race | Age | Period | Onset | Experience | AE | Discon | Grade | Serious | Relation | Action Taken | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **400mg QD continuous** | | | | | | | | | | | | | | |
| 683001 | 1048 | F | black | 46 | Treatment | 2 | Death | 1 day | 2 | 5 | Y | poss | discontinued PRx | fatal |
| 683005 | 1007 | M | white | 75 | Trt Cycle 1 | 8 | Bladder Cancer | 6 days | 10 | 5 | Y | def not | no action with test drug | fatal |
| | 1024 | M | white | 61 | Trt Cycle 1 | 38 | Diffuse Large B-Cell Lymphoma | 1 day | 38 | 5 | Y | def not | no action with test drug | fatal |
| **300mg BID 3/7** | | | | | | | | | | | | | | |
| 683006 | 1071 | M | white | 51 | Trt Cycle 2 | 50 | Lung Disorder | 6 days | 45 | 5 | Y | def not | interrupted PRx | fatal |
| 683013 | 422 | M | white | 78 | Trt Cycle 2 | 40 | Diffuse Large B-Cell Lymphoma | 1 day | 30 | 5 | Y | def not | no action with test drug | fatal |
| | | | | | | | Gastrointestinal Haemorrhage | 1 day | 30 | 5 | Y | prob not | no action with test drug | fatal |
| | | | | | | | Shock Haemorrhagic | 1 day | 30 | 5 | Y | prob not | no action with test drug | fatal |
| **200mg BID continuous** | | | | | | | | | | | | | | |
| 683005 | 1038 | F | black | 67 | Trt Cycle 2 | 88 | Sepsis | 11 days | 35 | 4 | Y | def not | interrupted PRx | fatal |
| 683006 | 1047 | M | white | 59 | Trt Cycle 5 | 118 | Diffuse Large B-Cell Lymphoma Recurrent | 24 days | 118 | 3 | Y | def not | no action with test drug | fatal |
| **200mg BID 14/21** | | | | | | | | | | | | | | |
| 683002 | 1030 | M | white | 76 | Trt Cycle 1 | 37 | Acute Myeloid Leukaemia | 1 day | 14 | 5 | Y | def not | no action with test drug | fatal |
| 683011 | 5 | F | white | 39 | Cycle 2 | 34 | Tumour Haemorrhage | 8 days | 40 | 3 | Y | prob | discontinued PRx | fatal |
| | 38 | M | white | 66 | Cycle 3-4 | 50 | General Physical Health Deterioration | | 50 | 5 | Y | def not | discontinued PRx | fatal |
| | 39 | F | white | 59 | Cycle 1 | 14 | Neoplasm Progression | | 14 | 5 | Y | def not | discontinued PRx | fatal |
| **doses above MTD** | | | | | | | | | | | | | | |
| 683003 | 1008 | M | white | 90 | Trt Cycle 2 | 40 | Death | 1 day | 37 | 5 | Y | def not | no action with test drug | fatal |
| | 1009 | M | white | 53 | Trt Cycle 3 | 67 | Acute Myeloid Leukaemia | 1 day | 52 | 5 | Y | def not | no action with test drug | fatal |
| | 1015 | F | white | 74 | Trt Cycle 1 | 18 | Acute Myeloid Leukaemia | 2 days | 15 | 5 | Y | def not | no action with test drug | fatal |
| | 1012 | F | white | 71 | Trt Cycle 2 | 37 | Pneumonia Fungal | 10 days | 33 | 5 | Y | def not | no action with test drug | fatal |
| | 1037 | F | white | 46 | Trt Cycle 1 | 20 | Acute Myeloid Leukaemia | 1 day | 12 | 5 | Y | def not | no action with test drug | fatal |
| 683005 | 1015 | F | white | 73 | Trt Cycle 19 | 499 | T-Cell Lymphoma | 24 days | 467 | 2 | Y | def not | no action with test drug | fatal |
| 683006 | 1014 | M | white | 70 | Trt Cycle 1 | 42 | Death | 1 day | 15 | 5 | Y | def not | no action with test drug | fatal |
| 683006 | 1066 | M | white | 55 | Trt Cycle 1 | 11 | Mesothelioma | 2 days | 10 | 5 | Y | def not | no action with test drug | fatal |
| 683011 | 16 | M | white | 61 | Cycle 1 | 28 | Neoplasm Malignant | | 10 | 2 | Y | def not | no action with test drug | fatal |
| | 32 | M | white | 59 | Cycle 1 | 22 | General Physical Health Deterioration | | 14 | 5 | Y | def not | discontinued PRx | fatal |
| **doses below MTD** | | | | | | | | | | | | | | |
| 683001 | 1002 | F | white | 71 | Treatment | 227 | Ischaemic Stroke | 30 days | 227 | 4 | Y | poss | discontinued PRx | fatal |
| | 1033 | F | black | 75 | Treatment | 52 | T-Cell Lymphoma | 1 day | 45 | 5 | Y | def not | no action with test drug | fatal |
| 683006 | 1003 | M | black | 25 | Trt Cycle 1 | 8 | Renal Cell Carcinoma Stage Unspecified | 13 days | 8 | 5 | Y | def not | no action with test drug | fatal |

AN = Allocation number
def = Definitely; def not = Definitely not; poss = Possibly; prob = Probably; prob not = Probably not
PRx = prime therapy.
Adverse experience terms are from MedDRA Version 8.1
[Ref. 5.3.5.2: P001] [Ref. 5.3.5.4: P002, P003V1, P004V1, P006, P011V1, P012V1, P013V1, P015V1, P016V1]

## Table 109. Details of Serious Adverse Experiences that resulted in Deaths in Protocol 014 (Applicant's Table)

| Allocation Number | Age | Gender | Adverse Experience | Body System | Onset Date | Stop Date | Duration (days) | Date of Death | NCI Common Toxicity Criteria | Causality | Action | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 10002 | 59 | M | Pleural mesothelioma | Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 21-Sep-05 | 21-Sep-05 | 1 | | 5 | def not | no action with test drug | fatal |
| 10004 | 52 | M | Mesothelioma malignant | Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 26-Oct-05 | 9-Nov-05 | 15 | | 5 | def not | interrupted PRx | fatal |
| 10005 | 64 | M | Pleural mesothelioma malignant | Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 4-Nov-05 | 9-Nov-05 | 6 | | 5 | def not | no action with test drug | fatal |
| 10606 | 56 | F | Pleural mesothelioma | Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 28-Oct-05 | Not Available | Not Available | | 5 | not related | no action with test drug | fatal |
| 11521 | 51 | M | Pleural mesothelioma malignant advanced | Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 21-Oct-05 | Not Available | Not Available | | 5 | def not | discontinued PRx | fatal |
| 11525 | 43 | M | Mesothelioma malignant advanced | Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 24-Nov-05 | Not Available | Not Available | | 5 | not related | no action with test drug | fatal |

[Ref. 5.3.5.4: P014V1]

## Vorinostat Monotherapy – CTCL

The following table lists by dose level the clinical adverse experiences in CTCL patients who died during treatment or within 30 days after the last dose of Vorinostat.

- Among the 107 patients with CTCL there were 5 (4.7%) deaths.
- All of these patients had stage IIB or higher CTCL.
- Three (3) of these deaths were considered ***not related*** to the study drug by the Investigator as they reflected either concurrent medical conditions or the underlying disease.
  - One of the *unrelated* deaths due to progression of T-cell lymphoma occurred in a patient whose initial treatment dose was 400 mg once daily, later modified to a dose below the MTD in Protocol 001
- Two (2) deaths were considered by the Investigator to be ***possibly related*** to the study drug.
  - One was reported at 400 mg once daily dose level. The patient, AN1048 (Protocol 001), was dispensed Vorinostat at a dose of 400 mg once daily. The following day the patient was found dead at home. The Investigator could not determine if any dose of Vorinostat had been taken by the patient, and the cause of death remained unknown. No autopsy was performed.
  - The second death, due to an ischemic stroke, occurred in a patient who had undergone a dose modification to 300 mg once daily dose in Protocol 001.

**Table 110. Details of Patients with Clinical Adverse Experiences Resulting in Death by Dose Level (Vorinostat Monotherapy – CTCL) (Applicant's Table)**

| Study Number | AN | Gender | Race | Age | Period | Rel Day of AE Onset | Adverse Experience | Duration of AE | Rel Day of Drug Discon | Toxicity Grade | Serious | Drug Relation | Action Taken | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **400mg QD continuous** | | | | | | | | | | | | | | |
| 683001 | 1048 | F | black | 46 | Treatment | 2 | Death | 1 day | 2 | 5 | Y | poss | discontinued PRx | fatal |
| **700mg BID continuous** | | | | | | | | | | | | | | |
| 683005 | 1038 | F | black | 67 | Trt Cycle 2 | 38 | Sepsis | 11 days | 35 | 4 | Y | def not | interrupted PRx | fatal |
| **doses above MTD** | | | | | | | | | | | | | | |
| 683005 | 1015 | F | white | 73 | Trt Cycle 19 | 409 | T-Cell Lymphoma | 24 days | 467 | 2 | Y | def not | no action with test drug | fatal |
| **doses below MTD** | | | | | | | | | | | | | | |
| 683001 | 1006 | F | white | 71 | Treatment | 227 | Ischaemic Stroke | 30 days | 227 | 4 | Y | poss | discontinued PRx | fatal |
| | 1033 | F | black | 75 | Treatment | 52 | T-Cell Lymphoma | 1 day | 43 | 5 | Y | def not | no action with test drug | fatal |

AN = Allocation number
def = Definitely; def not = Definitely not; poss = Possibly; prob = Probably; prob not = Probably not
PRx = prime therapy.
Adverse experience terms are from MedDRA Version 8.1
[Ref. 5.3.5.2: P001] [Ref. 5.3.5.4: P002]

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## Vorinostat Monotherapy - Solid Tumors

The following table lists the patients with solid tumors by dose level who were treated with Vorinostat monotherapy and died on treatment or within 30 days after the last dose of study drug. Deaths are grouped in the table by the last dose level which the patient received in the study, not the assigned treatment group.

- Among the 101 patients with solid tumors, there were 10 patients (9.9%) with adverse experiences that resulted in death.
- Only 1 of 10 deaths (AN 003) was considered by the Investigator to be ***related*** to the study drug. The death, due to tumor hemorrhage, occurred in a patient whose initial treatment dose was 300 mg twice daily 14 out of 21 days and had undergone a dose modification to 300 mg once daily dose in Protocol 011.

**Table 111. Details of Patients with Clinical Adverse Experiences Resulting in Death by Dose Level (Vorinostat Monotherapy – Solid Tumors) (Applicant's Table)**

| Study Number | AN | Gender | Race | Age | Period | Onset | Experience | AE | Discon | Grade | Serious | Relation | Action Taken | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **400mg QD continuous** | | | | | | | | | | | | | | |
| 683006 | 1097 | M | white | 75 | Trt Cycle 1 | 8 | Bladder Cancer | 6 days | 10 | 5 | Y | def not | no action with test drug | fatal |
| **300mg BID 3/7** | | | | | | | | | | | | | | |
| 683006 | 1071 | M | white | 51 | Trt Cycle 2 | 50 | Lung Disorder | 6 days | 45 | 5 | Y | def not | interrupted PRx | fatal |
| **200mg BID 14/21** | | | | | | | | | | | | | | |
| 683011 | 3 | F | white | 39 | Cycle 2 | 34 | Tumour Haemorrhage | 8 days | 40 | 3 | Y | prob | discontinued PRx | fatal |
| | 38 | M | white | 66 | Cycle 3-4 | 50 | General Physical Health Deterioration | | 56 | 5 | Y | def not | discontinued PRx | fatal |
| | 39 | F | white | 59 | Cycle 1 | 14 | Neoplasm Progression | | 14 | 5 | Y | def not | discontinued PRx | fatal |
| **doses above MTD** | | | | | | | | | | | | | | |
| 683006 | 1014 | M | white | 70 | Trt Cycle 1 | 42 | Death | 1 day | 15 | 5 | Y | def not | no action with test drug | fatal |
| | 1066 | M | white | 55 | Trt Cycle 1 | 11 | Mesothelioma | 2 days | 10 | 5 | Y | def not | no action with test drug | fatal |
| 683011 | 16 | M | white | 61 | Cycle 1 | 28 | Neoplasm Malignant | | 10 | 2 | Y | def not | no action with test drug | fatal |
| | 32 | M | white | 59 | Cycle 1 | 22 | General Physical Health Deterioration | | 14 | 5 | Y | def not | discontinued PRx | fatal |
| **doses below MTD** | | | | | | | | | | | | | | |
| 683006 | 1003 | M | black | 25 | Trt Cycle 1 | 8 | Renal Cell Carcinoma Stage Unspecified | 13 days | 8 | 5 | Y | def not | no action with test drug | fatal |

AN = Allocation number
def = Definitely; def not = Definitely not; poss = Possibly; prob = Probably; prob not = Probably not
PRx = prime therapy.
Adverse experience terms are from MedDRA Version 8.1.

[Ref. 5.3.3.2: P008] [Ref. 5.3.5.4: P002, P006, P011V1]

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## Vorinostat Monotherapy - Hematologic Malignancies

The following table summarizes by dose level the patients in this population who died during treatment or within 30 days after the last dose of study drug.

- Of the 87 patients with hematologic malignancies, 9 patients (10.3%) had adverse experiences that resulted in death; 1 death was reported in a patient receiving Vorinostat at a dose of 400 mg once daily. All clinical adverse experiences that resulted in death were considered ***not related*** to the study drug by the Investigator.

**Table 112. Details of Patients with Clinical Adverse Experiences resulting in Death by Dose Level (Vorinostat Monotherapy-Hematologic Malignancies) (Applicant's Table)**

| Study Number | AN | Gender | Race | Age | Period | Rel Day of AE Onset | Adverse Experience | Duration of AE | Rel Day of Drug Discon | Toxicity Grade | Serious | Drug Relation | Action Taken | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **400mg QD continuous** | | | | | | | | | | | | | | |
| 683006 | 1024 | M | white | 61 | Trt Cycle 1 | 38 | Diffuse Large B-Cell Lymphoma | 1 day | 19 | 5 | Y | def not | no action with test drug | fatal |
| **300mg BID 3/7** | | | | | | | | | | | | | | |
| 683013 | 422 | M | white | 78 | Trt Cycle 2 | 40 | Diffuse Large B-Cell Lymphoma | 1 day | 30 | 5 | Y | def not | no action with test drug | fatal |
| | | | | | | | Gastrointestinal Haemorrhage | 1 day | 30 | 5 | Y | prob not | no action with test drug | fatal |
| | | | | | | | Shock Haemorrhagic | 1 day | 30 | 5 | Y | prob not | no action with test drug | fatal |
| **200mg BID continuous** | | | | | | | | | | | | | | |
| 683006 | 1047 | M | white | 59 | Trt Cycle 5 | 118 | Diffuse Large B-Cell Lymphoma Recurrent | 24 days | 118 | 5 | Y | def not | no action with test drug | fatal |
| **200mg BID 14/21** | | | | | | | | | | | | | | |
| 683003 | 1030 | M | white | 76 | Trt Cycle 1 | 37 | Acute Myeloid Leukaemia | 1 day | 14 | 5 | Y | def not | no action with test drug | fatal |
| **doses above MTD** | | | | | | | | | | | | | | |
| 683003 | 1008 | M | white | 90 | Trt Cycle 2 | 40 | Death | 1 day | 37 | 5 | Y | def not | no action with test drug | fatal |
| | 1009 | M | white | 53 | Trt Cycle 3 | 67 | Acute Myeloid Leukaemia | 1 day | 52 | 5 | Y | def not | no action with test drug | fatal |
| | 1015 | F | white | 74 | Trt Cycle 1 | 18 | Acute Myeloid Leukaemia | 2 days | 15 | 5 | Y | def not | no action with test drug | fatal |
| | 1022 | F | white | 71 | Trt Cycle 2 | 37 | Pneumonia Fungal | 10 days | 33 | 5 | Y | def not | no action with test drug | fatal |
| | 1037 | F | white | 46 | Trt Cycle 1 | 20 | Acute Myeloid Leukaemia | 1 day | 12 | 5 | Y | def not | no action with test drug | fatal |

AN = Allocation number
def = Definitely; def not = Definitely not; poss = Possibly; prob = Probably; prob not = Probably not
PRx = prime therapy.
Adverse experience terms are from MedDRA Version 8.1.
[Ref. 5.3.5.4: P003V1, P004V1, P006, P013V1]

## Vorinostat Combination Therapies

- No deaths were reported among patients receiving combination therapies.

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## 7.1.2 Other Serious Adverse Events

**Other Serious Adverse Experiences**

**Definition of a Serious Adverse Experience/Event (SAE)**

A serious adverse experience is defined as an untoward (unfavorable) medical occurrence at any dose that:

- Results in death
- Is life-threatening (the term "life-threatening" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Jeopardizes the subject/patient and may require medical or surgical intervention to prevent one of the outcomes listed above.
- Is an overdose (i.e. the patient, accidentally or intentionally, takes an amount of the study drug that exceeds the dose prescribed by the protocol or an amount of a marketed drug that exceeds the maximal daily dose recommended in the package circular)
- Cancer (that is not the condition under study)

- Any SAE, regardless of relationship to the study drug, that occurs after study drug administration to 30 days from the last dose of the study drug or until the initiation of a new anticancer therapy, whichever comes first, must be reported to the sponsor via telephone and by fax within 24 hours of the first knowledge of the occurrence of the event.
- Any SAE occurring at any time after completion of the study must be promptly reported to the sponsor, if a causal relationship to the study drug is suspected.
- The Investigator is required to fill out the SAE form provided by the sponsor. Sufficient details must be provided to allow a complete medical assessment of the adverse event and independent determination of possible causality.

**Summary Comparison of Serious Clinical Adverse by Population**

**Vorinostat Monotherapy – CTCL**

Among the 107 patients on Vorinostat monotherapy for CTCL, the highest incidence of serious clinical adverse experiences in all dose levels were reported in the System-Organ Class(s) of Infections and Infestations and Neoplasms (Benign, Malignant and Unspecified; including Cysts and Polyps)—occurring in 8 patients each.

- Of the 8 patients in the **Neoplasms** (Benign, Malignant and Unspecified; including Cysts and Polyps) SOC, five (5) patients reported serious clinical adverse experiences that were attributed to worsening of the primary indication, and the remaining patients to squamous cell carcinoma or lung neoplasm.
- Of the 8 patients with **infections**, seven (7) (87.5%) were considered by the Investigator to be *not related* to study drug (see the following two tables)

The serious clinical adverse experiences that occurred during the course of the study, including 30 days after discontinuation of study treatment, were consistent with the underlying diseases and expected in patients who had undergone prior oncology treatments.

**400 mg once daily dose level**

In the 86 CTCL patients who received Vorinostat at a dose of **400 mg once daily** the frequency of all serious clinical adverse experiences by SOC occurring at an incidence of ≥2% are summarized in the table below. Notables:

- **Pulmonary embolism** in 4 patients (4.7%)
- **Squamous cell carcinoma** in 3 patients (3.5%)
- **Anemia** in 2 patients (2.3%)

**Other dose levels**

Serious clinical adverse experiences were also observed in the CTCL population at **other dose levels**:

- Five (5) of 14 patients (35.7%) who received Vorinostat at a dose of **300 mg twice daily, 3 out of 7 days,** and 3 of 10 patients who received Vorinostat at a dose of **200 mg twice daily** reported serious clinical adverse experiences.
- **Dehydration** was common to both dose levels occurring at an incidence of 7.1% and 10.0%, respectively.
- Other serious adverse experiences at a dose of **300 mg twice daily 3 out of 7 days**: **vomiting, nausea, diarrhea, deep vein thrombosis, pyrexia** and **hypotension**—all at a single incidence of 7.1%.
- **200 mg twice daily dose** had each of **sepsis, urinary tract infection, subdural hematoma** and **T-cell lymphoma** at a single incidence of 10.0%, and **thrombocytopenia** in 2 of 10 patients (20.0%)

- At **doses below the MTD**, 3 of 12 patients (25.0%) reported tumor related serious clinical adverse experiences, 1 patient (8.3%) with **herpes zoster** and 1 patient (8.3%) with **ischemic stroke** and **dehydration**.
- At **doses above the MTD** 3 of 20 patients (15.0%) reported a serious clinical adverse experience with **vomiting** and **dehydration** occurring at the highest incidence of 10.0%. The remaining serious clinical adverse experiences all occurred at an incidence of 5.0%. They included **thrombocytopenia, anemia, nausea, pyrexia, chest pain, hepatic ischemia, sepsis, infection, wound infection, reduced oral intake, T-cell lymphoma, hypotension** and **orthostatic hypotension**.

Overall, the data suggests that even at doses above the MTD, the frequency of serious clinical adverse experiences in the CTCL population is generally low.

**Table 113. Number (%) of Patients with Specific Serious Clinical Adverse Experiences by System Organ Class (Incidence ≥ 2% in One or More Dose Levels) Vorinostat Monotherapy – CTCL (Applicant's Table)**

| | 400mg QD continuous (N=86) | | 300mg BID 5/7 (N=14) | | 200mg BID continuous (N=10) | | doses above MTD (N=20) | | doses below MTD (N=12) | | Total Patients (N=107) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % | n | % | n | % |
| *Patients With One Or More Clinical Adverse Experiences* | *16* | *(18.6)* | *5* | *(35.7)* | *3* | *(30.0)* | *3* | *(15.0)* | *5* | *(41.7)* | *29* | *(27.1)* |
| *Patients With No Clinical Adverse Experiences* | *70* | *(81.4)* | *9* | *(64.3)* | *7* | *(70.0)* | *17* | *(85.0)* | *7* | *(58.3)* | *78* | *(72.9)* |
| **Blood And Lymphatic System Disorders** | 2 | (2.3) | 0 | (0.0) | 2 | (20.0) | 2 | (10.0) | 0 | (0.0) | 6 | (5.6) |
| Thrombocytopenia | 1 | (1.2) | 0 | (0.0) | 2 | (20.0) | 1 | (5.0) | 0 | (0.0) | 4 | (3.7) |
| Anaemia | 2 | (2.3) | 0 | (0.0) | 0 | (0.0) | 1 | (5.0) | 0 | (0.0) | 3 | (2.8) |
| **Gastrointestinal Disorders** | 1 | (1.2) | 1 | (7.1) | 0 | (0.0) | 2 | (10.0) | 0 | (0.0) | 4 | (3.7) |
| Vomiting | 0 | (0.0) | 1 | (7.1) | 0 | (0.0) | 2 | (10.0) | 0 | (0.0) | 3 | (2.8) |
| Nausea | 0 | (0.0) | 1 | (7.1) | 0 | (0.0) | 1 | (5.0) | 0 | (0.0) | 2 | (1.9) |
| Diarrhoea | 0 | (0.0) | 1 | (7.1) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| **General Disorders And Administration Site Conditions** | 1 | (1.2) | 1 | (7.1) | 0 | (0.0) | 2 | (10.0) | 0 | (0.0) | 4 | (3.7) |
| Pyrexia | 0 | (0.0) | 1 | (7.1) | 0 | (0.0) | 1 | (5.0) | 0 | (0.0) | 2 | (1.9) |
| Chest Pain | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (5.0) | 0 | (0.0) | 1 | (0.9) |
| **Hepatobiliary Disorders** | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (5.0) | 0 | (0.0) | 1 | (0.9) |
| Hepatic Ischaemia | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (5.0) | 0 | (0.0) | 1 | (0.9) |
| **Infections And Infestations** | 5 | (5.8) | 0 | (0.0) | 1 | (10.0) | 2 | (10.0) | 1 | (8.3) | 8 | (7.5) |
| Sepsis | 1 | (1.2) | 0 | (0.0) | 1 | (10.0) | 1 | (5.0) | 0 | (0.0) | 3 | (2.8) |
| Infection | 1 | (1.2) | 0 | (0.0) | 0 | (0.0) | 1 | (5.0) | 0 | (0.0) | 2 | (1.9) |
| Herpes Zoster | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (8.3) | 1 | (0.9) |
| Lobar Pneumonia | 1 | (1.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| Urinary Tract Infection | 0 | (0.0) | 0 | (0.0) | 1 | (10.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| Wound Infection | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (5.0) | 0 | (0.0) | 1 | (0.9) |
| **Injury, Poisoning And Procedural Complications** | 1 | (1.2) | 0 | (0.0) | 1 | (10.0) | 0 | (0.0) | 0 | (0.0) | 2 | (1.9) |
| Subdural Haematoma | 0 | (0.0) | 0 | (0.0) | 1 | (10.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| **Metabolism And Nutrition Disorders** | 0 | (0.0) | 1 | (7.1) | 1 | (10.0) | 2 | (10.0) | 1 | (8.3) | 5 | (4.7) |
| Dehydration | 0 | (0.0) | 1 | (7.1) | 1 | (10.0) | 2 | (10.0) | 1 | (8.3) | 5 | (4.7) |
| Oral Intake Reduced | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (5.0) | 0 | (0.0) | 1 | (0.9) |
| **Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)** | 4 | (4.7) | 0 | (0.0) | 1 | (10.0) | 1 | (5.0) | 3 | (25.0) | 8 | (7.5) |
| T-Cell Lymphoma | 1 | (1.2) | 0 | (0.0) | 1 | (10.0) | 1 | (5.0) | 2 | (16.7) | 5 | (4.7) |
| Squamous Cell Carcinoma | 3 | (3.5) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (8.3) | 3 | (2.8) |
| Lung Neoplasm | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (8.3) | 1 | (0.9) |
| **Nervous System Disorders** | 1 | (1.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (8.3) | 2 | (1.9) |
| Ischaemic Stroke | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (8.3) | 1 | (0.9) |
| **Respiratory, Thoracic And Mediastinal Disorders** | 4 | (4.7) | 2 | (14.3) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 6 | (5.6) |
| Pulmonary Embolism | 4 | (4.7) | 2 | (14.3) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 6 | (5.6) |
| **Vascular Disorders** | 1 | (1.2) | 2 | (14.3) | 0 | (0.0) | 2 | (10.0) | 0 | (0.0) | 5 | (4.7) |
| Deep Vein Thrombosis | 1 | (1.2) | 1 | (7.1) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 2 | (1.9) |
| Hypotension | 0 | (0.0) | 1 | (7.1) | 0 | (0.0) | 1 | (5.0) | 0 | (0.0) | 2 | (1.9) |
| Orthostatic Hypotension | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (5.0) | 0 | (0.0) | 1 | (0.9) |

A patient is counted only once within a System Organ Class category, even if more than one adverse experience with specific preferred terms occurred. Only the highest grade of a given adverse experience is counted per dose level for the individual patient.
Adverse experience terms are from MedDRA Version 8.1.
[Ref. 5.3.5.2: P001, P005]

***Drug-related*** **Serious Clinical Adverse Experiences by SOC and Dose Level in the CTCL Population**

**400 mg once daily dose**

86 patients received Vorinostat at a dose of 400 mg once daily and the incidence of *drug-related* serious adverse experiences at a frequency > 0% are summarized (see the following table):

- **Pulmonary embolism** 4 (4.7%)
- **Anemia** 2 (2.3%)
- **Thrombocytopenia, death, deep vein thrombosis, gastrointestinal hemorrhage, streptococcal bacteremia** and **syncope** (each) 1 (1.2%)

**300 mg twice daily 3 out of 7 days**

- 4 of 14 patients (28.6%) had study *drug-related* SAEs
- **Diarrhea, nausea, vomiting, pyrexia, dehydration, pulmonary embolism** and **hypotension** occurred once each in the 14 patients (7.1%)

**200 mg twice daily**

- 2 of 10 patients (20.0%) had study *drug-related* SAEs
- **Thrombocytopenia** occurred in 2 patients (20.0%) and **dehydration** occurred in 1 patient (10.0%)

**Dose below the MTD**

- One (1) of the 12 patients (8.3%) developed a study *drug-related* serious adverse experience of **dehydration** and **ischemic stroke**.

**Doses above the MTD**

- Two (2) of the 20 patients (10.0%) experienced a study *drug-related* serious adverse experience: **thrombocytopenia, chest pain, hepatic ischemia** and **dehydration**.

**Table 114. Patients with Serious Drug-Related Clinical Adverse Experiences by System Organ Class (Incidence > 0% in One or More Dose Levels) Vorinostat Monotherapy – CTCL (Applicant's Table)**

| | 400mg QD continuous (N=65) | | 300mg BID 3/7 (N=14) | | 200mg BID continuous (N=10) | | doses above MTD (N=20) | | doses below MTD (N=12) | | Total Patients (N=107) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % | n | % | n | % |
| *Patients With One Or More Clinical Adverse Experiences* | *5* | *(9.3)* | *4* | *(28.6)* | *2* | *(20.0)* | *2* | *(10.0)* | *1* | *(8.3)* | *16* | *(15.0)* |
| *Patients With No Clinical Adverse Experiences* | *78* | *(90.7)* | *10* | *(71.4)* | *8* | *(80.0)* | *18* | *(90.0)* | *11* | *(91.7)* | *91* | *(85.0)* |
| **Blood And Lymphatic System Disorders** | **2** | **(2.3)** | **0** | **(0.0)** | **2** | **(20.0)** | **1** | **(5.0)** | **0** | **(0.0)** | **5** | **(4.7)** |
| Thrombocytopenia | 1 | (1.2) | 0 | (0.0) | 2 | (20.0) | 1 | (5.0) | 0 | (0.0) | 4 | (3.7) |
| Anaemia | 2 | (2.3) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 2 | (1.9) |
| **Gastrointestinal Disorders** | **1** | **(1.2)** | **1** | **(7.1)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **2** | **(1.9)** |
| Diarrhoea | 0 | (0.0) | 1 | (7.1) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| Gastrointestinal Haemorrhage | 1 | (1.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| Nausea | 0 | (0.0) | 1 | (7.1) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| Vomiting | 0 | (0.0) | 1 | (7.1) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| **General Disorders And Administration Site Conditions** | **1** | **(1.2)** | **1** | **(7.1)** | **0** | **(0.0)** | **1** | **(5.0)** | **0** | **(0.0)** | **3** | **(2.8)** |
| Chest Pain | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (5.0) | 0 | (0.0) | 1 | (0.9) |
| Death | 1 | (1.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| Pyrexia | 0 | (0.0) | 1 | (7.1) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| **Hepatobiliary Disorders** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(5.0)** | **0** | **(0.0)** | **1** | **(0.9)** |
| Hepatic Ischaemia | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (5.0) | 0 | (0.0) | 1 | (0.9) |
| **Infections And Infestations** | **1** | **(1.2)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(0.9)** |
| Streptococcal Bacteraemia | 1 | (1.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| **Metabolism And Nutrition Disorders** | **0** | **(0.0)** | **1** | **(7.1)** | **1** | **(10.0)** | **1** | **(5.0)** | **1** | **(8.3)** | **4** | **(3.7)** |
| Dehydration | 0 | (0.0) | 1 | (7.1) | 1 | (10.0) | 1 | (5.0) | 1 | (8.3) | 4 | (3.7) |
| **Nervous System Disorders** | **1** | **(1.2)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(8.3)** | **2** | **(1.9)** |
| Ischaemic Stroke | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (8.3) | 1 | (0.9) |
| Syncope | 1 | (1.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| **Respiratory, Thoracic And Mediastinal Disorders** | **4** | **(4.7)** | **1** | **(7.1)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **5** | **(4.7)** |
| Pulmonary Embolism | 4 | (4.7) | 1 | (7.1) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 5 | (4.7) |
| **Vascular Disorders** | **1** | **(1.2)** | **1** | **(7.1)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **2** | **(1.9)** |
| Deep Vein Thrombosis | 1 | (1.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| Hypotension | 0 | (0.0) | 1 | (7.1) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |

A patient is counted only once within a System Organ Class category, even if more than one adverse experience with specific preferred terms occurred. Only the highest grade of a given adverse experience is counted per dose level for the individual patient.
Adverse experience terms are from MedDRA Version 8.1.

[Ref. 5.3.5.2: P001, P005]

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**Vorinostat Monotherapy CTCL Stage IIB and Higher**

This population is a subset of the above described *all stages* CTCL population

**400 mg once daily dose**

In the 71 CTCL Stage IIB and Higher patients who received Vorinostat at a dose of 400 mg once daily, the frequency of all serious clinical adverse experiences occurring at an incidence of ≥2% are summarized in the table below. Of note:

- Pulmonary embolism 4 (5.6%)
- Squamous cell carcinoma 3 (4.2%)
- Anemia 2 (2.8%)

Serious clinical adverse experiences were also observed in the CTCL Stage IIB and Higher population at **other dose levels**:

**300 mg twice daily, 3 out of 7 days dose**

- Five (5) of 13 patients (38.5%) at a dose of 300 mg twice daily 3 out of 7 days dose experienced serious clinical adverse events

**200 mg twice daily dose**

- Three (3) of 8 patients (37.5%) at a dose of 200 mg twice daily experienced serious clinical adverse experiences

**Doses above the MTD**

- Two (2) of 17 patients (11.8%) treated at doses above the MTD reported a serious clinical adverse experience with vomiting and dehydration at the highest incidence of 11.8% each.
- The remaining serious clinical adverse experiences occurred at an incidence of 5.9% and included thrombocytopenia, anemia, nausea, pyrexia, hepatic ischemia, sepsis, infection, wound infection, reduced oral intake, T-cell lymphoma, hypotension and orthostatic hypotension.

**Doses below the MTD**

- Three (3) of 12 patients (25.0%) treated at doses below the MTD reported tumor related serious clinical adverse experiences, 1 patient (8.3%) had herpes zoster and 1 patient (8.3%) had ischemic stroke and dehydration.

## Table 115. Serious Clinical Adverse Experiences by System Organ Class (Incidence ≥ 2% in One or More Dose Levels) Vorinostat Monotherapy-CTCL Stage IIB and Higher (Applicant's Table)

| | 400mg QD continuous (N=71) | | 300mg BID 3-7 (N=13) | | 200mg BID continuous (N=8) | | doses above MTD (N=17) | | doses below MTD (N=12) | | Total Patients (N=89) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % | n | % | n | % |
| *Patients With One Or More Clinical Adverse Experiences* | *15* | *(21.1)* | *5* | *(38.5)* | *3* | *(37.5)* | *2* | *(11.8)* | *5* | *(41.7)* | *27* | *(30.3)* |
| *Patients With No Clinical Adverse Experiences* | *56* | *(78.9)* | *8* | *(61.5)* | *5* | *(62.5)* | *15* | *(88.2)* | *7* | *(58.3)* | *62* | *(69.7)* |
| **Blood And Lymphatic System Disorders** | **2** | **(2.8)** | **0** | **(0.0)** | **2** | **(25.0)** | **2** | **(11.8)** | **0** | **(0.0)** | **6** | **(6.7)** |
| Thrombocytopenia | 1 | (1.4) | 0 | (0.0) | 2 | (25.0) | 1 | (5.9) | 0 | (0.0) | 4 | (4.5) |
| Anaemia | 2 | (2.8) | 0 | (0.0) | 0 | (0.0) | 1 | (5.9) | 0 | (0.0) | 3 | (3.4) |
| **Gastrointestinal Disorders** | **1** | **(1.4)** | **1** | **(7.7)** | **0** | **(0.0)** | **2** | **(11.8)** | **0** | **(0.0)** | **4** | **(4.5)** |
| Vomiting | 0 | (0.0) | 1 | (7.7) | 0 | (0.0) | 2 | (11.8) | 0 | (0.0) | 3 | (3.4) |
| Nausea | 0 | (0.0) | 1 | (7.7) | 0 | (0.0) | 1 | (5.9) | 0 | (0.0) | 2 | (2.2) |
| Diarrhoea | 0 | (0.0) | 1 | (7.7) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.1) |
| **General Disorders And Administration Site Conditions** | **1** | **(1.4)** | **1** | **(7.7)** | **0** | **(0.0)** | **1** | **(5.9)** | **0** | **(0.0)** | **3** | **(3.4)** |
| Pyrexia | 0 | (0.0) | 1 | (7.7) | 0 | (0.0) | 1 | (5.9) | 0 | (0.0) | 2 | (2.2) |
| **Hepatobiliary Disorders** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(5.9)** | **0** | **(0.0)** | **1** | **(1.1)** |
| Hepatic Ischaemia | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (5.9) | 0 | (0.0) | 1 | (1.1) |
| **Infections And Infestations** | **5** | **(7.0)** | **0** | **(0.0)** | **1** | **(12.5)** | **2** | **(11.8)** | **1** | **(8.3)** | **8** | **(9.0)** |
| Sepsis | 1 | (1.4) | 0 | (0.0) | 1 | (12.5) | 1 | (5.9) | 0 | (0.0) | 3 | (3.4) |
| Infection | 1 | (1.4) | 0 | (0.0) | 0 | (0.0) | 1 | (5.9) | 0 | (0.0) | 2 | (2.2) |
| Herpes Zoster | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (8.3) | 1 | (1.1) |
| Urinary Tract Infection | 0 | (0.0) | 0 | (0.0) | 1 | (12.5) | 0 | (0.0) | 0 | (0.0) | 1 | (1.1) |
| Wound Infection | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (5.9) | 0 | (0.0) | 1 | (1.1) |
| **Injury, Poisoning And Procedural Complications** | **1** | **(1.4)** | **0** | **(0.0)** | **1** | **(12.5)** | **0** | **(0.0)** | **0** | **(0.0)** | **2** | **(2.2)** |
| Subdural Haematoma | 0 | (0.0) | 0 | (0.0) | 1 | (12.5) | 0 | (0.0) | 0 | (0.0) | 1 | (1.1) |
| *Grade 3* | *0* | *(0.0)* | *0* | *(0.0)* | *1* | *(12.5)* | *0* | *(0.0)* | *0* | *(0.0)* | *1* | *(1.1)* |
| **Metabolism And Nutrition Disorders** | **0** | **(0.0)** | **1** | **(7.7)** | **1** | **(12.5)** | **2** | **(11.8)** | **1** | **(8.3)** | **5** | **(5.6)** |
| Dehydration | 0 | (0.0) | 1 | (7.7) | 1 | (12.5) | 2 | (11.8) | 1 | (8.3) | 5 | (5.6) |
| Oral Intake Reduced | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (5.9) | 0 | (0.0) | 1 | (1.1) |
| **Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)** | **4** | **(5.6)** | **0** | **(0.0)** | **1** | **(12.5)** | **1** | **(5.9)** | **3** | **(25.0)** | **8** | **(9.0)** |
| T-Cell Lymphoma | 1 | (1.4) | 0 | (0.0) | 1 | (12.5) | 1 | (5.9) | 2 | (16.7) | 5 | (5.6) |
| Squamous Cell Carcinoma | 3 | (4.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (8.3) | 3 | (3.4) |
| Lung Neoplasm | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (8.3) | 1 | (1.1) |
| **Nervous System Disorders** | **1** | **(1.4)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(8.3)** | **2** | **(2.2)** |
| Ischaemic Stroke | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (8.3) | 1 | (1.1) |
| Syncope | 1 | (1.4) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.1) |
| **Respiratory, Thoracic And Mediastinal Disorders** | **4** | **(5.6)** | **2** | **(15.4)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **6** | **(6.7)** |
| Pulmonary Embolism | 4 | (5.6) | 2 | (15.4) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 6 | (6.7) |
| **Vascular Disorders** | **1** | **(1.4)** | **2** | **(15.4)** | **0** | **(0.0)** | **2** | **(11.8)** | **0** | **(0.0)** | **5** | **(5.6)** |
| Deep Vein Thrombosis | 1 | (1.4) | 1 | (7.7) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 2 | (2.2) |
| Hypotension | 0 | (0.0) | 1 | (7.7) | 0 | (0.0) | 1 | (5.9) | 0 | (0.0) | 2 | (2.2) |
| Orthostatic Hypotension | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (5.9) | 0 | (0.0) | 1 | (1.1) |

A patient is counted only once within a System Organ Class category, even if more than one adverse experience with specific preferred terms occurred. Only the highest grade of a given adverse experience is counted per dose level for the individual patient.
Adverse experience terms are from MedDRA Version 8.1.

[Ref. 5.3.5.2: P001, P005]

***Drug-related*** **Serious Clinical Adverse Experiences by SOC and Dose Level in the CTCL Stage IIB or Higher Population**

**400 mg once daily dose**

71 patients in the above population received Vorinostat at a dose of 400 mg once daily, the frequency of > 0% incidence of drug-related serious adverse experiences is summarized in the table below. 15 patients had a serious adverse experience at the 400 mg once daily dose, 8 of these were determined by the Investigator to be related to the study drug:

- Pulmonary embolism 4 (5.6%)
- Anemia 2 (2.8%)
- Thrombocytopenia, death, deep vein thrombosis, gastrointestinal hemorrhage, streptococcal bacteremia and syncope (each) 1 (1.4%)

Drug-related serious clinical adverse experiences in the CTCL Stage II or Higher population at other dose levels:

**300 mg twice daily, 3 out of 7 days dose**

- Patients with one or more clinical adverse experiences = 4 of 13 patients (30.8%)
- Diarrhea, nausea, vomiting, pyrexia, dehydration, pulmonary embolism and hypotension—each a single incidence (7.7%)

**200 mg twice daily dose**

- Patients with one or more clinical adverse experiences = 2 of 8 patients (25.0%)
- Thrombocytopenia 2 (25.0%)
- Dehydration 1 (12.5%)

**Doses below the MTD**

- One (1) of the 12 patients (8.3%) developed dehydration and ischemic stroke

**Doses above the MTD**

- Thrombocytopenia, hepatic ischemia and dehydration—each reported in 1 of the 17 patients (5.9%)

Overall, the data from the drug-related serious adverse experiences suggest no notable differences across the dose levels in the CTCL Stage IIB and Higher population when compared with the overall CTCL population.

**Table 116. Specific Serious Drug-Related Clinical Adverse Experiences by System Organ Class (Incidence > 0% in One or More Dose Levels) Vorinostat Monotherapy-CTCL Stage IIB and Higher (Applicant's Table)**

| | 400mg QD continuous (N=71) | | 300mg BID 3/7 (N=13) | | 200mg BID continuous (N=8) | | doses above MTD (N=17) | | doses below MTD (N=12) | | Total Patients (N=89) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % | n | % | n | % |
| *Patients With One Or More Clinical Adverse Experiences* | *8* | *(11.3)* | *4* | *(30.8)* | *2* | *(25.0)* | *1* | *(5.9)* | *1* | *(8.3)* | *15* | *(16.9)* |
| *Patients With No Clinical Adverse Experiences* | *63* | *(88.7)* | *9* | *(69.2)* | *6* | *(75.0)* | *16* | *(94.1)* | *11* | *(91.7)* | *74* | *(83.1)* |
| **Blood And Lymphatic System Disorders** | 2 | **(2.8)** | 0 | **(0.0)** | 2 | **(25.0)** | 1 | **(5.9)** | 0 | **(0.0)** | 5 | **(5.6)** |
| Thrombocytopenia | 1 | (1.4) | 0 | (0.0) | 2 | (25.0) | 1 | (5.9) | 0 | (0.0) | 4 | (4.5) |
| Anaemia | 2 | (2.8) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 2 | (2.2) |
| **Gastrointestinal Disorders** | 1 | **(1.4)** | 1 | **(7.7)** | 0 | **(0.0)** | 0 | **(0.0)** | 0 | **(0.0)** | 2 | **(2.2)** |
| Diarrhoea | 0 | (0.0) | 1 | (7.7) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.1) |
| Gastrointestinal Haemorrhage | 1 | (1.4) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.1) |
| Nausea | 0 | (0.0) | 1 | (7.7) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.1) |
| Vomiting | 0 | (0.0) | 1 | (7.7) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.1) |
| **General Disorders And Administration Site Conditions** | 1 | **(1.4)** | 1 | **(7.7)** | 0 | **(0.0)** | 0 | **(0.0)** | 0 | **(0.0)** | 2 | **(2.2)** |
| Death | 1 | (1.4) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.1) |
| Pyrexia | 0 | (0.0) | 1 | (7.7) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.1) |
| **Hepatobiliary Disorders** | 0 | **(0.0)** | 0 | **(0.0)** | 0 | **(0.0)** | 1 | **(5.9)** | 0 | **(0.0)** | 1 | **(1.1)** |
| Hepatic Ischaemia | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (5.9) | 0 | (0.0) | 1 | (1.1) |
| **Infections And Infestations** | 1 | **(1.4)** | 0 | **(0.0)** | 0 | **(0.0)** | 0 | **(0.0)** | 0 | **(0.0)** | 1 | **(1.1)** |
| Streptococcal Bacteraemia | 1 | (1.4) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.1) |
| **Metabolism And Nutrition Disorders** | 0 | **(0.0)** | 1 | **(7.7)** | 1 | **(12.5)** | 1 | **(5.9)** | 1 | **(8.3)** | 4 | **(4.5)** |
| Dehydration | 0 | (0.0) | 1 | (7.7) | 1 | (12.5) | 1 | (5.9) | 1 | (8.3) | 4 | (4.5) |
| **Nervous System Disorders** | 1 | **(1.4)** | 0 | **(0.0)** | 0 | **(0.0)** | 0 | **(0.0)** | 1 | **(8.3)** | 2 | **(2.2)** |
| Ischaemic Stroke | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (8.3) | 1 | (1.1) |
| Syncope | 1 | (1.4) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.1) |
| **Respiratory, Thoracic And Mediastinal Disorders** | 4 | **(5.6)** | 1 | **(7.7)** | 0 | **(0.0)** | 0 | **(0.0)** | 0 | **(0.0)** | 5 | **(5.6)** |
| Pulmonary Embolism | 4 | (5.6) | 1 | (7.7) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 5 | (5.6) |
| **Vascular Disorders** | 1 | **(1.4)** | 1 | **(7.7)** | 0 | **(0.0)** | 0 | **(0.0)** | 0 | **(0.0)** | 2 | **(2.2)** |
| Deep Vein Thrombosis | 1 | (1.4) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.1) |
| Hypotension | 0 | (0.0) | 1 | (7.7) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.1) |

A patient is counted only once within a System Organ Class category, even if more than one adverse experience with specific preferred terms occurred. Only the highest grade of a given adverse experience is counted per dose level for the individual patient.
Adverse experience terms are from MedDRA Version 8.1.

{Ref. 5.3.5.2: P001, P005}

**Vorinostat Monotherapy – Solid Tumors**

Serious clinical adverse experiences in the solid tumor population by SOC and dose levels are summarized in this section and in the table below.

- Forty-five (45) of 101 patients in the solid tumor population received Vorinostat monotherapy at a dose of **400 mg once daily**. Eleven (11) patients (24.4%) experienced a serious clinical adverse experience. With the exception of pyrexia in 2 patients (4.4%), all serious adverse experiences at this dose level occurred in only 1 patient each (2.2%): abdominal pain, dysphagia, peripheral edema, infection, bacteremia, pneumonia, sepsis, staphylococcal infection, rib fracture, dehydration, back pain, bladder cancer, malignant pleural effusion, cerebrovascular accident, hallucination, hemoptysis and thrombosis.
    - The types of serious adverse experiences seen the solid tumor population at the 400 mg once daily dose level are not seen in the CTCL population at this dose level. As almost all adverse experiences are single cases, it is difficult to define a pattern of adverse experiences in this population.
- At a dose of **300 mg twice daily 3 out of 7 days**, serious clinical adverse experiences were observed in 6 of 16 (37.5%) patients
- At **200 mg twice daily dose**, serious clinical adverse experiences were observed in 1 of 8 patients (12.5%) and in 5 of 6 (83.3%) patients who received Vorinostat at a dose of 200 mg twice daily 14 out of 21 days.
- Most of the serious adverse experiences observed at the above two dose levels occurred at a frequency of 6.3% to 16.7% in up to 2 patients.

At **doses above the MTD**, serious clinical adverse experiences occurred more frequently:

- 19 (50.0%) of the 38 patients experienced at least one serious adverse experience and these ranged in frequency from 2.6% to 7.9% in up to 3 patients.
- Unique serious adverse experiences that were only observed at doses above the MTD in this population included vomiting, nausea, gastric outlet obstruction, peritoneal disorder, death, lung infection, viral infection, anorexia, hypokalemia, mesothelioma, metastatic pain, neoplasm malignant, confusional state, ureter obstruction and vasculitis.
- Although the frequency of serious adverse experiences is greater in the solid tumor population, qualitative similarities are observed when compared with the CTCL population.
- A higher incidence of serious clinical adverse experiences is observed in the System Organ Class of Gastrointestinal Disorders (11.9% vs. 3.7%) and the General Disorder and Administration Site Conditions (8.9% vs. 3.7%) in the solid tumor population when compared with the CTCL population.

## Table 117. Specific Serious Clinical Adverse Experiences by System Organ Class (Incidence ≥ 2% in One or More Dose Levels) Vorinostat Monotherapy – Solid Tumor (Applicant's Table)

| | 400mg QD continuous (N=45) | | 300mg BID 3/7 (N=16) | | 200mg BID continuous (N=8) | | 200mg BID 14/21 (N=8) | | doses above MTD (N=38) | | doses below MTD (N=15) | | Total Patients (N=101) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % | n | % | n | % | n | % |
| *Patients With One Or More Clinical Adverse Experiences* | *12* | *(26.4)* | *9* | *(57.5)* | *7* | *(12.5)* | *5* | *(63.3)* | *19* | *(50.0)* | *8* | *(53.3)* | *47* | *(46.5)* |
| *Patients With No Clinical Adverse Experiences* | *34* | *(73.6)* | *10* | *(62.5)* | *7* | *(87.5)* | *1* | *(16.7)* | *19* | *(50.0)* | *7* | *(46.7)* | *54* | *(53.5)* |
| **Blood And Lymphatic System Disorders** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **2** | **(33.3)** | **3** | **(7.9)** | **0** | **(0.0)** | **4** | **(4.0)** |
| Thrombocytopenia | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (16.7) | 2 | (5.3) | 0 | (0.0) | 3 | (3.0) |
| Anaemia | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (16.7) | 1 | (2.6) | 0 | (0.0) | 2 | (2.0) |
| **Eye Disorders** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(16.7)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(1.0)** |
| Vision Blurred | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (16.7) | 0 | (0.0) | 0 | (0.0) | 1 | (1.0) |
| **Gastrointestinal Disorders** | **2** | **(4.4)** | **2** | **(12.5)** | **0** | **(0.0)** | **1** | **(16.7)** | **6** | **(15.8)** | **1** | **(6.7)** | **12** | **(11.9)** |
| Abdominal Pain | 1 | (2.2) | 1 | (6.3) | 0 | (0.0) | 0 | (0.0) | 1 | (2.6) | 0 | (0.0) | 3 | (3.0) |
| Vomiting | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 3 | (7.9) | 0 | (0.0) | 3 | (3.0) |
| Dysphagia | 1 | (2.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.6) | 0 | (0.0) | 2 | (2.0) |
| Nausea | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 2 | (5.3) | 0 | (0.0) | 2 | (2.0) |
| Anal Haemorrhage | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (16.7) | 0 | (0.0) | 0 | (0.0) | 1 | (1.0) |
| Constipation | 0 | (0.0) | 1 | (6.3) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.0) |
| Gastric Outlet Obstruction | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.6) | 0 | (0.0) | 1 | (1.0) |
| Intestinal Obstruction | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (6.7) | 1 | (1.0) |
| Peritoneal Disorder | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.6) | 0 | (0.0) | 1 | (1.0) |
| **General Disorders And Administration Site Conditions** | **2** | **(4.4)** | **0** | **(0.0)** | **0** | **(0.0)** | **3** | **(50.0)** | **4** | **(10.5)** | **0** | **(0.0)** | **9** | **(8.9)** |
| Pyrexia | 2 | (4.4) | 0 | (0.0) | 0 | (0.0) | 1 | (16.7) | 1 | (2.6) | 0 | (0.0) | 4 | (4.0) |
| General Physical Health Deterioration | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 2 | (33.3) | 1 | (2.6) | 0 | (0.0) | 3 | (3.0) |
| Fatigue | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (16.7) | 1 | (2.6) | 0 | (0.0) | 2 | (2.0) |
| Asthenia | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (16.7) | 0 | (0.0) | 0 | (0.0) | 1 | (1.0) |
| Death | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.6) | 0 | (0.0) | 1 | (1.0) |
| Oedema Peripheral | 1 | (2.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.0) |
| **Infections And Infestations** | **3** | **(6.7)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **3** | **(7.9)** | **1** | **(6.7)** | **7** | **(6.9)** |
| Infection | 1 | (2.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.6) | 1 | (6.7) | 3 | (3.0) |
| Bacteraemia | 1 | (2.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.0) |
| Lung Infection | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.6) | 0 | (0.0) | 1 | (1.0) |
| Pneumonia | 1 | (2.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.0) |
| Sepsis | 1 | (2.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.0) |
| Staphylococcal Infection | 1 | (2.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.0) |
| Viral Infection | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.6) | 0 | (0.0) | 1 | (1.0) |
| **Injury, Poisoning And Procedural Complications** | **1** | **(2.2)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(1.0)** |
| Rib Fracture | 1 | (2.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.0) |
| **Metabolism And Nutrition Disorders** | **1** | **(2.2)** | **1** | **(6.3)** | **0** | **(0.0)** | **0** | **(0.0)** | **5** | **(13.2)** | **1** | **(6.7)** | **8** | **(7.9)** |
| Dehydration | 1 | (2.2) | 1 | (6.3) | 0 | (0.0) | 0 | (0.0) | 3 | (7.9) | 1 | (6.7) | 6 | (5.9) |
| Anorexia | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.6) | 0 | (0.0) | 1 | (1.0) |
| Hypokalaemia | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.6) | 0 | (0.0) | 1 | (1.0) |
| **Musculoskeletal And Connective Tissue Disorders** | **1** | **(2.2)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(1.0)** |
| Back Pain | 1 | (2.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.0) |
| **Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)** | **2** | **(4.4)** | **1** | **(6.3)** | **0** | **(0.0)** | **2** | **(33.3)** | **3** | **(7.9)** | **1** | **(6.7)** | **9** | **(8.9)** |
| Bladder Cancer | 1 | (2.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.0) |
| Cancer Pain | 0 | (0.0) | 1 | (6.3) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.0) |
| Malignant Pleural Effusion | 1 | (2.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.0) |
| Mesothelioma | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.6) | 0 | (0.0) | 1 | (1.0) |
| Metastatic Pain | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.6) | 0 | (0.0) | 1 | (1.0) |
| Neoplasm Malignant | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.6) | 0 | (0.0) | 1 | (1.0) |
| Neoplasm Progression | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (16.7) | 0 | (0.0) | 0 | (0.0) | 1 | (1.0) |
| Renal Cell Carcinoma Stage Unspecified | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (6.7) | 1 | (1.0) |
| Tumour Haemorrhage | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (16.7) | 0 | (0.0) | 0 | (0.0) | 1 | (1.0) |
| **Nervous System Disorders** | **1** | **(2.2)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(16.7)** | **0** | **(0.0)** | **2** | **(13.2)** | **4** | **(4.0)** |
| Cerebrovascular Accident | 1 | (2.2) | 0 | (0.0) | 0 | (0.0) | 1 | (16.7) | 0 | (0.0) | 0 | (0.0) | 2 | (2.0) |
| Convulsion | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (6.7) | 1 | (1.0) |
| Ruptured Cerebral Aneurysm | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (6.7) | 1 | (1.0) |
| **Psychiatric Disorders** | **1** | **(2.2)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(2.6)** | **1** | **(6.7)** | **3** | **(3.0)** |
| Confusional State | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.6) | 1 | (6.7) | 2 | (2.0) |
| Hallucination | 1 | (2.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.0) |
| **Renal And Urinary Disorders** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(2.6)** | **0** | **(0.0)** | **1** | **(1.0)** |
| Ureteric Obstruction | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.6) | 0 | (0.0) | 1 | (1.0) |
| **Respiratory, Thoracic And Mediastinal Disorders** | **1** | **(2.2)** | **2** | **(12.5)** | **1** | **(12.5)** | **1** | **(16.7)** | **1** | **(2.6)** | **2** | **(13.2)** | **7** | **(6.9)** |
| Dyspnoea | 0 | (0.0) | 1 | (6.3) | 0 | (0.0) | 1 | (16.7) | 0 | (0.0) | 1 | (6.7) | 3 | (3.0) |
| Cough | 0 | (0.0) | 0 | (0.0) | 1 | (12.5) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.0) |
| Haemoptysis | 1 | (2.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.6) | 0 | (0.0) | 1 | (1.0) |
| Hypoxia | 0 | (0.0) | 1 | (6.3) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.0) |
| Lung Disorder | 0 | (0.0) | 1 | (6.3) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.0) |
| Pulmonary Embolism | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (6.7) | 1 | (1.0) |
| Tracheal Stenosis | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (6.7) | 1 | (1.0) |
| **Vascular Disorders** | **1** | **(2.2)** | **2** | **(12.5)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(2.6)** | **1** | **(6.7)** | **5** | **(5.0)** |
| Thrombosis | 1 | (2.2) | 2 | (12.5) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 3 | (3.0) |
| Embolism | 0 | (0.0) | 2 | (12.5) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 2 | (2.0) |
| Deep Vein Thrombosis | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (6.7) | 1 | (1.0) |
| Vasculitis | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.6) | 0 | (0.0) | 1 | (1.0) |

A patient is counted only once within a System Organ Class category, even if more than one adverse experience with specific preferred terms occurred. Only the highest grade of a given adverse experience is counted per dose level for the individual patient
Adverse experience terms are from MedDRA Version 8.1.

[Ref. 5.3.3.2: P008] [Ref. 5.3.5.4: P002, P006, P011V1]

***Drug-related*** **Serious Clinical Adverse Experiences by SOC and Dose Level in the Solid Tumor Population**

**400 mg once daily dose**

- 3 of the 45 patients (6.7%) treated at the 400 mg once daily dose had serious adverse experiences determined by the Investigator to be related to study drug.
- These occurred at an incidence of 2.2 % in one patient each and included pyrexia, dehydration, hemoptysis and thrombosis.

**200 mg twice daily dose level**

- 1 of 8 patients (12.5%) on the 200 mg twice daily dose, and 3 of 6 (50.0%) on the 200 mg twice daily 14 out of 21 days dose had a drug-related serious adverse experience
- All experiences on the above dose levels occurred as a single incidence ranging 12.5% to 16.7% and included thrombocytopenia, anemia, blurred vision, asthenia, tumor hemorrhage, and cough.

**300 mg twice daily, 3 out of 7 days**

- No drug-related serious adverse experiences were observed in the 16 patients on the 300 mg twice daily 3 out of 7 days dose

**At doses above the MTD**

- 11 of the 38 patients (28.9%) had a drug-related serious adverse experience.
- Drug-related serious adverse experiences unique to the doses above the MTD were nausea, vomiting, fatigue, anorexia and vasculitis.

Overall, the data from the serious adverse experiences suggest that the incidence of the serious adverse experiences may be higher in the solid tumor population, but only about a third of the serious adverse experiences are drug-related, and there are similarities to the CTCL population.

**Table 118. *Drug-Related* Serious Clinical Adverse Experiences by System Organ Class (Incidence > 0% in One or More Dose Levels) Vorinostat Monotherapy-Solid Tumor (Applicant's Table)**

| | 400mg QD continuous (N=45) | | 300mg BID 3/7 (N=16) | | 200mg BID continuous (N=8) | | 200mg BID 14/21 (N=6) | | doses above MTD (N=38) | | doses below MTD (N=15) | | Total Patients (N=101) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % | n | % | n | % | n | % |
| *Patients With One Or More Clinical Adverse Experiences* | *3* | *(6.7)* | *0* | *(0.0)* | *1* | *(12.5)* | *3* | *(50.0)* | *11* | *(28.9)* | *1* | *(6.7)* | *17* | *(16.8)* |
| *Patients With No Clinical Adverse Experiences* | *42* | *(93.3)* | *16* | *(100)* | *7* | *(87.5)* | *3* | *(50.0)* | *27* | *(71.1)* | *14* | *(93.3)* | *84* | *(83.2)* |
| **Blood And Lymphatic System Disorders** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **2** | **(33.3)** | **3** | **(7.9)** | **0** | **(0.0)** | **4** | **(4.0)** |
| Thrombocytopenia | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (16.7) | 2 | (5.3) | 0 | (0.0) | 3 | (3.0) |
| Anaemia | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (16.7) | 1 | (2.6) | 0 | (0.0) | 2 | (2.0) |
| **Eye Disorders** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(16.7)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(1.0)** |
| Vision Blurred | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (16.7) | 0 | (0.0) | 0 | (0.0) | 1 | (1.0) |
| **Gastrointestinal Disorders** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **2** | **(5.3)** | **0** | **(0.0)** | **2** | **(2.0)** |
| Nausea | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 2 | (5.3) | 0 | (0.0) | 2 | (2.0) |
| Vomiting | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 2 | (5.3) | 0 | (0.0) | 2 | (2.0) |
| **General Disorders And Administration Site Conditions** | **1** | **(2.2)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(16.7)** | **2** | **(5.3)** | **0** | **(0.0)** | **4** | **(4.0)** |
| Pyrexia | 1 | (2.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.6) | 0 | (0.0) | 2 | (2.0) |
| Asthenia | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (16.7) | 0 | (0.0) | 0 | (0.0) | 1 | (1.0) |
| Fatigue | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.6) | 0 | (0.0) | 1 | (1.0) |
| **Metabolism And Nutrition Disorders** | **1** | **(2.2)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **4** | **(10.5)** | **1** | **(6.7)** | **6** | **(5.9)** |
| Dehydration | 1 | (2.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 3 | (7.9) | 1 | (6.7) | 5 | (5.0) |
| Anorexia | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.6) | 0 | (0.0) | 1 | (1.0) |
| **Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(16.7)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(1.0)** |
| Tumour Haemorrhage | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (16.7) | 0 | (0.0) | 0 | (0.0) | 1 | (1.0) |
| **Respiratory, Thoracic And Mediastinal Disorders** | **1** | **(2.2)** | **0** | **(0.0)** | **1** | **(12.5)** | **0** | **(0.0)** | **1** | **(2.6)** | **0** | **(0.0)** | **2** | **(2.0)** |
| Cough | 0 | (0.0) | 0 | (0.0) | 1 | (12.5) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.0) |
| Haemoptysis | 1 | (2.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.6) | 0 | (0.0) | 1 | (1.0) |
| **Vascular Disorders** | **1** | **(2.2)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(2.6)** | **0** | **(0.0)** | **2** | **(2.0)** |
| Thrombosis | 1 | (2.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.0) |
| Vasculitis | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.6) | 0 | (0.0) | 1 | (1.0) |

A patient is counted only once within a System Organ Class category, even if more than one adverse experience with specific preferred terms occurred. Only the highest grade of a given adverse experience is counted per dose level for the individual patient.
Adverse experience terms are from MedDRA Version 8.1

[Ref. 5.3.3.2: P008] [Ref. 5.3.5.4: P002, P006, P011V1]

**Vorinostat Monotherapy – Hematologic Malignancies**

Serious clinical adverse experiences in the hematologic malignancies population are summarized below by SOC and dose level

Sixteen (16) of 87 patients (18.4%) received Vorinostat monotherapy in this population at a dose of **400 mg once daily** of which 9 patients (56.3%) experienced a serious clinical adverse experience.

- Dehydration 5 (31.3%)
- Diarrhea 3 (18.8%)
- Staphylococcal infection 2 (12.5%)
- Thrombocytopenia, confusional state, upper respiratory infection, diffuse large B-cell lymphoma, Guillain-Barré Syndrome, dyspnea, hypoxia, and confusional state (each) 1 (6.3%)

- Serious clinical adverse experiences were observed in 1 of 3 patients (33.3%) who received Vorinostat at a dose of 300 mg twice daily 3 out of 7 days
- Serious clinical adverse experiences were observed in 3 of 6 patients (30.0%) who received Vorinostat at a dose of 200 mg twice daily, and 6 of 14 patients (42.9%) who received Vorinostat at a dose of 200 mg twice daily 14 out of 21 days.
- Most of the serious adverse experiences at the above doses occurred at a frequency of 7.1% to 33.3% in up to 2 patients. Since the number of patients treated at these doses and schedules is relatively low, it is difficult to attribute any meaningful population specific interpretations.

**Doses above the MTD**

Of the 51 patients who received Vorinostat at doses above the MTD, 30 patients (58.8%) experienced at least 1 serious adverse experience.

- With the exception of subdural hematoma in 2 patients (3.9%), all unique serious adverse experiences that were observed at doses above the MTD in this population occurred in 1 patient (2.0%) and can mainly be grouped into gastrointestinal and hematologic disorders, as well as infections. These unique serious adverse experiences included anemia, neutropenia, myocardial ischemia, blurred vision, abdominal pain, intestinal obstruction, pneumatosis intestinalis, vomiting, clostridium colitis, depressed level of consciousness, death, infection, pneumonia, fungal pneumonia, hepatic enzyme increase, bone pain, muscular weakness, shoulder pain, cerebral ischemia, syncope, urinary retention, deep vein thrombosis, hypertension and hypotension.
- A higher incidence of serious clinical adverse experiences occurred in the hematologic malignancy population in the SOC of Blood and Lymphatic System Disorders, Infections and Infestation Disorders, Gastrointestinal Disorders and Metabolism and Nutrition Disorders.

- The types of clinical serious adverse experiences observed were usually those associated with age of the population and cytopenias related to hematologic malignancies. In fact, 25 of 44 (56.8%) patients with serious clinical adverse experiences were ≥65 years old.

Overall, these data suggest that at doses other than the 400 mg once daily, the potential exists for increased frequency of gastrointestinal and hematologic events with resulting complications. These types of adverse experiences in hematologic malignancies may be attributable to the elderly population and the underlying disease and are not observed in the overall CTCL population.

## Table 119. Serious Clinical Adverse Experiences by System Organ Class (Vorinostat Monotherapy – Hematologic Malignancies) (Applicant's Table)

| | 400mg QD continuous (N=16) | | 300mg BID 5/7 (N=3) | | 200mg BID continuous (N=6) | | 300mg BID 14/21 (N=14) | | doses above MTD (N=51) | | doses below MTD (N=13) | | Total Patients (N=87) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % | n | % | n | % | n | % |
| *Patients With One Or More Clinical Adverse Experiences* | *9* | *(56.3)* | *1* | *(33.3)* | *3* | *(50.0)* | *6* | *(42.9)* | *30* | *(58.8)* | *4* | *(30.8)* | *48* | *(55.2)* |
| *Patients With No Clinical Adverse Experiences* | *7* | *(43.8)* | *2* | *(66.7)* | *3* | *(50.0)* | *8* | *(57.1)* | *21* | *(41.2)* | *9* | *(69.2)* | *39* | *(44.8)* |
| **Blood And Lymphatic System Disorders** | **1** | **(6.3)** | **0** | **(0.0)** | **0** | **(0.0)** | **2** | **(14.3)** | **11** | **(21.6)** | **2** | **(15.4)** | **15** | **(17.2)** |
| Febrile Neutropenia | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (7.1) | 9 | (17.6) | 2 | (15.4) | 12 | (13.8) |
| Thrombocytopenia | 1 | (6.3) | 0 | (0.0) | 0 | (0.0) | 1 | (7.1) | 2 | (3.9) | 0 | (0.0) | 3 | (3.4) |
| Anaemia | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.0) | 0 | (0.0) | 1 | (1.1) |
| Neutropenia | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.0) | 0 | (0.0) | 1 | (1.1) |
| **Cardiac Disorders** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(2.0)** | **0** | **(0.0)** | **1** | **(1.1)** |
| Myocardial Ischaemia | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.0) | 0 | (0.0) | 1 | (1.1) |
| **Eye Disorders** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(2.0)** | **0** | **(0.0)** | **1** | **(1.1)** |
| Vision Blurred | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.0) | 0 | (0.0) | 1 | (1.1) |
| **Gastrointestinal Disorders** | **3** | **(18.8)** | **1** | **(33.3)** | **1** | **(16.7)** | **0** | **(0.0)** | **8** | **(15.7)** | **1** | **(7.7)** | **14** | **(16.1)** |
| Diarrhoea | 3 | (18.8) | 0 | (0.0) | 1 | (16.7) | 0 | (0.0) | 5 | (9.8) | 0 | (0.0) | 7 | (8.0) |
| Gastrointestinal Haemorrhage | 0 | (0.0) | 1 | (33.3) | 0 | (0.0) | 0 | (0.0) | 2 | (3.9) | 1 | (7.7) | 4 | (4.6) |
| Abdominal Pain | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.0) | 0 | (0.0) | 1 | (1.1) |
| Intestinal Obstruction | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.0) | 0 | (0.0) | 1 | (1.1) |
| Melaena | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (7.7) | 1 | (1.1) |
| Pneumatosis Intestinalis | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.0) | 0 | (0.0) | 1 | (1.1) |
| Vomiting | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.0) | 0 | (0.0) | 1 | (1.1) |
| **General Disorders And Administration Site Conditions** | **0** | **(0.0)** | **1** | **(33.3)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(2.0)** | **0** | **(0.0)** | **2** | **(2.3)** |
| Death | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.0) | 0 | (0.0) | 1 | (1.1) |
| General Physical Health Deterioration | 0 | (0.0) | 1 | (33.3) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.1) |
| **Hepatobiliary Disorders** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(7.1)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(1.1)** |
| Cholecystitis | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (7.1) | 0 | (0.0) | 0 | (0.0) | 1 | (1.1) |
| **Infections And Infestations** | **3** | **(18.8)** | **0** | **(0.0)** | **0** | **(0.0)** | **2** | **(14.3)** | **7** | **(13.7)** | **2** | **(15.4)** | **14** | **(16.1)** |
| Infection | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.0) | 1 | (7.7) | 2 | (2.3) |
| Pneumonia | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 2 | (3.9) | 0 | (0.0) | 2 | (2.3) |
| Staphylococcal Infection | 2 | (12.5) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 2 | (2.3) |
| Upper Respiratory Tract Infection | 1 | (6.3) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.0) | 0 | (0.0) | 2 | (2.3) |
| Urinary Tract Infection | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (7.1) | 1 | (2.0) | 0 | (0.0) | 2 | (2.3) |
| Clostridium Colitis | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.0) | 0 | (0.0) | 1 | (1.1) |
| Hepatobiliary Infection | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (7.1) | 0 | (0.0) | 0 | (0.0) | 1 | (1.1) |
| Herpes Zoster | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (7.7) | 1 | (1.1) |
| Pneumonia Fungal | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.0) | 0 | (0.0) | 1 | (1.1) |
| **Injury, Poisoning And Procedural Complications** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(7.1)** | **2** | **(3.9)** | **0** | **(0.0)** | **3** | **(3.4)** |
| Subdural Haematoma | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 2 | (3.9) | 0 | (0.0) | 2 | (2.3) |
| Transfusion Reaction | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (7.1) | 0 | (0.0) | 0 | (0.0) | 1 | (1.1) |
| **Investigations** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(2.0)** | **0** | **(0.0)** | **1** | **(1.1)** |
| Hepatic Enzyme Increased | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.0) | 0 | (0.0) | 1 | (1.1) |
| **Metabolism And Nutrition Disorders** | **5** | **(31.3)** | **1** | **(33.3)** | **2** | **(33.3)** | **0** | **(0.0)** | **5** | **(9.8)** | **1** | **(7.7)** | **13** | **(14.9)** |
| Dehydration | 5 | (31.3) | 0 | (0.0) | 2 | (33.3) | 0 | (0.0) | 5 | (9.8) | 1 | (7.7) | 12 | (13.8) |
| Hyponatraemia | 0 | (0.0) | 1 | (33.3) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.1) |
| **Musculoskeletal And Connective Tissue Disorders** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(7.1)** | **3** | **(5.9)** | **0** | **(0.0)** | **4** | **(4.6)** |
| Back Pain | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (7.1) | 0 | (0.0) | 0 | (0.0) | 1 | (1.1) |
| Bone Pain | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.0) | 0 | (0.0) | 1 | (1.1) |
| Muscular Weakness | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.0) | 0 | (0.0) | 1 | (1.1) |
| Shoulder Pain | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.0) | 0 | (0.0) | 1 | (1.1) |
| **Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)** | **1** | **(6.3)** | **1** | **(33.3)** | **1** | **(16.7)** | **1** | **(7.1)** | **3** | **(5.9)** | **0** | **(0.0)** | **7** | **(8.0)** |
| Acute Myeloid Leukaemia | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (7.1) | 3 | (5.9) | 0 | (0.0) | 4 | (4.6) |
| Diffuse Large B-Cell Lymphoma | 1 | (6.3) | 1 | (33.3) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 2 | (2.3) |
| Diffuse Large B-Cell Lymphoma Recurrent | 0 | (0.0) | 0 | (0.0) | 1 | (16.7) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.1) |
| **Nervous System Disorders** | **1** | **(6.3)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(7.1)** | **3** | **(5.9)** | **0** | **(0.0)** | **5** | **(5.7)** |
| Cerebral Haemorrhage | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (7.1) | 0 | (0.0) | 0 | (0.0) | 1 | (1.1) |
| Cerebral Ischaemia | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.0) | 0 | (0.0) | 1 | (1.1) |
| Depressed Level Of Consciousness | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.0) | 0 | (0.0) | 1 | (1.1) |
| Guillain-Barre Syndrome | 1 | (6.3) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.1) |
| Syncope | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.0) | 0 | (0.0) | 1 | (1.1) |
| **Psychiatric Disorders** | **1** | **(6.3)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(1.1)** |
| Confusional State | 1 | (6.3) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.1) |
| **Renal And Urinary Disorders** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(2.0)** | **0** | **(0.0)** | **1** | **(1.1)** |
| Urinary Retention | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.0) | 0 | (0.0) | 1 | (1.1) |
| **Respiratory, Thoracic And Mediastinal Disorders** | **1** | **(6.3)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **2** | **(3.9)** | **0** | **(0.0)** | **3** | **(3.4)** |
| Dyspnoea | 1 | (6.3) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 2 | (3.9) | 0 | (0.0) | 3 | (3.4) |
| Hypoxia | 1 | (6.3) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.1) |
| **Vascular Disorders** | **0** | **(0.0)** | **1** | **(33.3)** | **0** | **(0.0)** | **0** | **(0.0)** | **3** | **(5.9)** | **0** | **(0.0)** | **4** | **(4.6)** |
| Deep Vein Thrombosis | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.0) | 0 | (0.0) | 1 | (1.1) |
| Hypertension | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.0) | 0 | (0.0) | 1 | (1.1) |
| Hypotension | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.0) | 0 | (0.0) | 1 | (1.1) |
| Shock Haemorrhagic | 0 | (0.0) | 1 | (33.3) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.1) |

A patient is counted only once within a System Organ Class category, even if more than one adverse experience with specific preferred terms occurred. Only the highest grade of a given adverse experience is counted per dose level for the individual patient.
Adverse experience terms are from MedDRA Version 8.1

[Ref. 5.3.5.4: P003V1, P004V1, P006, P013V1]

***Drug-related*** **Serious Clinical Adverse Experiences by SOC and Dose Level (Hematologic Malignancies Population)**

N = 87

**400 mg once daily dose (n = 16)**

- 7 of the 16 patients (43.8%) had serious adverse experiences that were determined by the Investigator to be related to study drug.
- With the exception of dehydration in 5 patients (31.3%) and thrombocytopenia in 1 patient (6.3%), the drug-related serious clinical adverse experiences of diarrhea in 3 (18.8%) and Guillain-Barré Syndrome in 1 (6.3%) were unique to this patient population at the 400 mg once daily dose.

**200 mg twice daily doses**

- Drug-related serious clinical adverse experiences were observed in 2 of 6 patients (33.3%) who received Vorinostat at a dose of 200 mg twice daily, 1 of 14 patients (7.1%) who received Vorinostat at a dose of 200 mg twice daily 14 out of 21 days

**300 mg twice daily, 3 out of 7 days**

- Drug-related serious clinical adverse experiences were observed in 1 of 3 patients (33.3%) who received Vorinostat at a dose of 300 mg twice daily 3 out of 7 days.

In the above three dose level sub-populations, with the exception of dehydration in 2 patients (33.3%), all other drug-related serious adverse experiences were observed in a single patient with incidence ranging from 7.1% to 33.3%.

**Doses above the MTD**

- 6 of the 51 patients (11.8%) experienced a drug-related serious adverse experience.
- The drug-related serious adverse experiences that were unique to the doses above the MTD occurred in a single patient with incidence of 2.0% and included urinary retention, hypertension, anemia and vomiting.

While these serious adverse experiences were unique to the doses above the MTD, there are notable similarities when compared with the serious adverse experiences observed in the CTCL population. Overall, the data from the drug-related serious adverse experiences suggest that with the exception of dehydration, vomiting, anemia and thrombocytopenia, the types of drug-related serious adverse experiences observed in the hematologic malignancies are unique to this population and may be attributed to the underlying disease and age.

## Table 120. Drug-Related Serious Clinical Adverse Experiences by System Organ Class (Incidence > 0% in One or More Dose Levels) Vorinostat Monotherapy – Hematologic Malignancies (Applicant's Table)

| | 400mg QD continuous (N=16) | | 300mg BID 3-7 (N=3) | | 200mg BID continuous (N=6) | | 200mg BID 14-21 (N=14) | | doses above MTD (N=51) | | doses below MTD (N=13) | | Total Patients (N=87) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % | n | % | n | % | n | % |
| *Patients With One Or More Clinical Adverse Experiences* | *7* | *(43.8)* | *1* | *(33.3)* | *2* | *(33.3)* | *1* | *(7.1)* | *6* | *(11.8)* | *2* | *(15.4)* | *16* | *(18.4)* |
| *Patients With No Clinical Adverse Experiences* | *9* | *(56.3)* | *2* | *(66.7)* | *4* | *(66.7)* | *13* | *(92.9)* | *45* | *(88.2)* | *11* | *(84.6)* | *71* | *(81.6)* |
| **Blood And Lymphatic System Disorders** | **1** | **(6.3)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(7.1)** | **2** | **(3.9)** | **0** | **(0.0)** | **3** | **(3.4)** |
| Thrombocytopenia | 1 | (6.3) | 0 | (0.0) | 0 | (0.0) | 1 | (7.1) | 2 | (3.9) | 0 | (0.0) | 3 | (3.4) |
| Anaemia | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.0) | 0 | (0.0) | 1 | (1.1) |
| **Gastrointestinal Disorders** | **3** | **(18.8)** | **0** | **(0.0)** | **1** | **(16.7)** | **0** | **(0.0)** | **3** | **(5.9)** | **0** | **(0.0)** | **7** | **(8.0)** |
| Diarrhoea | 3 | (18.8) | 0 | (0.0) | 1 | (16.7) | 0 | (0.0) | 3 | (5.9) | 0 | (0.0) | 7 | (8.0) |
| Vomiting | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.0) | 0 | (0.0) | 1 | (1.1) |
| **General Disorders And Administration Site Conditions** | **0** | **(0.0)** | **1** | **(33.3)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(1.1)** |
| General Physical Health Deterioration | 0 | (0.0) | 1 | (33.3) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.1) |
| **Infections And Infestations** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(7.7)** | **1** | **(1.1)** |
| Herpes Zoster | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (7.7) | 1 | (1.1) |
| **Metabolism And Nutrition Disorders** | **5** | **(31.3)** | **1** | **(33.3)** | **2** | **(33.3)** | **0** | **(0.0)** | **2** | **(3.9)** | **1** | **(7.7)** | **10** | **(11.5)** |
| Dehydration | 5 | (31.3) | 0 | (0.0) | 2 | (33.3) | 0 | (0.0) | 2 | (3.9) | 1 | (7.7) | 9 | (10.3) |
| Hyponatraemia | 0 | (0.0) | 1 | (33.3) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.1) |
| **Nervous System Disorders** | **1** | **(6.3)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(1.1)** |
| Guillain-Barré Syndrome | 1 | (6.3) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (1.1) |
| **Renal And Urinary Disorders** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(2.0)** | **0** | **(0.0)** | **1** | **(1.1)** |
| Urinary Retention | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.0) | 0 | (0.0) | 1 | (1.1) |
| **Vascular Disorders** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(2.0)** | **0** | **(0.0)** | **1** | **(1.1)** |
| Hypertension | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.0) | 0 | (0.0) | 1 | (1.1) |

A patient is counted only once within a System Organ Class category, even if more than one adverse experience with specific preferred terms occurred. Only the highest grade of a given adverse experience is counted per dose level for the individual patient

Adverse experience terms are from MedDRA Version 8.1

[Ref. 5.3.5.4: P003V1, P004V1, P006, P013V1]

## Vorinostat Monotherapy – Combination Therapies

This section reviews the serious clinical adverse experiences in combination therapies population (n = 10) by SOC and dose level. Due to the small number of patients treated with combination therapies no meaningful comparisons can be made across populations.

- 1 of the 10 patients (10%) receiving combination therapies reported serious clinical adverse experiences: accidental overdose, dehydration and T-cell lymphoma.
- AN3152 (Protocol 012) who received 300 mg once daily 14 out of 21 days, reported an accidental overdose on study Day 5. No adverse experiences related to the overdose were reported.
- None of the serious clinical adverse experiences were considered by the Investigator to be related to study drug.

**Table 121. Number (%) of Patients with Specific Serious Clinical Adverse Experiences by System Organ Class (Vorinostat Monotherapy – Combination Therapies) (Applicant's Table)**

| | 200mg BID 14/21 (N=7) | | doses below MTD (N=7) | | Total Patients (N=10) | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| *Patients With One Or More Clinical Adverse Experiences* | *1* | *(14.3)* | *2* | *(28.6)* | *3* | *(30.0)* |
| *Patients With No Clinical Adverse Experiences* | *6* | *(85.7)* | *5* | *(71.4)* | *7* | *(70.0)* |
| **Injury, Poisoning And Procedural Complications** | **0** | **(0.0)** | **1** | **(14.3)** | **1** | **(10.0)** |
| Accidental Overdose | 0 | (0.0) | 1 | (14.3) | 1 | (10.0) |
| **Metabolism And Nutrition Disorders** | **1** | **(14.3)** | **0** | **(0.0)** | **1** | **(10.0)** |
| Dehydration | 1 | (14.3) | 0 | (0.0) | 1 | (10.0) |
| **Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)** | **0** | **(0.0)** | **1** | **(14.3)** | **1** | **(10.0)** |
| T-Cell Lymphoma | 0 | (0.0) | 1 | (14.3) | 1 | (10.0) |

A patient is counted only once within a System Organ Class category, even if more than one adverse experience with specific preferred terms occurred. Only the highest grade of a given adverse experience is counted per dose level for the individual patient.

Adverse experience terms are from MedDRA Version 8.1

[Ref. 5.3.5.4: P012V1, P015V1, P016V1]

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**Summary Comparison of Serious Clinical Adverse Experiences – All Populations**

- Across all populations, 127 of 305 patients (41.6%) treated with Vorinostat had at least 1 serious clinical adverse experience and 7 patients (2.3%) had at least 1 serious laboratory adverse experience
  - 31 of 127 (24.4%) of the serious clinical adverse experiences remained unresolved and 24 patients (18.9%) experienced a serious adverse experience that resulted in death
  - In forty-nine (49) of these 127 patients (38.6%) at least 1 serious clinical adverse experience was determined by the Investigator to be *related to the study drug.*
  - 18 of the 49 patients (36.7%) with drug-related serious clinical adverse experiences had received Vorinostat at a dose of 400 mg once daily and 19 patients (38.8%) received doses above the MTD.

- Majority of the patients (111 of 147 or 75.5%) who received Vorinostat at a dose of 400 mg once daily did not have any serious clinical adverse experience
- The highest frequency of clinical adverse experiences was reported at doses above the MTD: in 52 of 109 patients (47.7%)

- Four (4) of the 7 patients (57.1%) with at least 1 serious laboratory adverse experience also had 1 or more serious clinical adverse experiences.

The following table summarizes the serious clinical adverse experience by SOC and preferred terms occurring at an incidence of ≥2% in any dose level. Serious clinical adverse experiences are grouped by the dose level the patient received at the time of the serious adverse experience and not by the assigned treatment group.

- Of the 147 patients who received Vorinostat at a dose of 400 mg once daily, 36 patients (24.5%) experienced at least 1 serious clinical adverse experience that included dehydration (4.1%), pulmonary embolism (2.7%), staphylococcal infection (2.0%), diarrhea (2.0%) and squamous cell carcinoma (2.0%).
- Serious adverse experiences were observed in 12 of 33 patients (36.4%) who received Vorinostat at a dose of 300 mg twice daily 3 out of 7 days, 7 of 24 patients (29.2%) who received Vorinostat at a dose of 200 mg twice daily, and 12 of 27 patients (44.4%) who received Vorinostat at a dose of 200 mg twice daily 14 out of 21 days.
  - For these 3 doses and schedules, the safety profiles are similar in frequency.
- One hundred and nine (109) patients were treated at doses that exceeded the MTD. Fifty-two (52) patients (47.7%) reported at least 1 serious clinical adverse experience. Of these 52 patients, 30 (57.7%) were from the hematologic malignancy population.
  - The safety profile was similar in incidence to that of the 400 mg once daily dose with the exception of dehydration (9.2%), febrile neutropenia (8.3%), vomiting (5.5%) and thrombocytopenia (4.6%).
- The results for other safety evaluations including ECGs and physical examinations did not indicate any serious adverse experiences

## Table 122. Number (%) Of Patients with Specific Serious Clinical Adverse Experiences by System Organ Class (All Patients) (Applicant's Table)

| | 400mg QD continuous (N=147) | | 300mg BID 3-7 (N=33) | | 200mg BID continuous (N=24) | | 200mg BID 14-21 (N=27) | | doses above MTD (N=109) | | doses below MTD (N=47) | | Total Patients (N=305) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % | n | % | n | % | n | % |
| *Patients With One Or More Clinical Adverse Experiences* | *36* | *(24.5)* | *12* | *(36.4)* | *7* | *(29.2)* | *12* | *(44.4)* | *52* | *(47.7)* | *19* | *(40.4)* | *127* | *(41.6)* |
| *Patients With No Clinical Adverse Experiences* | *111* | *(75.5)* | *21* | *(63.6)* | *17* | *(70.8)* | *15* | *(55.6)* | *57* | *(52.3)* | *28* | *(59.6)* | *178* | *(58.4)* |
| **Blood And Lymphatic System Disorders** | **3** | **(2.0)** | **0** | **(0.0)** | **2** | **(8.3)** | **4** | **(14.8)** | **16** | **(14.7)** | **2** | **(4.3)** | **25** | **(8.2)** |
| Febrile Neutropenia | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (3.7) | 9 | (8.3) | 2 | (4.3) | 12 | (3.9) |
| Thrombocytopenia | 2 | (1.4) | 0 | (0.0) | 2 | (8.3) | 2 | (7.4) | 5 | (4.6) | 0 | (0.0) | 10 | (3.3) |
| Anaemia | 2 | (1.4) | 0 | (0.0) | 0 | (0.0) | 1 | (3.7) | 3 | (2.8) | 0 | (0.0) | 6 | (2.0) |
| **Eye Disorders** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(3.7)** | **1** | **(0.9)** | **0** | **(0.0)** | **2** | **(0.7)** |
| Vision Blurred | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (3.7) | 1 | (0.9) | 0 | (0.0) | 2 | (0.7) |
| **Gastrointestinal Disorders** | **6** | **(4.1)** | **4** | **(12.1)** | **1** | **(4.2)** | **1** | **(3.7)** | **16** | **(14.7)** | **2** | **(4.3)** | **30** | **(9.8)** |
| Diarrhoea | 3 | (2.0) | 1 | (3.0) | 1 | (4.2) | 0 | (0.0) | 3 | (2.8) | 0 | (0.0) | 8 | (2.6) |
| Vomiting | 0 | (0.0) | 1 | (3.0) | 0 | (0.0) | 0 | (0.0) | 6 | (5.5) | 0 | (0.0) | 7 | (2.3) |
| Gastrointestinal Haemorrhage | 1 | (0.7) | 1 | (3.0) | 0 | (0.0) | 0 | (0.0) | 2 | (1.8) | 1 | (2.1) | 5 | (1.6) |
| Abdominal Pain | 1 | (0.7) | 1 | (3.0) | 0 | (0.0) | 0 | (0.0) | 2 | (1.8) | 0 | (0.0) | 4 | (1.3) |
| Nausea | 0 | (0.0) | 1 | (3.0) | 0 | (0.0) | 0 | (0.0) | 3 | (2.8) | 0 | (0.0) | 4 | (1.3) |
| Intestinal Obstruction | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) | 1 | (2.1) | 2 | (0.7) |
| Anal Haemorrhage | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (3.7) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) |
| Constipation | 0 | (0.0) | 1 | (3.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) |
| **General Disorders And Administration Site Conditions** | **3** | **(2.0)** | **2** | **(6.1)** | **0** | **(0.0)** | **3** | **(11.1)** | **7** | **(6.4)** | **0** | **(0.0)** | **15** | **(4.9)** |
| Pyrexia | 2 | (1.4) | 1 | (3.0) | 0 | (0.0) | 1 | (3.7) | 2 | (1.8) | 0 | (0.0) | 6 | (2.0) |
| General Physical Health Deterioration | 0 | (0.0) | 1 | (3.0) | 0 | (0.0) | 2 | (7.4) | 1 | (0.9) | 0 | (0.0) | 4 | (1.3) |
| Fatigue | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (3.7) | 1 | (0.9) | 0 | (0.0) | 2 | (0.7) |
| Asthenia | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (3.7) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) |
| **Hepatobiliary Disorders** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(3.7)** | **1** | **(0.9)** | **0** | **(0.0)** | **2** | **(0.7)** |
| Cholecystitis | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (3.7) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) |
| **Infections And Infestations** | **11** | **(7.5)** | **0** | **(0.0)** | **1** | **(4.2)** | **2** | **(7.4)** | **12** | **(11.0)** | **4** | **(8.5)** | **29** | **(9.5)** |
| Infection | 2 | (1.4) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 3 | (2.8) | 2 | (4.3) | 7 | (2.3) |
| Sepsis | 2 | (1.4) | 0 | (0.0) | 1 | (4.2) | 0 | (0.0) | 1 | (0.9) | 0 | (0.0) | 4 | (1.3) |
| Staphylococcal Infection | 3 | (2.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 3 | (1.0) |
| Urinary Tract Infection | 0 | (0.0) | 0 | (0.0) | 1 | (4.2) | 1 | (3.7) | 1 | (0.9) | 0 | (0.0) | 3 | (1.0) |
| Herpes Zoster | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 2 | (4.3) | 2 | (0.7) |
| **Injury, Poisoning And Procedural Complications** | **2** | **(1.4)** | **0** | **(0.0)** | **1** | **(4.2)** | **1** | **(3.7)** | **2** | **(1.8)** | **1** | **(2.1)** | **7** | **(2.3)** |
| Subdural Haematoma | 0 | (0.0) | 0 | (0.0) | 1 | (4.2) | 0 | (0.0) | 2 | (1.8) | 0 | (0.0) | 3 | (1.0) |
| Accidental Overdose | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.1) | 1 | (0.3) |
| Transfusion Reaction | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (3.7) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) |
| **Metabolism And Nutrition Disorders** | **6** | **(4.1)** | **3** | **(9.1)** | **3** | **(12.5)** | **1** | **(3.7)** | **12** | **(11.0)** | **3** | **(6.4)** | **27** | **(8.9)** |
| Dehydration | 6 | (4.1) | 2 | (6.1) | 3 | (12.5) | 1 | (3.7) | 10 | (9.2) | 3 | (6.4) | 24 | (7.9) |
| Hyponatraemia | 0 | (0.0) | 1 | (3.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) |
| **Musculoskeletal And Connective Tissue Disorders** | **1** | **(0.7)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(3.7)** | **3** | **(2.8)** | **0** | **(0.0)** | **5** | **(1.6)** |
| Back Pain | 1 | (0.7) | 0 | (0.0) | 0 | (0.0) | 1 | (3.7) | 0 | (0.0) | 0 | (0.0) | 2 | (0.7) |
| **Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)** | **7** | **(4.8)** | **2** | **(6.1)** | **2** | **(8.3)** | **3** | **(11.1)** | **7** | **(6.4)** | **5** | **(10.6)** | **25** | **(8.2)** |
| T-Cell Lymphoma | 1 | (0.7) | 0 | (0.0) | 1 | (4.2) | 0 | (0.0) | 1 | (0.9) | 3 | (6.4) | 6 | (2.0) |
| Acute Myeloid Leukaemia | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (3.7) | 3 | (2.8) | 0 | (0.0) | 4 | (1.3) |
| Squamous Cell Carcinoma | 3 | (2.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.1) | 3 | (1.0) |
| Diffuse Large B-Cell Lymphoma | 1 | (0.7) | 1 | (3.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 2 | (0.7) |
| Cancer Pain | 0 | (0.0) | 1 | (3.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) |
| Diffuse Large B-Cell Lymphoma Recurrent | 0 | (0.0) | 0 | (0.0) | 1 | (4.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) |
| Lung Neoplasm | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.1) | 1 | (0.3) |
| Neoplasm Progression | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (3.7) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) |
| Renal Cell Carcinoma Stage Unspecified | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.1) | 1 | (0.3) |
| Tumour Haemorrhage | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (3.7) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) |
| **Nervous System Disorders** | **3** | **(2.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **2** | **(7.4)** | **3** | **(2.8)** | **3** | **(6.4)** | **11** | **(3.6)** |
| Cerebrovascular Accident | 1 | (0.7) | 0 | (0.0) | 0 | (0.0) | 1 | (3.7) | 0 | (0.0) | 0 | (0.0) | 2 | (0.7) |
| Cerebral Haemorrhage | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (3.7) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) |
| Convulsion | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.1) | 1 | (0.3) |
| Ischaemic Stroke | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.1) | 1 | (0.3) |
| Ruptured Cerebral Aneurysm | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.1) | 1 | (0.3) |
| **Psychiatric Disorders** | **2** | **(1.4)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(0.9)** | **1** | **(2.1)** | **4** | **(1.3)** |
| Confusional State | 1 | (0.7) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) | 1 | (2.1) | 3 | (1.0) |
| **Respiratory, Thoracic And Mediastinal Disorders** | **6** | **(4.1)** | **4** | **(12.1)** | **1** | **(4.2)** | **1** | **(3.7)** | **3** | **(2.8)** | **2** | **(4.3)** | **16** | **(5.2)** |
| Pulmonary Embolism | 4 | (2.7) | 2 | (6.1) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.1) | 7 | (2.3) |
| Dyspnoea | 1 | (0.7) | 1 | (3.0) | 0 | (0.0) | 1 | (3.7) | 2 | (1.8) | 1 | (2.1) | 6 | (2.0) |
| Hypoxia | 1 | (0.7) | 1 | (3.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 2 | (0.7) |
| Cough | 0 | (0.0) | 0 | (0.0) | 1 | (4.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) |
| Lung Disorder | 0 | (0.0) | 1 | (3.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) |
| Tracheal Stenosis | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.1) | 1 | (0.3) |
| **Vascular Disorders** | **2** | **(1.4)** | **5** | **(15.2)** | **0** | **(0.0)** | **0** | **(0.0)** | **6** | **(5.5)** | **1** | **(2.1)** | **14** | **(4.6)** |
| Deep Vein Thrombosis | 1 | (0.7) | 1 | (3.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) | 1 | (2.1) | 4 | (1.3) |
| Hypotension | 0 | (0.0) | 1 | (3.0) | 0 | (0.0) | 0 | (0.0) | 2 | (1.8) | 0 | (0.0) | 3 | (1.0) |
| Thrombosis | 1 | (0.7) | 2 | (6.1) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 3 | (1.0) |
| Embolism | 0 | (0.0) | 2 | (6.1) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 2 | (0.7) |
| Shock Haemorrhagic | 0 | (0.0) | 1 | (3.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) |

A patient is counted only once within a System Organ Class category, even if more than one adverse experience with specific preferred terms occurred. Only the highest grade of a given adverse experience is counted per dose level for the individual patient.
Adverse experience terms are from MedDRA Version 8.1.
[Ref: 5.3.5.2: P001] [Ref: 5.3.5.4: P002, P003V1, P004V1, P006, P011V1, P012V1, P013V1, P015V1, P016V1]

***Drug-related* Serious Clinical Adverse Experiences (All Populations)**

The following table summarizes the *drug-related* serious clinical adverse experiences across all populations.

- Of 127 patients with serious adverse experiences, 49 patients (38.6%) were determined by the Investigator to be related to study drug.

- Eighteen (18) of these 49 patients (36.7%) received Vorinostat at a dose of 400 mg once daily.
  - The most common drug-related serious adverse experience with an incidence ≥1% at the 400 mg once daily dose were dehydration (4.1%), diarrhea (2.0%), pulmonary embolism (2.7%), anemia (1.4%) and thrombocytopenia (1.4%).

- Serious clinical adverse experiences determined by the Investigator to be drug-related were observed in 5 patients who received Vorinostat at a dose of 300 mg twice daily 3 out of 7 days, 5 patients who received Vorinostat at a dose of 200 mg twice daily dose, and 4 patients who received Vorinostat at a dose of 200 mg twice daily 14 out of 21 days.
  - At these 3 dose levels, the safety profile is generally similar in frequency.

- The highest incidence of serious adverse experiences determined by the Investigator to be related to study drug occurred in 19 patients (17.4%) whose dose exceeded the MTD.
  - Overall, the safety profile in these patients is qualitatively similar across all populations in all dose levels.

## Table 123. Number (%) of Patients with Specific Serious Drug-Related Clinical Adverse Experiences by System Organ Class (All Patients) (Applicant's Table)

| | 400mg QD continuous (N=147) | | 300mg BID 3/7 (N=33) | | 200mg BID continuous (N=24) | | 200mg BID 14/21 (N=27) | | dose above MTD (N=109) | | dose below MTD (N=47) | | Total Patients (N=365) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % | n | % | n | % | n | % |
| *Patients With One Or More Clinical Adverse Experiences* | *18* | *(12.2)* | *5* | *(15.2)* | *5* | *(20.8)* | *4* | *(14.8)* | *19* | *(17.4)* | *4* | *(8.5)* | *49* | *(13.4)* |
| *Patients With No Clinical Adverse Experiences* | *129* | *(87.8)* | *28* | *(84.8)* | *19* | *(79.2)* | *23* | *(85.2)* | *90* | *(82.6)* | *43* | *(91.5)* | *256* | *(82.9)* |
| **Blood And Lymphatic System Disorders** | **3** | **(2.0)** | **0** | **(0.0)** | **2** | **(8.3)** | **3** | **(11.1)** | **6** | **(5.5)** | **0** | **(0.0)** | **12** | **(3.9)** |
| Thrombocytopenia | 2 | (1.4) | 0 | (0.0) | 2 | (8.3) | 2 | (7.4) | 5 | (4.6) | 0 | (0.0) | 10 | (3.3) |
| Anaemia | 2 | (1.4) | 0 | (0.0) | 0 | (0.0) | 1 | (3.7) | 2 | (1.8) | 0 | (0.0) | 5 | (1.6) |
| **Eye Disorders** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(3.7)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(0.3)** |
| Vision Blurred | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (3.7) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) |
| **Gastrointestinal Disorders** | **4** | **(2.7)** | **1** | **(3.0)** | **1** | **(4.2)** | **0** | **(0.0)** | **5** | **(4.6)** | **0** | **(0.0)** | **11** | **(3.6)** |
| Diarrhoea | 3 | (2.0) | 1 | (3.0) | 1 | (4.2) | 0 | (0.0) | 3 | (2.8) | 0 | (0.0) | 8 | (2.6) |
| Vomiting | 0 | (0.0) | 1 | (3.0) | 0 | (0.0) | 0 | (0.0) | 3 | (2.8) | 0 | (0.0) | 4 | (1.3) |
| Nausea | 0 | (0.0) | 1 | (3.0) | 0 | (0.0) | 0 | (0.0) | 2 | (1.8) | 0 | (0.0) | 3 | (1.0) |
| Gastrointestinal Haemorrhage | 1 | (0.7) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) |
| **General Disorders And Administration Site Conditions** | **2** | **(1.4)** | **2** | **(6.1)** | **0** | **(0.0)** | **1** | **(3.7)** | **3** | **(2.8)** | **0** | **(0.0)** | **8** | **(2.6)** |
| Pyrexia | 1 | (0.7) | 1 | (3.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) | 0 | (0.0) | 3 | (1.0) |
| Asthenia | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (3.7) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) |
| Chest Pain | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) | 0 | (0.0) | 1 | (0.3) |
| Death | 1 | (0.7) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) |
| Fatigue | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) | 0 | (0.0) | 1 | (0.3) |
| General Physical Health Deterioration | 0 | (0.0) | 1 | (3.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) |
| **Hepatobiliary Disorders** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(0.9)** | **0** | **(0.0)** | **1** | **(0.3)** |
| Hepatic Ischaemia | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) | 0 | (0.0) | 1 | (0.3) |
| **Infections And Infestations** | **1** | **(0.7)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(2.1)** | **2** | **(0.7)** |
| Herpes Zoster | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.1) | 1 | (0.3) |
| Streptococcal Bacteraemia | 1 | (0.7) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) |
| **Metabolism And Nutrition Disorders** | **6** | **(4.1)** | **2** | **(6.1)** | **3** | **(12.5)** | **0** | **(0.0)** | **7** | **(6.4)** | **3** | **(6.4)** | **20** | **(6.6)** |
| Dehydration | 6 | (4.1) | 1 | (3.0) | 3 | (12.5) | 0 | (0.0) | 6 | (5.5) | 3 | (6.4) | 18 | (5.9) |
| Anorexia | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) | 0 | (0.0) | 1 | (0.3) |
| Hyponatraemia | 0 | (0.0) | 1 | (3.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) |
| **Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(3.7)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(0.3)** |
| Tumour Haemorrhage | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (3.7) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) |
| **Nervous System Disorders** | **2** | **(1.4)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(2.1)** | **3** | **(1.0)** |
| Guillain-Barre Syndrome | 1 | (0.7) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) |
| Ischaemic Stroke | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.1) | 1 | (0.3) |
| Syncope | 1 | (0.7) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) |
| **Renal And Urinary Disorders** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(0.9)** | **0** | **(0.0)** | **1** | **(0.3)** |
| Urinary Retention | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) | 0 | (0.0) | 1 | (0.3) |
| **Respiratory, Thoracic And Mediastinal Disorders** | **5** | **(3.4)** | **1** | **(3.0)** | **1** | **(4.2)** | **0** | **(0.0)** | **1** | **(0.9)** | **0** | **(0.0)** | **7** | **(2.3)** |
| Pulmonary Embolism | 4 | (2.7) | 1 | (3.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 5 | (1.6) |
| Cough | 0 | (0.0) | 0 | (0.0) | 1 | (4.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) |
| Haemoptysis | 1 | (0.7) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) | 0 | (0.0) | 1 | (0.3) |
| **Vascular Disorders** | **2** | **(1.4)** | **1** | **(3.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **2** | **(1.8)** | **0** | **(0.0)** | **5** | **(1.6)** |
| Deep Vein Thrombosis | 1 | (0.7) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) |
| Hypertension | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) | 0 | (0.0) | 1 | (0.3) |
| Hypotension | 0 | (0.0) | 1 | (3.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) |
| Thrombosis | 1 | (0.7) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) |
| Vasculitis | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) | 0 | (0.0) | 1 | (0.3) |

A patient is counted only once within a System Organ Class category, even if more than one adverse experience with specific preferred terms occurred. Only the highest grade of a given adverse experience is counted per dose level for the individual patient.
Adverse experience terms are from MedDRA Version 8.1

[Ref. 5.3.5.2: P001] [Ref. 5.3.5.4: P002, P003V1, P004V1, P006, P011V1, P012V1, P013V1, P015V1, P016V1]

## 7.1.3 Dropouts and Other Significant Adverse Events

### 7.1.3.1 Overall profile of dropouts

- All of the patients who discontinued Vorinostat due to AEs in the studies reviewed in the safety analysis had advanced underlying cancers and many of these patients also had other medical conditions requiring treatment. All patients had previous exposures to chemotherapy, frequently to multiple regimens.
- Median age the patients in almost all studies was $\geq$ 60 years.

### 7.1.3.2 Adverse events associated with dropouts

- Most common cause of Vorinostat discontinuation was a lack of efficacy of Vorinostat—progression of the underlying disease. This is not unexpected as almost all patients had advanced cancers and had failed previous therapies.
- Other AEs such as pulmonary embolism, thrombocytopenia, hemorrhagic episodes, and cardiac and cerebrovascular events were also noted, and when taken together these constitute another common cause of Vorinostat discontinuations.

See section 7.2.9 Additional Submissions, Including Safety Update for a tabular listing of the AEs across different populations in different studies and a discussion of drug-demographic, drug-disease interactions.

- An important drug-drug interaction has been observed with another histone deacetylase inhibitor valproic acid—it led to thrombocytopenia and GI hemorrhage.

### 7.1.3.3 Other significant adverse events

**Other *Significant* Adverse Experiences**

This section summarizes the clinical and laboratory adverse experiences of special interest. *Clinical adverse experiences* include **cardiovascular**, **cerebrovascular**, and **venous thromboembolic** events; and *laboratory adverse experiences* include **hyperglycemia, increased serum creatinine,** and **thrombocytopenia**.

**Cardiovascular Events**

The following table summarizes the reported cardiovascular adverse experiences, the pertinent medical history, and prior and concomitant cardiac medications.

- Cardiovascular adverse experiences were reported in 6 patients, 2 were graded as serious (see table).

**Table 124. Summary of Patients with Cardiovascular Adverse Experiences (Applicant's Table)**

| Allocation Number/ Protocol Number | Cardiovascular Adverse Experience | NCI Toxicity Grade | Serious Adverse Experience | Pertinent Medical History | Prior Cardiac Medications | Concomitant Cardiac Medication |
|---|---|---|---|---|---|---|
| 1004/001 | Myocardial infarction, coronary artery disease | 4<br>2 | Yes<br>No | hypercholesterolemia, intermittent hypertension | None | clopidogrel bisulfate, lisinopril, aspirin, nitroglycerin, atenolol, losartan potassium |
| 1027/001 | Ischemia | 1 | No | hypertriglyceridemia, decreased HDL cholesterol | None | atorvastatin calcium |
| 1007/003 | Cardiac failure | 1 | No | atrial fibrillation, pacemaker placement | None | None |
| 1008/003 | Cardiac ischemia | 4 | Yes | aortic regurgitation, cardiac failure, chest pain, ischemic heart disease, pulmonary hypertension, anemia | furosemide, potassium chloride, metoprolol tartrate, nitroglycerine patch | aspirin, isosorbide mononitrate |
| 407/013 | Ischemia | 2 | No | hypotension, anemia, arrhythmia | None | darbopoietin, packed red blood cell transfusion, aspirin, metoprolol |
| 421/013 | Ischemia | 1 | No | age indeterminant myocardial infarction | None | None |

[Ref. 5.3.5.2: P001] [Ref. 5.3.5.4: P003V1, P013V1]

AN1004 (Protocol 001) experienced a Grade 4 myocardial infarction and Grade 2 coronary artery disease on Study Day 31. The Investigator considered the myocardial infarction to be serious and definitely *not related* to study therapy; the adverse experience of coronary artery disease was considered non-serious and *definitely not related* to study therapy. Both events resulted in an interruption of study therapy for 12 days. Study therapy was then re-started at the same dose. At the conclusion of the study, the outcome of the myocardial infarction was recovered; the outcome of the coronary artery disease was not recovered.

AN1027 (Protocol 001) experienced Grade 1 ischemia on Study Day 57. The Investigator determined this adverse experience to be non-serious and *possibly related* to study therapy. No change was made to study medication. At the conclusion of the study, the outcome of this adverse experience was recovered.

AN1008 (Protocol 003) experienced Grade 4 cardiac ischemia on Study Day 15. The Investigator determined this adverse experience to be serious and *definitely not related* to study therapy. No change was made to study medication. At the time of the data cut-off date for this submission, the outcome of this adverse experience was recovered.

AN1007 (Protocol 003) experienced Grade 1 cardiac failure on Study Day 19. The Investigator determined this adverse experience to be non-serious and *definitely not related* to study therapy. No change was made to study medication. At the time of the data cut-off date for this submission, the outcome of this adverse experience was recovered.

AN407 (Protocol 013) experienced Grade 2 ischemia on Study Day 42. The patient's baseline ECG demonstrated premature atrial contractions. Follow-up ECGs were performed on Study Days 15 and 60. These demonstrated left atrial enlargement and ST-T wave changes,

respectively. The Investigator determined this adverse experience to be non-serious and *probably not related* to study therapy. No change was made to study medication. At the time of the data cut-off date for this submission, the outcome of this adverse experience was not recovered.

AN0421 (Protocol 013) experienced Grade 1 ischemia on Study Day 23. The patient's baseline ECG demonstrated an age indeterminate anteroseptal myocardial infarction, and a follow-up ECG on Study Day 15 demonstrated ST-T wave changes. The Investigator determined this adverse experience to be non-serious and *definitely not related* to study therapy. No change was made to study medication. At the time of the data cut-off date for this submission, the outcome of this adverse experience was not recovered.

## Cerebrovascular Events

The following table summarizes the reported cerebrovascular adverse experiences, the pertinent past medical history, and prior and concomitant medications.

- Six (6) cerebrovascular adverse experiences were reported in 5 patients, five were graded serious.

**Table 125. Summary of Patients with Cerebrovascular Adverse Experiences (Applicant's Table)**

| Allocation Number/ Protocol Number | Cardiovascular Adverse Experience | NCI Toxicity Grade | Serious Adverse Experience | Pertinent Past Medical History | Prior Medications | Concomitant Medication |
|---|---|---|---|---|---|---|
| 1008/001 | Cerebral ischemia, ischemic stroke | 2<br>4 | No<br>Yes | Hypertension, diabetes mellitus | Quinapril, metformin hydrochloride | None |
| 1002/006 | Ruptured cerebral aneurysm | 3 | Yes | Prothrombin time abnormality | None | Aspirin, rofecoxib |
| 007/008 | Cerebrovascular accident | 3 | Yes | Diabetes mellitus, cerebrovascular accident, cerebral infarction | Glimepiride, insulin | Clopidogrel bisulfate |
| 1036/003 | Cerebral ischemia | 3 | Yes | Hypertension, diabetes mellitus with diabetic neuropathy, cerebrovascular accident | Atenolol, ramipril, insulin | None |
| 1030/003 | Cerebral hemorrhage | 2 | Yes | Diabetes mellitus, hypertension, thrombocytopenia | Diltiazem hydrochloride, atenolol, platelet transfusions | Platelet transfusions |

[Ref. 5.3.3.2: P008] [Ref. 5.3.5.2: P001] [Ref. 5.3.5.4: P003V1, P006]

AN1008 (Protocol 001) experienced Grade 2 cerebral ischemia on Study Day 205. This adverse experience was considered by the Investigator to be non-serious and *possibly related* to study therapy. Study drug was held for dehydration and vomiting from Study day 204 to Study Day 208. Following this interruption study therapy was continued at the same dose. On Study Day 227, Grade 4 ischemic stroke was reported which resulted in the death of the patient. This serious adverse experience was considered by the Investigator to be *possibly related* to study therapy.

AN1002 (Protocol 006) experienced Grade 3 ruptured cerebral aneurysm on Study Day 61. This adverse experience was considered by the Investigator to be serious and *definitely not related* to study therapy. Study medication was interrupted at this time. During the course of the study the patient's platelet count ranged from 247 to 397 x $10^3$/microL. Although not reported as an adverse experience, during the first 2 weeks of the study the patient was observed to have mild diastolic hypertension (90 to 100 mmHg), during the remainder of the study the patient was normotensive.

AN007 (Protocol 008) experienced Grade 1 facial and lower extremity numbness on Study Day 118. The Investigator considered this adverse experience to be non-serious and *probably not related* to study therapy. No change was made to study medication at this time. On Study Day 120 Grade 3 cerebrovascular accident was reported. The Investigator considered this adverse experience to be serious and *probably not related* to study therapy. Study medication was interrupted for 14 days. Following recovery from this serious adverse experience, the patient was re-started on study therapy at the same dose.

AN1036 (Protocol 003) experienced Grade 3 cerebral ischemia on Study Day 17. The Investigator considered this adverse experience to be serious and *definitely not related* to study therapy. No change was made to study medication. At the time of the data cut-off date for this submission, the outcome of this adverse experience was recovered.

AN1030 (Protocol 003) experienced a Grade 3 headache on Study Day 15. The Investigator considered this adverse experience to be non-serious and *definitely not related* to study therapy. On Study Day 16 Grade 2 cerebral hemorrhage was reported along with nausea, vomiting, speech impairment, hematuria, and ecchymosis. The cerebral hemorrhage adverse experience was considered by the Investigator to be serious and *definitely not related* to study therapy. No change was made to study medication at this time. Study medication had previously been discontinued on Study Day 14. During the course of the study the patient's platelet count ranged as low as 9 to 23 x 10$_3$/microL. Platelet count on Study Day 15 was noted to be 9 x 10$_3$/microL. The patient had received platelet transfusions on Study Days -13, -6, 6, and 14. At the time of the data cut-off date for this submission, the outcome of this adverse experience was recovered.

**Venous Thromboembolic Events**

- Venous thromboembolic adverse experiences were reported in a total of 17 patients; more than 1 episode was reported in some patients

**Vorinostat Monotherapy – CTCL and CTCL Stage IIB and Higher:**

- Six (6) CTCL patients had **pulmonary embolisms (Protocol 001:** AN1070, AN1015, AN1058, and AN1059; **Protocol 005:** AN1017 and AN1018)
  - Four (4) patients with CTCL in the 400 mg once daily treatment group reported pulmonary embolisms. The adverse experiences were considered by the Investigator to be *related* to the study drug.
    - All patients reported treatment with anticoagulation therapy on the serious adverse experience report.
    - Two (2) of the 4 patients required dose modifications or discontinuation and 2 patients recovered from this adverse experience.
  - Adverse experience of Grade 3 pulmonary embolism was also reported in 2 patients in the CTCL population who received Vorinostat at a dose of 300 mg twice daily, 3 out of 7 days. Among these patients, 1 had concomitant therapy with conjugated estrogens.
- 4 patients with **deep venous thrombosis (Protocol 001**: AN1015; **Protocol 005**: AN1017, AN1018, and AN1025)
  - Three (3) patients overall and 1 patient with CTCL in the 400 mg once daily treatment group reported deep vein thrombosis (a serious clinical adverse experience or a non-serious adverse experience Grade 3 or higher). The adverse experiences in these patients were considered by the Investigator to be *related* to study drug.
    - The one CTCL patient reported a prior medical history of leg pain and received anticoagulation therapy as documented on the serious adverse experience report. Although this event led to discontinuation of study therapy, the patient did recover.
    - In the overall CTCL population, 1 of 3 patients reported a prior medical history of leg pain. All patients were treated with anticoagulation therapy and all subsequently recovered from this adverse experience; two (2) of the 3 patients required discontinuation of study drug.

**Vorinostat Monotherapy – Solid Tumors:**

- 3 patients had **pulmonary embolisms (Protocol 006**: AN1005, AN1073, and AN1074)
- 2 patients had **deep venous thromboses** and 4 patients had **thrombosis (Protocol 006**: AN1020, AN1044, AN1073, AN1074, AN1075, and AN1071)

**Vorinostat Monotherapy – Hematologic Malignancies:**

- 1 patient had **deep venous thrombosis** (Protocol 013: AN366)
- 1 patient had **thrombosis** (Protocol 006: AN1011)

**Vorinostat Combination Therapies:**

- 1 patient had **deep venous thrombosis** (Protocol 012: AN3154)

The following tables summarize venous thromboembolic events for Vorinostat Monotherapy – CTCL and CTCL Stage IIB and Higher patients.

- Venous thromboembolic events were reported in a total of 7 patients in the 2 populations. Four (4) patients were receiving 400 mg once daily and 3 patients were receiving 300 mg twice daily 3d/wk.
- These adverse experiences resulted in study medication discontinuation in 3 patients and study therapy interruption in 2 patients.

**Table 126. Number (%) of Patients with Thromboembolic Adverse Experiences (Vorinostat Monotherapy – CTCL) (Applicant's Table)**

| Adverse Experience | 400 mg QD continuous (N=86) | 300 mg BID 3/7 (N=14) | 200 mg BID continuous (N=10) | Doses above MTD (N=20) | Doses below MTD (N=12) | Total (N=107) |
|---|---|---|---|---|---|---|
| Pulmonary embolism | 4 (4.6) | 2 (14.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 6 (5.6) |
| Deep venous thrombosis[†] | 1 (1.2) | 3 (21.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 4 (3.7) |
| [†] Events included lower extremity deep venous thromboses. | | | | | | |

**Table 127. Number (%) of Patients with Thromboembolic Adverse Experiences Vorinostat Monotherapy – CTCL Stage IIB and Higher (Applicant's Table)**

| Adverse Experience | 400 mg QD continuous (N=71) | 300 mg BID 3/7 (N=13) | 200 mg BID continuous (N=8) | Doses above MTD (N=17) | Doses below MTD (N=12) | Total (N=89) |
|---|---|---|---|---|---|---|
| Pulmonary embolism | 4 (5.6) | 2 (15.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 6 (6.7) |
| Deep venous thrombosis[†] | 1 (1.4) | 3 (23.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 4 (4.5) |
| [†] Events included lower extremity deep venous thromboses. | | | | | | |

## Table 128. Details of Patients with Thromboembolic Adverse Experiences Vorinostat Monotherapy – CTCL and Vorinostat Monotherapy – CTCL Stage IIB and Higher (Applicant's Table)

| AN | Adverse Experience | Rel Day of Onset | Duration (days) | Relation | Action Taken | Outcome | Past Medical History/Conditions[2] | Prior Medications[3] | Related Adverse Experiences/Conditions[4] | Concomitant Medications |
|---|---|---|---|---|---|---|---|---|---|---|
| **400 mg QD continuous** | | | | | | | | | | |
| 1035 | Grade 4 deep venous thrombosis | 56 | 15 | Possibly | Discontinued PRx | Recovered | None | None | Leg pain and swelling, fever | None |
| | Grade 4 pulmonary embolism | 63 | 8 | Possibly | | Recovered | None | None | Grade 4 deep venous thrombosis | None |
| 1058 | Grade 4 pulmonary embolism | 141 | | Possibly | No action with test drug | Not recovered | None | None | None | Aspirin[5], heparin[5], enoxaparin[5], warfarin[5] |
| 1059 | Grade 4 pulmonary embolism | 185 | | Possibly | Discontinued PRx | Not recovered | None | None | Chest pain, dyspnea | Enoxaparin[5], warfarin[5] |
| 1070 | Grade 4 pulmonary embolism | 28 | 7 | Possibly | Interrupted PRx | Recovered | Leg swelling | None | Chest pain, cough | None |
| **300 mg BID 3/7** | | | | | | | | | | |
| 1017 | Grade 1 deep venous thrombosis | 29 | 2 | Definitely not | Interrupted PRx | Recovered | Deep venous thrombosis, pulmonary embolism | Aspirin, warfarin | Grade 1 fatigue, fever, shortness of breath | Aspirin, warfarin, heparin[5] |
| | Grade 3 deep venous thrombosis | 49 | | Possibly | Interrupted PRx | Not recovered | | | Grade 1 deep venous thrombosis, Grade 1 fatigue | |
| | Grade 3 pulmonary embolism | 50 | 11 | Possibly | Discontinued PRx | Recovered | | | Grade 3 deep venous thrombosis | |
| 1018 | Grade 3 deep venous thrombosis | 3 | | Definitely not | No action with test drug | Not recovered | None | None | Grade 2 decreased INR, fever, shortness of breath | Enoxaparin[5], warfarin[5] |
| | Grade 3 pulmonary embolism | 3 | 13 | Definitely not | Interrupted | Recovered | | | Grade 3 deep venous thrombosis | |
| 1025 | Grade 3 deep venous thrombosis | 8 | | Definitely not | No action with test drug | Not recovered | None | None | None | Enoxaparin[5], warfarin[5] |

AN = Allocation Number,Rel Day = Study Day
[2] Medical conditions/risk factors related to the adverse experience.
[3] Anticoagulant and hormonal medications taken within 30 days of the first dose of study therapy.
[4] Events starting or ongoing within 14 days of the onset of the adverse experience.
[5] Medication started as a result of the adverse experience.

The following table summarizes venous thromboembolic events for Vorinostat Monotherapy – Solid Tumors.

- Venous thromboembolic events were reported in a total of 7 patients in this population.
- One (1) patient was receiving 400 mg once daily, 3 patients were receiving 300 mg twice daily 3d/wk, 1 patient was receiving a dose above the MTD (300 mg twice daily continuously), and 2 patients were receiving doses below the MTD (200 mg twice daily 3d/wk and 200 mg once daily continuously).
- These adverse experiences resulted in study medication discontinuation in 2 patients and study therapy interruption in 3 patients.

**Table 129. Number (%) of Patients with Thromboembolic Adverse Experiences Vorinostat Monotherapy – Solid Tumors (Applicant's Table)**

| Adverse Experience | 400 mg QD Continuous (N=45) | 300 mg BID 3/7 (N=16) | 200 mg BID continuous (N=8) | 200 mg BID 14/21 (N=6) | Doses above MTD (N=38) | Doses below MTD (N=15) | Total (N=101) |
|---|---|---|---|---|---|---|---|
| Pulmonary embolism | 0 (0.0) | 2 (12.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (6.7) | 3 (3.0) |
| Deep venous thrombosis† | 0 (0.0) | 1 (6.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (6.7) | 2 (1.9) |
| Thrombosis‡ | 1 (2.2) | 2 (12.5) | 0 (0.0) | 0 (0.0) | 1 (2.6) | 0 (0.0) | 4 (4.0) |

† Events include upper and lower extremity deep venous thromboses.
‡ Events include pulmonary thromboses, unspecified thrombosis, and venous sinus thrombosis.

**Table 130. Summary of Patients with Thromboembolic Adverse Experiences (Vorinostat Monotherapy – Solid Tumors) (Applicant's Table)**

| AN | Adverse Experience | Rel Day of Onset | Duration (days) | Relation | Action Taken | Outcome | Past Medical History Conditions[1] | Prior Medications[2] | Related Adverse Experiences/Conditions[3] | Concomitant Medications[4] |
|---|---|---|---|---|---|---|---|---|---|---|
| **400 mg QD continuous** | | | | | | | | | | |
| 1020 | Grade 3 venous sinus thrombosis | 960 | 4 | Possibly | Discontinued PRx | Recovered | None | Aspirin | None | Aspirin, heparin[5], tinzaparin[5], warfarin[5] |
| **300 mg BID continuous** | | | | | | | | | | |
| 1044 | Grade 3 thrombosis | 980 | | Definitely not | Discontinued PRx | Not recovered | None | Aspirin, enoxaparin | None | Aspirin, enoxaparin |
| **300 mg BID 3/7** | | | | | | | | | | |
| 1071 | Grade 3 deep venous thrombosis (lower and upper extremity) | 50 | | Definitely not | No action with test drug | Not recovered | Grade 1 fatigue | None | Grade 2 fatigue | Tinzaparin[5] |
| 1075 | Grade 4 pulmonary embolism, Grade 4 pulmonary thromboses | 51 | 4 | Definitely not | Interrupted PRx | Recovered | None | None | Grade 1 fatigue, Grade 3 fatigue, dyspnea | Tinzaparin[5], enoxaparin[5] |
| 1074 | Grade 4 pulmonary embolism, Grade 4 pulmonary thrombosis | 78 | 4 | Definitely not | Interrupted PRx | Recovered | Deep venous thrombosis | None | Grade 1 fatigue, dyspnea | Tinzaparin[5], warfarin[5] |
| **200 mg BID 3/7** | | | | | | | | | | |
| 1075 | Grade 3 deep venous thrombosis upper extremity | 132 | 12 | Definitely not | No action with test drug | Recovered | Obesity | None | Grade 2 fatigue, upper extremity edema | Tinzaparin[5] |
| **200 mg QD continuous** | | | | | | | | | | |
| 1005 | Grade 4 pulmonary embolism | 612 | 11 | Definitely not | Interrupted PRx | Recovered | None | Clopidogrel | Grade 2 fatigue, chest pain, shortness of breath | Clopidogrel, aspirin, heparin[5], tinzaparin[5] |

AN = Allocation Number; Rel Day = Study Day
[1] Medical conditions/risk factors related to the adverse experience.
[2] Anticoagulant and hormonal medications taken within 30 days of the first dose of study therapy.
[3] Events within 14 days of the onset of the adverse experience.
[4] Medication started as a result of the adverse experience.

The following table summarizes venous thromboembolic events for Vorinostat Monotherapy – Hematologic Malignancies.

- Venous thromboembolic events were reported in a total of 2 patients in this population. One (1) patient was receiving 400 mg once daily and 1 patient was receiving 300 mg twice daily 14 days/3 week. These adverse experiences did not result in any discontinuation or interruptions in study therapy.

**Table 131. Number (%) of Patients with Thromboembolic Adverse Experiences (Vorinostat Monotherapy – Hematologic Malignancies) (Applicant's Table)**

| Adverse Experience | 400 mg QD Continuous (N=16) | 300 mg BID 3/7 (N=3) | 200 mg BID continuous (N=6) | 200 mg BID 14/21 (N=14) | Doses above MTD (N=51) | Doses below MTD (N=13) | Total (N=87) |
|---|---|---|---|---|---|---|---|
| Deep venous thrombosis | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (2.0) | 0 (0.0) | 1 (1.1) |
| Thrombosis[†] | 1 (6.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (2.3) |

[†] Lower extremity deep venous thrombosis.

**Table 132. Summary of Patients with Thromboembolic Adverse Experiences (Vorinostat Monotherapy – Hematologic Malignancies) (Applicant's Table)**

| AN | Adverse Experience | Rel Day of Onset | Duration (days) | Relation | Action Taken | Outcome | Past Medical History/Conditions[1] | Prior Medications[2] | Related Adverse Experiences/Conditions[3] | Concomitant Medications |
|---|---|---|---|---|---|---|---|---|---|---|
| **400 mg QD continuous** | | | | | | | | | | |
| 1011 | Grade 3 deep venous thrombosis | 68 | 4 | Possibly | No action with test drug | Recovered | None | Ethinyl Estradiol & Norgestrel | None | Dalteparin[4] |
| **300 mg BID 14d/3wk** | | | | | | | | | | |
| 366 | Grade 3 deep venous thrombosis | 39 | | Probably not | No action with test drug | Not recovered | Fatigue, muscular weakness | None | None | Heparin[4], enoxaparin[4] |

AN = Allocation Number; Rel Day = Study Day
[1] Medical conditions/risk factors related to the adverse experience.
[2] Anticoagulant and hormonal medications taken within 30 days of the first dose of study therapy.
[3] Events within 14 days of the onset of the adverse experience.
[4] Medication started as a result of the adverse experience

The following table summarizes venous thromboembolic events for Vorinostat Combination Therapies.

- Venous thromboembolic events were reported in 1 patient in this population. The patient was receiving 300 mg twice daily 14 days/3 week. The adverse experience resulted in an interruption of study therapy.

**Table 133. Number (%) of Patients with Thromboembolic Adverse Experiences (Vorinostat Combination Therapies) (Applicant's Table)**

| Adverse Experience | 300 mg BID 14/21 (N=7) | 300 mg BID 14/21 (N=7) | Total (N=10) |
|---|---|---|---|
| Deep venous thrombosis | 0 (0.0) | 1 (14.3) | 1 (10.0) |

**Table 134. Summary of Patients with Thromboembolic Adverse Experiences (Vorinostat Combination Therapy) (Applicant's Table)**

| AN | Adverse Experience | Rel Day of Onset | Duration (days) | Relation | Action Taken | Outcome | Past Medical History-Conditions[1] | Prior Medications[2] | Related Adverse Experiences-Conditions[3] | Concomitant Medications |
|---|---|---|---|---|---|---|---|---|---|---|
| **300 mg BID 14d/3wk** | | | | | | | | | | |
| 3154 | Grade 2 deep venous thrombosis | 52 | 13 | Definitely not | Interrupted PRx | Recovered | Deep venous thrombosis, inferior vena cava filter placement | Warfarin | Leg pain, leg edema | Warfarin, enoxaparin[4] |
| | Grade 1 deep venous thrombosis | 133 | | Definitely not | No action with test drug | Not Recovered | | | | |

AN = Allocation Number; Rel Day = Study Day
[1] Medical conditions/risk factors related to the adverse experience.
[2] Anticoagulant and hormonal medications taken within 30 days of the first dose of study therapy.
[3] Events within 14 days of the onset of the adverse experience.
[4] Medication started as a result of the adverse experience.

**Hyperglycemia**

Hyperglycemia could be reported as either a *clinical* adverse experience or a *laboratory* adverse experience

- The *clinical* adverse experience of hyperglycemia (all grades) was reported in 118 of 305 patients (38.7%) and the *laboratory* adverse experience of increased serum glucose (all grades) was reported in 6 of 288 patients who had a serum glucose test (2.1%)

- In the entire CTCL population (107 patients) the *clinical* adverse experience of hyperglycemia was considered by the Investigators to be drug-related in 6 (5.6%)
- In the 400 mg once daily continuous dosing group, this *clinical* adverse experience was determined to be drug-related in 4 of 86 patients (4.7%)
- No patient discontinued study therapy due to a *clinical* adverse experience of hyperglycemia.

**Hyperglycemia ≥ grade 3 or SAE**

- Seven (7) patients overall and 1 CTCL patient in the 400 mg once daily treatment group reported a *serious (or Grade 3 or higher)* hyperglycemia; of these patients, in 5 patients overall and in the one CTCL patient, hyperglycemia was considered by the investigator to be *related* to the study drug. The CTCL patient had received prior corticosteroid therapy. There were *no dose modifications or treatment discontinuations* and the patients recovered from this event.

**CTCL patients with a history of diabetes or hyperglycemia**

- In the CTCL population, 6 of the 107 patients had a prior medical history of hyperglycemia or diabetes mellitus and 1 patient had received prior corticosteroid therapy.
- All 7 patients had adverse experience of hyperglycemia but did not require dose modifications or discontinuation of Vorinostat, and all patients recovered from this adverse experience.

**Vorinostat Monotherapy – CTCL**

79 of the 111 (71.2%) patients exposed to Vorinostat in **the CTCL population** had *the laboratory abnormality* of increased serum glucose. This abnormality was not reported as a *laboratory adverse experience* in any patient.

- Grade 1 and Grade 2 increases in 74 patients (66.7%)
- Grade 3 increases in 5 patients (4.5%)

Hyperglycemia was reported as a *clinical adverse experience* in 11 of 111 patients (9.9%).

- Grade 1 and Grade 2 hyperglycemia in 10 patients (9.0%)
- Grade 3 in 1 patient (0.9%)

In patients in **400 mg once daily dose group**, 60 of 87 (69.0%) reported the *laboratory abnormality* of increased serum glucose.

- Grade 1 and Grade 2 increased serum glucose was reported in 55 (63.2%).
- Grade 3 increased serum glucose was reported in 5 patients (5.7%).

The *clinical adverse experience* of hyperglycemia was reported in 9 of 87 patients (10.3%)

- Grade 1 and Grade 2 hyperglycemia was reported in 8 (9.2%).
- Grade 3 hyperglycemia was reported in 1 (1.1%)

**Vorinostat Monotherapy – CTCL Stage IIB and Higher**

This population is a subset of the Vorinostat Monotherapy – CTCL population, accordingly a similar distribution of laboratory abnormalities and adverse experiences of increased serum glucose can be expected, and was observed.

Of the 93 patients who had a serum glucose test, 67 patients (72.0%) were reported to have the *laboratory abnormality* of increased serum glucose.

- Grade 1 and Grade 2 increased serum glucose was reported in 63 patients (67.8%).
- Grade 3 increased serum glucose was reported in 4 patients (4.3%).

This abnormality was not reported as a *laboratory adverse experience* in any patient. Hyperglycemia was considered by Investigators to be drug-related in 4 of 93 patients (4.3%).

In **400 mg once daily** dosing group, 51 of 72 patients (70.8%) reported the *laboratory abnormality* of increased serum glucose.

- Grade 1 and Grade 2 increased serum glucose was reported in 47 patients (65.3%)
- Grade 3 increased serum glucose was reported in 4 patients (5.6%)

This adverse experience was determined to be drug-related in 4 of 72 patients (5.6%). No patients discontinued study therapy due to an adverse experience of hyperglycemia.

The *clinical adverse experience* of hyperglycemia was reported in 6 of 87 patients (8.3%).

- Grade 1 and Grade 2 hyperglycemia was reported in 5 patients (6.9%)
- Grade 3 hyperglycemia was reported in 1 patient (1.4%)

**Vorinostat Monotherapy – Solid Tumors**

59 of the 84 patients (72.0%) who had a serum glucose test were reported to have *laboratory abnormality* of increased serum glucose. This abnormality was not reported as a *laboratory adverse experience* in any patient.

Hyperglycemia was reported as a *clinical adverse experience* in 53 of 101 patients (52.5%) across **all dose groups**

- Grade 1 and Grade 2 *increased serum glucose* was reported in 51 patients (60.7%)
- Grade 3 increased serum glucose was reported in 2 patients (5.1%).
- Grade 1 and Grade 2 *hyperglycemia* was reported in 44 patients (43.6%)
- Grade 3 hyperglycemia were reported in 9 patient (8.9%)

Hyperglycemia was considered by Investigators to be drug-related in 43 of 53 patients (81%)

In the **400 mg once daily** dosing group, 16 of 39 patients (41.0%) reported the *laboratory abnormality* of increased serum glucose.

- Grade 1 and Grade 2 increased serum glucose was reported in 14 patients
- Grade 3 increased serum glucose was reported in 2 patients (12%)

The *clinical adverse experience* of hyperglycemia was reported in 19 of 45 patients (42.2%).

- Grade 1 and 2 hyperglycemia was reported in 14 patients
- Grade 3 hyperglycemia was reported in 5 patients (26%)

This adverse experience was determined to be drug-related in 17 of 19 patients
No patients in this population discontinued study therapy due to a clinical adverse experience of hyperglycemia.

**Vorinostat Monotherapy – Hematologic Malignancies**

82 of the 87 patients (94.3%) who had a serum glucose test were reported to have a *laboratory abnormality* of increased serum glucose.

- Grade 1 and Grade 2 increased serum glucose was reported in 4 patients
- Grade 1 increased serum glucose was reported in 67 patients
- Grade 3 increased serum glucose was reported in 11 of 87 patients (12.6%)

Hyperglycemia was reported as a *clinical adverse experience* in 53 of 87 patients (60.9%).

- Grade 1 and Grade 2 hyperglycemia was reported in 47 patients (54.0%)
- Grade 3 hyperglycemia was reported in 6 patients (6.9%)

The clinical adverse experience of hyperglycemia was considered by Investigators to be drug-related in 29 of 87 patients (33.3%)

In the **400 mg once daily dosing group**, 10 of 11 patients (90.9%) reported the *laboratory abnormality* of increased serum glucose.

- Grade 1 and Grade 2 increased serum glucose was reported in 10 patients (90.9%)
- Grade 3 abnormalities of increased serum glucose was reported in one patient

The *clinical adverse experience* of hyperglycemia was reported in 15 of 16 patients (93.8%).

- Grade 1 and Grade 2 hyperglycemia was reported in 14 patients (87.5%).
- Grade 3 hyperglycemia was reported in 1 patient (6.3%)

This clinical adverse experience was considered by Investigators as drug-related in 14 of 16 patients (87.5%).
No patients discontinued study therapy due to a clinical adverse experience of hyperglycemia.

**Vorinostat Combination Therapies**

Of the 10 patients in this population who had a serum glucose test, 7 (70.0%) were reported to have a *laboratory abnormality* of increased serum glucose.

- Grade 1 and Grade 2 reported in 5 patients (50.0%).
- Grade 3 laboratory abnormality reported in 2 patients (20.0%).

Grade 3 *clinical adverse experience* of hyperglycemia was reported in 1 patient (10.0%)
The clinical adverse experience of Grade 3 hyperglycemia was considered drug-related in 1 patient (10.0%).
No patients discontinued due to a clinical or laboratory adverse experience of hyperglycemia.

**Serum Creatinine**

The laboratory adverse experience of increased serum creatinine was reported in a total of 103 patients.

- Two (2) non-CTCL patients reported a serious (or a non-serious adverse experience Grade 3 or higher). One experience was considered by the Investigator to be related to the study drug.
- Both patients had reported a prior medical history of renal failure or nephrectomy and 1 patient experienced an adverse experience that led to dose interruption.

- One (1) patient experienced a lab shift from Grade 0 to Grade 3 as the worst value (3.8 mg/dL) and had later improved to Grade 2 (2.0 mg/dL) at the last observation.
  - Time to recovery was 19 days.
- The other patient experienced a lab shift from Grade 1 to Grade 2 (2.6 mg/dL) as the worst value—it remained at Grade 2 (1.9 mg/dL) at the last observation.

**Vorinostat Monotherapy – CTCL**

In all dose groups, 44 of the 111 patients (39.6%) who had a serum creatinine test reported laboratory abnormality of increased serum creatinine. This abnormality was considered an adverse experience in 20 patients (18.0%).

- Grade 1 and Grade 2 increases in serum creatinine were reported in 42 patients (37.8%), and considered adverse experiences in 17 patients (15.3%).
- Grade 3 increased serum creatinine was reported in 2 patients (1.8%)
- This was considered by the Investigators to be drug-related in 15 of 107 patients (14.0%).

In the treatment group of **400 mg once daily** dosing, 39 of 87 patients (44.8%) reported the laboratory abnormality of increased serum creatinine. These abnormalities were reported as adverse experiences in 15 of these patients (17.2%).

- Grade 1 and Grade 2 increases in serum creatinine were reported in 37 of 87 patients (42.5%).
- Grade 3 increase in serum creatinine occurred in 2 patients.

- Increased serum creatinine was determined to be drug-related in 10 of 86 patients (11.6%).
- One (1) patient in this dosing group had a dose modification as a result a Grade 2 increase in serum creatinine.
- No patients were discontinued as a result of this adverse experience.

**Vorinostat Monotherapy – CTCL Stage IIB and Higher**

***Reviewer Comments:*** *As this population is a subset of the Vorinostat Monotherapy – CTCL population, a similar distribution of laboratory abnormality and adverse experience of increased serum creatinine was expected and observed.*

Across all dose groups, 39 of the 93 patients (41.9%) who had a serum creatinine test were reported to have a laboratory abnormality of increased serum creatinine.

- These increases were Grade 1 and 2 in 37 patients
- This abnormality was considered a clinically significant adverse experience in 15 patients.
- Overall, this adverse experience was considered by Investigators to be drug-related in 13 patients.

In the treatment group of 400 mg once daily dosing, 34 of 72 patients (47.2%) reported the laboratory abnormality of increased serum creatinine. Increased creatinine was reported as an adverse experience in 11 of these patients (15.3%).

- These increases were Grade 1 and 2 in 32 patients
- This abnormality was considered an adverse experience in 13 patients
- Increased serum creatinine was determined to be drug-related in 8 of 71 patients (11.0%)
- One (1) patient in this dosing group had a dose modification as a result a Grade 2 increase in serum creatinine
- No patients were discontinued as a result of this adverse experience.

**Vorinostat Monotherapy – Solid Tumors**

Across all dose groups, 59 of the 100 patients (59.0%) who had a serum creatinine test were reported to have a laboratory abnormality of increased serum creatinine. This abnormality was considered clinically significant adverse experience in 41 patients.

- Grade 1 and Grade 2 increases in serum creatinine were reported in 57 patients (57.0%) and were considered adverse experiences in 39
- Grade 3 increased serum creatinine was reported in 2 patients
- Overall, this adverse experience was considered by Investigators to be drug-related in 38 of 101 patients (37.6%).

At a dose of 400 mg once daily, 21 of 39 patients (53.8%) reported the laboratory abnormality of increased serum creatinine. This abnormality was considered an adverse experience in 15 of these patients.

- Grade 1 and Grade 2 increases in serum creatinine were reported in 20 of 39 patients and reported as adverse experiences in 14 of these patients (36.0%)
- Grade 3 increase in serum creatinine was reported in 1 patient at this dose.
- Increased serum creatinine was determined to be drug-related in 17 patients
- No patients were discontinued or dose modified as a result of this adverse experience.

**Vorinostat Monotherapy – Hematologic Malignancies**

Across all dose groups, 44 of the 87 patients (50.6%) who had a serum creatinine test were reported to have a laboratory abnormality of increased serum creatinine. This abnormality was considered an adverse experience in 30 patients.

- This adverse experience was considered by Investigators to be drug-related in 22 patients

In the treatment group of 400 mg once daily dosing, 10 of 11 patients (90.9%) reported the laboratory abnormality of increased serum creatinine (Grade 1 and Grade 2). This abnormality was considered an adverse experience in 9 of these patients (81.8%).

- Increased serum creatinine was determined to be drug-related in 10 patients
- No patients were discontinued or dose modified as a result of this adverse experience.

**Vorinostat Combination Therapies**

Of the 10 patients in this population who had a serum creatinine test, 5 (50.0%) were reported to have a laboratory abnormality of increased serum creatinine. No adverse experiences of increased serum creatinine were reported.

- Reported abnormalities were Grade 1 in 4 patients and Grade 2 in 1 patient

**Thrombocytopenia and Decreased Platelet Count**

The *clinical adverse experience* of thrombocytopenia was reported in 106 of 305 patients (34.8%).
The *laboratory adverse experience* of decreased platelet count was reported in 44 patients.

**In the CTCL population**, thrombocytopenia was reported as a **serious** or non-serious adverse experience **Grade 3 or higher** in 14 of 107 patients (13.1%)

- Four (4) of these patients received Vorinostat at a dose of 400 mg once daily, 4 at a dose of 200 mg twice daily, and three (3) at doses above the MTD.
- Thrombocytopenia was considered by the Investigator to be related to study therapy in all of these patients.
- This adverse experience led to discontinuation of study medication in 1 patient, dose reduction in 3 patients, and dose interruption in 3 patients.
- All of these patients recovered from thrombocytopenia, but 1 patient who received Vorinostat at a dose of 200 mg twice daily required platelet replacement on Study Day 27.

**In the non-CTCL populations**, thrombocytopenia was reported as a **serious** or non-serious adverse experience **Grade 3 or higher** in 20 of 101 patients (19.8%) with solid tumors, and 23 of 87 patients (26.4%) with hematologic malignancies.

- Seven (7) of these patients received Vorinostat at a dose of 400 mg once daily (solid tumor = 6, hematologic malignancies = 1) and 5 patients received Vorinostat at a dose of 200 mg twice daily (solid tumor = 2, hematologic malignancies = 3). Twelve (12) of these patients received Vorinostat at doses above the MTD (solid tumor = 7, hematologic malignancies = 5).
- Thrombocytopenia was considered by the Investigator to be related to study therapy in all of these patients.
- Thrombocytopenia led to discontinuation of study medication in 2 patients, dose reduction in 8 patients, and dose interruption in 5 patients.
- Of the 20 solid tumor patients developing thrombocytopenia, a past history of thrombocytopenia was reported in 3 patients.
- Three (3) patients required platelet replacement.
- Two (2) of these patients received Vorinostat at a dose above the MTD and required replacement on Study Day 14 and Study Day 17, the third patient received Vorinostat at a dose of 200 mg twice daily 14 out of 21 days and required 7 replacements beginning on Study Day 1 end ending on Study Day 29. This patient had a past history of thrombocytopenia and received study therapy for a total of 13 days. All of these patients recovered from this adverse experience.

**Vorinostat Monotherapy – CTCL**

In all dose groups, 56 of the 111 (50.5%) patients who had a platelet count evaluation were reported to have a *laboratory abnormality* of decreased platelet count. This abnormality was not reported as a laboratory adverse experience in any patient.

- Grade 1 and Grade 2 decreased platelet count was reported in 45 patients
- Grade 3 and Grade 4 decreased platelet count was reported in 7 and 4 patients respectively.
- Overall, the adverse experience of thrombocytopenia was considered by Investigators to be drug-related in 33 patients
- One (1) patient (0.9%) discontinued study therapy due to a Grade 3 thrombocytopenia, this patient was treated in the 200 mg twice daily continuous dosing group.

Thrombocytopenia was reported as a *clinical adverse experience* in 35 patients (31.5%).

- Grade 1 and Grade 2 thrombocytopenia was reported in 25 patients (22.5%)
- Grade 3 and Grade 4 adverse experiences of thrombocytopenia were reported in 6 (5.4%) and 4 (3.6%) patients, respectively.

In the treatment group of 400 mg once daily dosing, 40 of 87 patients (46.0%) reported the *laboratory abnormality* of decreased platelet count.

- Grade 1 and Grade 2 decreased platelet count were reported in 35 of 87 patients (40.2%)
- Grade 3 and Grade 4 abnormalities were reported in 4 (4.6%) and 1 patient (1.1%) respectively.

In the 400 mg once daily dosing group, the *clinical adverse experience* of Grade 1 and 2 thrombocytopenia was reported in 18 patients (20.7%), and Grade 3 and Grade 4 in 3 (3.4%) and 1 patient (1.1%), respectively.

- This adverse experience was determined to be drug-related in 21 of 86 patients (24.4%)

**Vorinostat Monotherapy – CTCL Stage IIB and Higher**

***Reviewer Comments:*** *As this population is a subset of the Vorinostat Monotherapy – CTCL population, a similar distribution of laboratory abnormality and adverse experience of thrombocytopenia was observed.*

In all dose groups, of the 93 patients who had a platelet count evaluation, 46 (49.5%) were reported to have a *laboratory abnormality* of decreased platelet count.

- Grade 1 and Grade 2 decreased platelet count was reported in 35 patients (40.5%).
- Grade 3 and Grade 4 decreased platelet count was reported in 7 patients (7.5%) and 4 patients (4.3%), respectively.

- The *clinical adverse experience* of Grade 1 and Grade 2 thrombocytopenia was reported in 18 patients (19.4%), and Grade 3 and Grade 4 in 6 patients (6.5%) and 4 patients (4.3%), respectively.

- Overall, the adverse experience of thrombocytopenia was considered by Investigators to be drug-related in 26 of 89 patients (29.2%).
- One (1) patient (1.1%) discontinued study therapy due to a Grade 3 thrombocytopenia, this patient was treated in the 200 mg twice daily continuous dosing group.

In the treatment group of 400 mg once daily dosing, 33 of 72 patients (45.8%) reported the *laboratory abnormality* of decreased platelet count.

- Grade 1 and Grade 2 decreased platelet count were reported in 28 of 72 patients (38.9%).
- Grade 3 and Grade 4 abnormalities were reported in 4 patients (5.6%) and 1 patient (1.4%), respectively.
- The *clinical adverse experience* of Grade 1 and 2 thrombocytopenia was reported in 13 patients (18.1%), and Grade 3 and Grade 4 in 3 patients (4.2%) and 1 patient (1.4%), respectively.
- In the 400 mg once daily dosing group, this adverse experience was determined to be drug-related in 16 of 71 patients (22.5%)

**Vorinostat Monotherapy – Solid Tumors**

**Across all dose groups**, of the 99 patients who had a platelet count evaluation, 53 (53.5%) were reported to have a *laboratory abnormality* of decreased platelet count. This abnormality was considered an adverse experience in 21 patients.

- Grade 1 and Grade 2 decreased platelet count was reported in 35 patients (35.4%). These abnormalities were considered adverse experiences in 17 patients (16.8%).
- Grade 3 and Grade 4 decreased platelet count was reported in 14 patients (14.1%) and 4 patients (4.0%), respectively. The abnormality of Grade 3 decreased platelet count was considered an adverse experience in 4 patients (4.0%).

The *clinical adverse experience* of thrombocytopenia was reported in 24 of 101 patients (23.8%).

- Grade 1 and Grade 2 thrombocytopenia was reported in 8 patients (7.9%).
- Grade 3 and Grade 4 adverse experiences of thrombocytopenia were reported in 12 patients (11.9%) and 4 patients (4.0%), respectively.
- Overall, the adverse experience of thrombocytopenia was considered by Investigators to be drug-related in all 24 patients
- One (1) patient (1.0%) each discontinued study therapy due to a Grade 2 and Grade 3 thrombocytopenia, these patients were treated in the 200 mg twice daily 14/21 days dosing group and at a dose above the MTD, respectively.

In the **dose group of 400 mg once daily**, 22 of 38 patients (57.9%) reported the *laboratory abnormality* of decreased platelet count.

- Grade 1 decreased platelet count was reported in 16 patients
- Grade 3 and Grade 4 abnormalities were reported in 5 and 1 patient respectively.

In the dose group of 400 mg once daily, the *clinical adverse experience* of thrombocytopenia was reported in 13 of 40 patients (32.5).

- Grade 1 and Grade 2 adverse experiences were reported in 7 patients (17.5%).
- Grade 3 adverse experiences of thrombocytopenia were reported in 6 patients (15.0%)
- In the 400 mg once daily continuous dosing group, this adverse experience was determined to be drug-related in all 13 patients

**Vorinostat Monotherapy – Hematologic Malignancies**

**Across all dose groups**, 76 of the 87 patients (87.4%) who had a platelet count evaluation were reported to have a *laboratory abnormality* of decreased platelet count. This abnormality was considered an adverse experience in 23

- Grade 1 and Grade 2 decreased platelet count was reported in 25 patients (28.7%). These abnormalities were considered adverse experiences in 12 patients (13.8%).
- Grade 3 and Grade 4 decreased platelet count was reported in 5 patients (5.7%) and 46 patients (50.6%), respectively. The abnormality of Grade 3 and Grade 4 decreased platelet count was considered an adverse experience in 7 patients (8.0%) and 4 patients (4.6%), respectively.

**Across all dose groups**, the *clinical adverse experience* of thrombocytopenia was reported in 27 of 87 patients (31.0%).

- Grade 1 and Grade 2 thrombocytopenia was reported in 6 patients (6.9%).
- Grade 3 and Grade 4 adverse experiences of thrombocytopenia were reported in 4 patients (4.6%) and 17 patients (19.5%), respectively.
- Overall, the adverse experience of thrombocytopenia was considered by Investigators to be drug-related in 24 patients
- One (1) patient (1.0%) each discontinued study therapy due to a Grade 2 and Grade 3 thrombocytopenia, these patients were treated in the 200 mg twice daily 14/21 dosing group and at a dose above the MTD, respectively.

**At a dose of 400 mg once daily**, 9 of 11 patients (81.8%) reported the *laboratory abnormality* of decreased platelet count.

- Grade 1 and Grade 2 decreased platelet count were reported in 6 patients (64.5%), reported as adverse experience in 5
- Grade 3 and Grade 4 abnormalities were reported in 1 patient (9.1%) and 2 patients (18.2%), respectively; reported as adverse experience in 3

**At a dose of 400 mg once daily**, the *clinical adverse experience* of thrombocytopenia was reported in 13 of 40 patients (32.5%).

- Grade 1 and Grade 2 adverse experiences were reported in 7 patients (17.5%).
- Grade 3 adverse experiences of thrombocytopenia were reported in 6 patients (15.0%).
- In the 400 mg once dosing group, this adverse experience was determined to be drug-related in all 13

**Vorinostat Combination Therapies**

Of the 10 patients in this population who had a platelet count, 5 (50.0%) were reported to have a laboratory abnormality of decreased platelet count. No adverse experiences of decreased platelet count were reported.

- Those abnormalities reported were Grade 1 in 4 patients (40.0%) and Grade 2 in 1 patient (10.0%).

**Analysis of Adverse Experiences by Organ System or Syndrome**

- Evaluation of the safety data, by System Organ Class of the clinical and laboratory AEs in all patient populations, did not reveal evidence of AEs by syndromes.
- Several AEs were prevalent in the symptom complexes of gastrointestinal disorders such as nausea and vomiting; hematology disorders including thrombocytopenia (decreased platelets) and anemia (decreased hemoglobin) and constitutional disorders of fatigue, malaise and weight loss. (These AEs were reviewed by population in previous sections. Other reported adverse experiences that were significant were cardiovascular events and thromboembolic events and have been discussed).

## 7.1.4 Other Search Strategies

- Non-clinical toxicology studies do not point to any toxicity not observed in the clinical studies.
- As Vorinostat has not been marketed anywhere in the world so far, there is no postmarketing data or literature with more toxicity information, at present.

## 7.1.5 Common Adverse Events

### 7.1.5.1 Eliciting adverse events data in the development program

- In all of the clinical studies in Vorinostat development program the patients who were considered eligible underwent extensive evaluations prior to enrollment in the trial.
- These baseline studies included detailed history and physical exams, blood chemistry and hematology tests, and relevant imagines studies for tumor assessment. In Protocol 008, patients also had baseline and follow up ECGs after drug administration.
- In all the studies patients were followed up at weekly to two weekly intervals in the beginning of the studies, and four to eight weekly later on. They were monitored by history taking, physical exams, blood tests (chemistry and hematology), and imaging studies.

Study flow chart from the CTCL pivotal trial (Protocol 001) is shown below; patients were followed up similarly in other studies.

**Table 135. Study Flow Chart (Protocol 001) (Applicant's Table)**

| | Baseline (within 2 wks of 1st study visit) | Visit 1 Wk 1 (±3 days) | Visit 2 Wk 3 (±3 days) | Visit 3 Wk 5 (±3 days) | Visit 4 Wk 7 (±3 days) | Visit 5 Wk 9 and every 4 wks thereafter until off study (±1 week) | Posttreatment follow-up visit[a] |
|---|---|---|---|---|---|---|---|
| Study drug administration and count | | X | X | X | X | X | X |
| Informed consent | X | | | | | | |
| Demographics, medical history | X | | | | | | |
| Physical exam, weight, vital signs, performance status | X | X | X | X | X | X | X |
| Lymph node assessment (by physical exam) | X | | | X | | X | X |
| Concomitant meds | X | X | X | X | X | X | X |
| Biopsy of clinically abnormal lymph nodes for accurate staging | X | | | | | | |
| CT scan of chest, abdomen, and pelvis | X[d] | | | | | X[d] | |
| CBC w/diff, platelets, comprehensive panel[e] | X | X | X | X | X | X | X |
| PT, aPTT | X | | | | | | X |
| Thyroid function | X | | | | | X[g] | X |
| B-HCG[b] | X | | | | | | |
| Urinalysis | X | | | X | | X | X |
| ECG | X | | | X | | X[i] | X |
| Adverse events assessment | | X | X | X | X | X | X |
| Efficacy evaluation: SWAT , BSA involvement, photos, body diagram [c] | X | | | X | | X | X |
| Pruritus intensity assessment | X | X | X | X | X | X | X |
| Peripheral blood flow cytometry for SS patients | X[f] | | | | | X[f] | |
| Correlative studies | X[h] | | X[h] | | | | |

a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT[ALT], sodium, uric acid, cholesterol, triglyceride, LDL, HDL.

b: Serum pregnancy test (women of childbearing potential).

c : Photos must include full body (front and back).

d: Baseline CT or PET/CT scans to be performed within 6 weeks of the first dose of study drug ;
Repeat (using the same technique and slice thickness as baseline scan) in patients who have achieved a PR or CR after a second assessment confirms the response.

e: Within 4 weeks after the last dose of study medication or prior to the initiation of new treatment.

f: Repeat every 8 weeks for Sezary cell patients who have evidence of at least a PR.

g: Every 8 weeks during treatment.

h: Samples (skin biopsies and blood samples) for correlative studies will be obtained from patients who have consented to these procedures at baseline, 2 hours post-dosing at Visit 2, and at the time of disease progression. Skin biopsies must be obtained from sites that have not been exposed to any topical agents within 12h prior to biopsies. Up to two skin biopsies should be obtained: (1)a patch or plaque lesion, and (2) a skin tumor nodule (if present). For Visit 2 only, vorinostat dose should be given in the clinic, whenever possible, to ensure that samples are collected at two hours following dosing. If this is not possible, patients should be instructed to time that day's dose of vorinostat to 2 hours prior to tissue sample acquisition.

i: At least one of these examinations should be performed 2 hours post that day's vorinostat dose. If the baseline ECG for this study was not performed on the same model of ECG machine, also repeat an ECG on the same day just priot to the daily vorinostat dose. The baseline and 2-hour post dose ECG tracings will be shipped directly to Merck & Co., Inc.

## 7.1.5.2 Appropriateness of adverse event categorization and preferred terms

- Adverse experiences categorization and use of MedDRA terms was appropriate.

## 7.1.5.3 Incidence of common adverse events

**Summary Comparison of Serious Clinical Adverse Experiences – All Populations**

- Across all populations, 127 of 305 patients (41.6%) treated with Vorinostat had at least 1 serious clinical adverse experience and 7 patients (2.3%) had at least 1 serious laboratory adverse experience
  - 31 of 127 (24.4%) of the serious clinical adverse experiences remained unresolved and 24 patients (18.9%) experienced a serious adverse experience that resulted in death
  - In forty-nine (49) of these 127 patients (38.6%) at least 1 serious clinical adverse experience was determined by the Investigator to be *related to the study drug*.
  - 18 of the 49 patients (36.7%) with drug-related serious clinical adverse experiences had received Vorinostat at a dose of 400 mg once daily and 19 patients (38.8%) received doses above the MTD.

- Majority of the patients (111 of 147 or 75.5%) who received Vorinostat at a dose of 400 mg once daily did not have any serious clinical adverse experience

- The highest frequency of clinical adverse experiences was reported at doses above the MTD: in 52 of 109 patients (47.7%)

- Four (4) of the 7 patients (57.1%) with at least 1 serious laboratory adverse experience also had 1 or more serious clinical adverse experiences.

The following table summarizes the serious clinical adverse experience by SOC and preferred terms occurring at an incidence of ≥2% in any dose level. Serious clinical adverse experiences are grouped by the dose level the patient received at the time of the serious adverse experience and not by the assigned treatment group.

- Of the 147 patients who received Vorinostat at a dose of 400 mg once daily, 36 patients (24.5%) experienced at least 1 serious clinical adverse experience that included dehydration (4.1%), pulmonary embolism (2.7%), staphylococcal infection (2.0%), diarrhea (2.0%) and squamous cell carcinoma (2.0%).
- Serious adverse experiences were observed in 12 of 33 patients (36.4%) who received Vorinostat at a dose of 300 mg twice daily 3 out of 7 days, 7 of 24 patients (29.2%) who received Vorinostat at a dose of 200 mg twice daily, and 12 of 27 patients (44.4%) who received Vorinostat at a dose of 200 mg twice daily 14 out of 21 days.
    - For these 3 doses and schedules, the safety profiles are similar in frequency.
- One hundred and nine (109) patients were treated at doses that exceeded the MTD. Fifty-two (52) patients (47.7%) reported at least 1 serious clinical adverse experience. Of these 52 patients, 30 (57.7%) were from the hematologic malignancy population.
    - The safety profile was similar in incidence to that of the 400 mg once daily dose with the exception of dehydration (9.2%), febrile neutropenia (8.3%), vomiting (5.5%) and thrombocytopenia (4.6%).
- The results for other safety evaluations including ECGs and physical examinations did not indicate any serious adverse experiences

## Table 136. Number (%) Of Patients with Specific Serious Clinical Adverse Experiences by System Organ Class (All Patients) (Applicant's Table)

| | 400mg QD continuous (N=147) | | 300mg BID 3-7 (N=33) | | 200mg BID continuous (N=24) | | 200mg BID 14-21 (N=27) | | doses above MTD (N=109) | | doses below MTD (N=47) | | Total Patients (N=305) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % | n | % | n | % | n | % |
| *Patients With One Or More Clinical Adverse Experiences* | *56* | *(24.5)* | *12* | *(36.4)* | *7* | *(29.2)* | *12* | *(44.4)* | *52* | *(47.7)* | *19* | *(40.4)* | *127* | *(41.6)* |
| *Patients With No Clinical Adverse Experiences* | *111* | *(75.5)* | *21* | *(63.6)* | *17* | *(70.8)* | *15* | *(55.6)* | *57* | *(52.3)* | *28* | *(59.6)* | *178* | *(58.4)* |
| **Blood And Lymphatic System Disorders** | **3** | **(2.0)** | **0** | **(0.0)** | **2** | **(8.3)** | **4** | **(14.8)** | **16** | **(14.7)** | **2** | **(4.3)** | **25** | **(8.2)** |
| Febrile Neutropenia | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (3.7) | 9 | (8.3) | 2 | (4.3) | 12 | (3.9) |
| Thrombocytopenia | 2 | (1.4) | 0 | (0.0) | 2 | (8.3) | 2 | (7.4) | 5 | (4.6) | 0 | (0.0) | 10 | (3.3) |
| Anaemia | 2 | (1.4) | 0 | (0.0) | 0 | (0.0) | 1 | (3.7) | 3 | (2.8) | 0 | (0.0) | 6 | (2.0) |
| **Eye Disorders** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(3.7)** | **1** | **(0.9)** | **0** | **(0.0)** | **2** | **(0.7)** |
| Vision Blurred | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (3.7) | 1 | (0.9) | 0 | (0.0) | 2 | (0.7) |
| **Gastrointestinal Disorders** | **6** | **(4.1)** | **4** | **(12.1)** | **1** | **(4.2)** | **1** | **(3.7)** | **16** | **(14.7)** | **2** | **(4.3)** | **30** | **(9.8)** |
| Diarrhoea | 3 | (2.0) | 1 | (3.0) | 1 | (4.2) | 0 | (0.0) | 3 | (2.8) | 0 | (0.0) | 8 | (2.6) |
| Vomiting | 0 | (0.0) | 1 | (3.0) | 0 | (0.0) | 0 | (0.0) | 6 | (5.5) | 0 | (0.0) | 7 | (2.3) |
| Gastrointestinal Haemorrhage | 1 | (0.7) | 1 | (3.0) | 0 | (0.0) | 0 | (0.0) | 2 | (1.8) | 1 | (2.1) | 5 | (1.6) |
| Abdominal Pain | 1 | (0.7) | 1 | (3.0) | 0 | (0.0) | 0 | (0.0) | 2 | (1.8) | 0 | (0.0) | 4 | (1.3) |
| Nausea | 0 | (0.0) | 1 | (3.0) | 0 | (0.0) | 0 | (0.0) | 3 | (2.8) | 0 | (0.0) | 4 | (1.3) |
| Intestinal Obstruction | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) | 1 | (2.1) | 2 | (0.7) |
| Anal Haemorrhage | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (3.7) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) |
| Constipation | 0 | (0.0) | 1 | (3.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) |
| **General Disorders And Administration Site Conditions** | **3** | **(2.0)** | **2** | **(6.1)** | **0** | **(0.0)** | **3** | **(11.1)** | **7** | **(6.4)** | **0** | **(0.0)** | **15** | **(4.9)** |
| Pyrexia | 2 | (1.4) | 1 | (3.0) | 0 | (0.0) | 1 | (3.7) | 2 | (1.8) | 0 | (0.0) | 6 | (2.0) |
| General Physical Health Deterioration | 0 | (0.0) | 1 | (3.0) | 0 | (0.0) | 2 | (7.4) | 1 | (0.9) | 0 | (0.0) | 4 | (1.3) |
| Fatigue | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (3.7) | 1 | (0.9) | 0 | (0.0) | 2 | (0.7) |
| Asthenia | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (3.7) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) |
| **Hepatobiliary Disorders** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(3.7)** | **1** | **(0.9)** | **0** | **(0.0)** | **2** | **(0.7)** |
| Cholecystitis | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (3.7) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) |
| **Infection: And Infestations** | **11** | **(7.5)** | **0** | **(0.0)** | **1** | **(4.2)** | **2** | **(7.4)** | **12** | **(11.0)** | **4** | **(8.5)** | **29** | **(9.5)** |
| Infection | 2 | (1.4) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 3 | (2.8) | 2 | (4.3) | 7 | (2.3) |
| Sepsis | 2 | (1.4) | 0 | (0.0) | 1 | (4.2) | 0 | (0.0) | 1 | (0.9) | 0 | (0.0) | 4 | (1.3) |
| Staphylococcal Infection | 3 | (2.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 3 | (1.0) |
| Urinary Tract Infection | 0 | (0.0) | 0 | (0.0) | 1 | (4.2) | 1 | (3.7) | 1 | (0.9) | 0 | (0.0) | 3 | (1.0) |
| Herpes Zoster | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 2 | (4.3) | 2 | (0.7) |
| **Injury, Poisoning And Procedural Complications** | **2** | **(1.4)** | **0** | **(0.0)** | **1** | **(4.2)** | **1** | **(3.7)** | **2** | **(1.8)** | **1** | **(2.1)** | **7** | **(2.3)** |
| Subdural Haematoma | 0 | (0.0) | 0 | (0.0) | 1 | (4.2) | 0 | (0.0) | 2 | (1.8) | 0 | (0.0) | 3 | (1.0) |
| Accidental Overdose | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.1) | 1 | (0.3) |
| Transfusion Reaction | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (3.7) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) |
| **Metabolism And Nutrition Disorders** | **6** | **(4.1)** | **3** | **(9.1)** | **3** | **(12.5)** | **1** | **(3.7)** | **12** | **(11.0)** | **3** | **(6.4)** | **27** | **(8.9)** |
| Dehydration | 6 | (4.1) | 2 | (6.1) | 3 | (12.5) | 1 | (3.7) | 10 | (9.2) | 3 | (6.5) | 24 | (7.9) |
| Hyponatraemia | 0 | (0.0) | 1 | (3.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) |
| **Musculoskeletal And Connective Tissue Disorders** | **1** | **(0.7)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(3.7)** | **3** | **(2.8)** | **0** | **(0.0)** | **5** | **(1.6)** |
| Back Pain | 1 | (0.7) | 0 | (0.0) | 0 | (0.0) | 1 | (3.7) | 0 | (0.0) | 0 | (0.0) | 2 | (0.7) |
| **Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)** | **7** | **(4.8)** | **2** | **(6.1)** | **2** | **(8.3)** | **3** | **(11.1)** | **7** | **(6.4)** | **5** | **(10.6)** | **25** | **(8.2)** |
| T-Cell Lymphoma | 1 | (0.7) | 0 | (0.0) | 1 | (4.2) | 0 | (0.0) | 1 | (0.9) | 3 | (6.4) | 6 | (2.0) |
| Acute Myeloid Leukaemia | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (3.7) | 3 | (2.8) | 0 | (0.0) | 4 | (1.3) |
| Squamous Cell Carcinoma | 3 | (2.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.1) | 3 | (1.0) |
| Diffuse Large B-Cell Lymphoma | 1 | (0.7) | 1 | (3.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 2 | (0.7) |
| Cancer Pain | 0 | (0.0) | 1 | (3.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) |
| Diffuse Large B-Cell Lymphoma Recurrent | 0 | (0.0) | 0 | (0.0) | 1 | (4.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) |
| Lung Neoplasm | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.1) | 1 | (0.3) |
| Neoplasm Progression | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (3.7) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) |
| Renal Cell Carcinoma Stage Unspecified | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.1) | 1 | (0.3) |
| Tumour Haemorrhage | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (3.7) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) |
| **Nervous System Disorders** | **3** | **(2.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **2** | **(7.4)** | **3** | **(2.8)** | **3** | **(6.4)** | **11** | **(3.6)** |
| Cerebrovascular Accident | 1 | (0.7) | 0 | (0.0) | 0 | (0.0) | 1 | (3.7) | 0 | (0.0) | 0 | (0.0) | 2 | (0.7) |
| Cerebral Haemorrhage | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (3.7) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) |
| Convulsion | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.1) | 1 | (0.3) |
| Ischaemic Stroke | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.1) | 1 | (0.3) |
| Ruptured Cerebral Aneurysm | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.1) | 1 | (0.3) |
| **Psychiatric Disorders** | **2** | **(1.4)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(0.9)** | **1** | **(2.1)** | **4** | **(1.3)** |
| Confusional State | 1 | (0.7) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) | 1 | (2.1) | 3 | (1.0) |
| **Respiratory, Thoracic And Mediastinal Disorders** | **6** | **(4.1)** | **4** | **(12.1)** | **1** | **(4.2)** | **1** | **(3.7)** | **3** | **(2.8)** | **2** | **(4.3)** | **16** | **(5.2)** |
| Pulmonary Embolism | 4 | (2.7) | 2 | (6.1) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.1) | 7 | (2.3) |
| Dyspnoea | 1 | (0.7) | 1 | (3.0) | 0 | (0.0) | 1 | (3.7) | 2 | (1.8) | 1 | (2.1) | 6 | (2.0) |
| Hypoxia | 1 | (0.7) | 1 | (3.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 2 | (0.7) |
| Cough | 0 | (0.0) | 0 | (0.0) | 1 | (4.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) |
| Lung Disorder | 0 | (0.0) | 1 | (3.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) |
| Tracheal Stenosis | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.1) | 1 | (0.3) |
| **Vascular Disorders** | **2** | **(1.4)** | **5** | **(15.2)** | **0** | **(0.0)** | **0** | **(0.0)** | **6** | **(5.5)** | **1** | **(2.1)** | **14** | **(4.6)** |
| Deep Vein Thrombosis | 1 | (0.7) | 1 | (3.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) | 1 | (2.1) | 4 | (1.3) |
| Hypotension | 0 | (0.0) | 1 | (3.0) | 0 | (0.0) | 0 | (0.0) | 2 | (1.8) | 0 | (0.0) | 3 | (1.0) |
| Thrombosis | 1 | (0.7) | 2 | (6.1) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 3 | (1.0) |
| Embolism | 0 | (0.0) | 2 | (6.1) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 2 | (0.7) |
| Shock Haemorrhagic | 0 | (0.0) | 1 | (3.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) |

A patient is counted only once within a System Organ Class category even if more than one adverse experience with specific preferred terms occurred. Only the highest grade of a given adverse experience is counted per dose level for the individual patient.
Adverse experience terms are from MedDRA Version 8.1.
[Ref. 5.3.5.2: P001] [Ref. 5.3.5.4: P002, P003V1, P004V1, P006, P011V1, P012V1, P013V1, P015V1, P016V1]

## 7.1.5.4 Common adverse event tables

- See the tables above in 7.1.5.3

## 7.1.5.5 Identifying common and drug-related adverse events

***Drug-related* Serious Clinical Adverse Experiences (All Populations)**

The following table summarizes the *drug-related* serious clinical adverse experiences across all populations.

- Of 127 patients with serious adverse experiences, 49 patients (38.6%) were determined by the Investigator to be related to study drug.

- Eighteen (18) of these 49 patients (36.7%) received Vorinostat at a dose of 400 mg once daily.
  - The most common drug-related serious adverse experience with an incidence ≥1% at the 400 mg once daily dose were dehydration (4.1%), diarrhea (2.0%), pulmonary embolism (2.7%), anemia (1.4%) and thrombocytopenia (1.4%).

- Serious clinical adverse experiences determined by the Investigator to be drug-related were observed in 5 patients who received Vorinostat at a dose of 300 mg twice daily 3 out of 7 days, 5 patients who received Vorinostat at a dose of 200 mg twice daily dose, and 4 patients who received Vorinostat at a dose of 200 mg twice daily 14 out of 21 days.
  - At these 3 dose levels, the safety profile is generally similar in frequency.

- The highest incidence of serious adverse experiences determined by the Investigator to be related to study drug occurred in 19 patients (17.4%) whose dose exceeded the MTD.
  - Overall, the safety profile in these patients is qualitatively similar across all populations in all dose levels.

## Table 137. Number (%) of Patients with Specific Serious Drug-Related Clinical Adverse Experiences by System Organ Class (All Patients) (Applicant's Table)

| | 400mg QD continuous (N=147) | | 300mg BID 3/7 (N=33) | | 200mg BID continuous (N=24) | | 200mg BID 14/21 (N=27) | | doses above MTD (N=109) | | doses below MTD (N=47) | | Total Patients (N=385) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % | n | % | n | % | n | % |
| *Patients With One Or More Clinical Adverse Experiences* | *18* | *(12.2)* | *5* | *(15.2)* | *5* | *(20.8)* | *4* | *(14.8)* | *19* | *(17.4)* | *4* | *(8.5)* | *49* | *(16.1)* |
| *Patients With No Clinical Adverse Experiences* | *129* | *(87.8)* | *28* | *(84.8)* | *19* | *(79.2)* | *23* | *(85.2)* | *90* | *(82.6)* | *43* | *(91.5)* | *256* | *(83.9)* |
| **Blood And Lymphatic System Disorders** | **3** | **(2.0)** | **0** | **(0.0)** | **2** | **(8.3)** | **3** | **(11.1)** | **6** | **(5.5)** | **0** | **(0.0)** | **12** | **(3.9)** |
| Thrombocytopenia | 2 | (1.4) | 0 | (0.0) | 2 | (8.3) | 2 | (7.4) | 5 | (4.6) | 0 | (0.0) | 10 | (3.3) |
| Anaemia | 2 | (1.4) | 0 | (0.0) | 0 | (0.0) | 1 | (3.7) | 2 | (1.8) | 0 | (0.0) | 5 | (1.6) |
| **Eye Disorders** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(3.7)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(0.3)** |
| Vision Blurred | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (3.7) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) |
| **Gastrointestinal Disorders** | **4** | **(2.7)** | **1** | **(3.0)** | **1** | **(4.2)** | **0** | **(0.0)** | **5** | **(4.6)** | **0** | **(0.0)** | **11** | **(3.6)** |
| Diarrhoea | 3 | (2.0) | 1 | (3.0) | 1 | (4.2) | 0 | (0.0) | 3 | (2.8) | 0 | (0.0) | 8 | (2.6) |
| Vomiting | 0 | (0.0) | 1 | (3.0) | 0 | (0.0) | 0 | (0.0) | 3 | (2.8) | 0 | (0.0) | 4 | (1.3) |
| Nausea | 0 | (0.0) | 1 | (3.0) | 0 | (0.0) | 0 | (0.0) | 2 | (1.8) | 0 | (0.0) | 3 | (1.0) |
| Gastrointestinal Haemorrhage | 1 | (0.7) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) |
| **General Disorders And Administration Site Conditions** | **2** | **(1.4)** | **2** | **(6.1)** | **0** | **(0.0)** | **1** | **(3.7)** | **3** | **(2.8)** | **0** | **(0.0)** | **5** | **(2.6)** |
| Pyrexia | 1 | (0.7) | 1 | (3.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) | 0 | (0.0) | 3 | (1.0) |
| Asthenia | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (3.7) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) |
| Chest Pain | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) | 0 | (0.0) | 1 | (0.3) |
| Death | 1 | (0.7) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) |
| Fatigue | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) | 0 | (0.0) | 1 | (0.3) |
| General Physical Health Deterioration | 0 | (0.0) | 1 | (3.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) |
| **Hepatobiliary Disorders** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(0.9)** | **0** | **(0.0)** | **1** | **(0.3)** |
| Hepatic Ischaemia | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) | 0 | (0.0) | 1 | (0.3) |
| **Infections And Infestations** | **1** | **(0.7)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(2.1)** | **2** | **(0.7)** |
| Herpes Zoster | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.1) | 1 | (0.3) |
| Streptococcal Bacteraemia | 1 | (0.7) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) |
| **Metabolism And Nutrition Disorders** | **6** | **(4.1)** | **2** | **(6.1)** | **3** | **(12.5)** | **0** | **(0.0)** | **7** | **(6.4)** | **3** | **(6.4)** | **20** | **(6.6)** |
| Dehydration | 6 | (4.1) | 1 | (3.0) | 3 | (12.5) | 0 | (0.0) | 6 | (5.5) | 3 | (6.4) | 18 | (5.9) |
| Anorexia | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) | 0 | (0.0) | 1 | (0.3) |
| Hyponatraemia | 0 | (0.0) | 1 | (3.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) |
| **Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(3.7)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(0.3)** |
| Tumour Haemorrhage | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (3.7) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) |
| **Nervous System Disorders** | **2** | **(1.4)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(2.1)** | **3** | **(1.0)** |
| Guillain-Barre Syndrome | 1 | (0.7) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) |
| Ischaemic Stroke | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (2.1) | 1 | (0.3) |
| Syncope | 1 | (0.7) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) |
| **Renal And Urinary Disorders** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(0.9)** | **0** | **(0.0)** | **1** | **(0.3)** |
| Urinary Retention | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) | 0 | (0.0) | 1 | (0.3) |
| **Respiratory, Thoracic And Mediastinal Disorders** | **5** | **(3.4)** | **1** | **(3.0)** | **1** | **(4.2)** | **0** | **(0.0)** | **1** | **(0.9)** | **0** | **(0.0)** | **7** | **(2.3)** |
| Pulmonary Embolism | 4 | (2.7) | 1 | (3.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 5 | (1.6) |
| Cough | 0 | (0.0) | 0 | (0.0) | 1 | (4.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) |
| Haemoptysis | 1 | (0.7) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) | 0 | (0.0) | 1 | (0.3) |
| **Vascular Disorders** | **2** | **(1.4)** | **1** | **(3.0)** | **0** | **(0.0)** | **0** | **(0.0)** | **2** | **(1.8)** | **0** | **(0.0)** | **5** | **(1.6)** |
| Deep Vein Thrombosis | 1 | (0.7) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) |
| Hypertension | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) | 0 | (0.0) | 1 | (0.3) |
| Hypotension | 0 | (0.0) | 1 | (3.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) |
| Thrombosis | 1 | (0.7) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) |
| Vasculitis | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) | 0 | (0.0) | 1 | (0.3) |

A patient is counted only once within a System Organ Class category, even if more than one adverse experience with specific preferred terms occurred. Only the highest grade of a given adverse experience is counted per dose level for the individual patient.
Adverse experience terms are from MedDRA Version 8.1

[Ref. 5.3.5.2: P001] [Ref. 5.3.5.4: P002, P003V1, P004V1, P006, P011V1, P012V1, P013V1, P015V1, P016V1]