

7.1.5.6 Additional analyses and explorations

Explorations of demographic interactions

- No formal studies to evaluate the effects of intrinsic demographic factors (age, gender, and race) on the safety of Vorinostat were conducted.
- With the exception of a slight male predominance, demographics including age, gender and race were similar across all study populations.
- A slightly higher median age in the overall non-CTCL population was observed.
- Safety outcomes by age, gender and race in those patients who received Vorinostat at a dose of 400 mg in the CTCL population were reviewed. No effect on safety was observed. In all other population, the patients were too few to allow a meaningful evaluation.

Age

The following table summarizes the clinical and laboratory adverse experiences for patients <65, ≥65, and ≥75 years for the Vorinostat Monotherapy – CTCL population.

- In those patients who received Vorinostat 400 mg once daily, clinical adverse experiences were reported for comparable proportions of patients in all age groups.
- A slightly lower proportion of patients ≥75 years of age at this dose had laboratory adverse experiences; however, the subset is small (n = 12).

Table 138. Number (%) of Patients with Clinical and Laboratory Adverse Experiences Vorinostat Monotherapy – CTCL (Applicant's Table)

Age Level (Years)	Clinical Adverse Experiences			Laboratory Adverse Experiences		
	400 mg QD continuous	300 mg BID 3/7	Doses above MTD	400 mg QD continuous	300 mg BID 3/7	Doses above MTD
<65	48/50 (96.0%)	5/5 (100.0%)	5/5 (100.0%)	14/50 (28.0%)	3/5 (60.0%)	1/5 (20.0%)
≥65	34/37 (91.9%)	7/7 (100.0%)	7/7 (100.0%)	12/37 (32.4%)	4/7 (57.1%)	3/7 (42.9%)
≥75	11/12 (91.7%)	1/1 (100.0%)	4/4 (100.0%)	2/12 (16.7%)	0/1 (0.0%)	2/4 (50.0%)

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Gender

The following table summarizes by gender the proportion of patients with clinical and laboratory adverse experiences for the Vorinostat Monotherapy – CTCL population.

- Clinical adverse experiences were reported in comparable proportions of male and female patients in the population that received Vorinostat 400 mg once daily

Table 139. Number (%) of Patients with Clinical and Laboratory Adverse Experiences (Vorinostat Monotherapy – CTCL) (Applicant's Table)

Gender	Clinical Adverse Experiences			Laboratory Adverse Experiences		
	400 mg QD continuous	300 mg BID 3/7	Doses above MTD	400 mg QD continuous	300 mg BID 3/7	Doses above MTD
Male	42/46 (91.3%)	5/5 (100.0%)	6/6 (100.0%)	14/46 (30.4%)	3/5 (60.0%)	2/6 (33.3%)
Female	40/41 (97.6%)	7/7 (100.0%)	6/6 (100.0%)	12/41 (29.3%)	4/7 (57.1%)	2/6 (33.3%)

Race

The following table summarizes by race the proportion of patients with clinical and laboratory adverse experiences in the Vorinostat Monotherapy – CTCL population.

- Comparable proportions of patients reported clinical adverse experiences in the population that received Vorinostat at 400 mg once daily.

Table 140. Number (%) of Patients with Clinical and Laboratory Adverse Experiences (Vorinostat Monotherapy – CTCL) (Applicant's Table)

Race	Clinical Adverse Experiences			Laboratory Adverse Experiences		
	400 mg QD continuous	300 mg BID 3/7	Dose above MTD	400 mg QD continuous	300 mg BID 3/7	Doses above MTD
White	68/71 (95.8%)	8/8 (100.0%)	9/9 (100.0%)	21/71 (29.6%)	4/8 (50.0%)	3/9 (33.3%)
Black	13/14 (92.9%)	4/4 (100.0%)	3/3 (100.0%)	5/14 (75.0%)	1/3 (33.3%)	1/3 (33.3%)
Asian	1/1 (100.0%)	0/0 (0.0%)	0/0 (0.0%)	0/1 (0.0%)	0/0 (0.0%)	0/0 (0.0%)
Other	1/1 (100.0%)	0/0 (0.0%)	0/0 (0.0%)	0/1 (0.0%)	0/0 (0.0%)	0/0 (0.0%)

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7.1.6 Less Common Adverse Events

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Laboratory tests were performed as specified in each protocol—these were not identical across protocols. In order to evaluate any potential laboratory abnormalities, all laboratory test values were analyzed irrespective of whether a clinical or laboratory adverse experience was reported by the Investigator.

- All laboratory values were assigned a grade in accordance with the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0.
- In these tabulations, if a patient had more than one graded abnormality for a laboratory test category, only the highest grade was counted.
- The percentage of patients with the laboratory abnormality was calculated by using as the denominator the number of patients who *had* the laboratory test post-baseline (N).

Laboratory evaluation data is presented by individual study populations. The focus of this analysis is Vorinostat Monotherapy – CTCL population assigned to 400 mg once daily dosing.

- For each population, a general summary of laboratory evaluations is followed by a summary of the shifts in laboratory parameters from the baseline values (observed at each dose level studied within the population).
- In addition, comparisons are performed across different doses within a population, and where appropriate, comparisons are made to 400 mg once daily dosing in the Vorinostat Monotherapy – CTCL population.

Shift Analysis

As the overall incidence of an abnormality may not be relevant when many abnormalities are present at the baseline in many of the patients, the shifts (the frequency of *changes* in the laboratory values for worse or better) were determined and analyzed (Shift Analysis).

In the laboratory shift data tables, the number of patients (M) who had a CTCAE grade change in at least 1 post-baseline value is compared to the number of all patients who had at least 1 post-baseline value for the laboratory test (N).

- To be included in the analysis, patients had to have at least one post-baseline test.
- Missing baseline values were assigned Grade 0.

A *clinically meaningful* shift in the CTCAE Grade was defined as:

- A shift from *less than* Grade 3 to Grade 3, Grade 4 or Grade 5, or

- A shift from Grade 0 to Grade 2

The change in CTCAE Grade from baseline to the worst post-baseline value included Grade changes in both directions of the baseline value to include improved and worsened shifts.

- Patients with >1 post-baseline value with a shift that worsened and later improved, as well as patients with >1 post-baseline value with a shift that showed consistent improvement from baseline, were reported in these tables.
- Changes in the Grades with respect to the actions taken in Vorinostat treatment are also displayed on the laboratory shift tables.
- All percentages are calculated with the number of patients who had a post-baseline change in the safety analysis (M) as the denominator (and not the number of patients with a *clinically meaningful* shift).

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

- Data from all the studies listed in the safety analysis for AEs (See 7.1 METHODS AND FINDINGS) was used in the analysis of laboratory values in this section.

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7.1.7.3 Standard analyses and explorations of laboratory data

Vorinostat Monotherapy – CTCL

Summary Comparison of Clinical Laboratory Evaluations – Vorinostat Monotherapy – CTCL

Of the 87 patients in the Vorinostat Monotherapy CTCL population assigned to Vorinostat monotherapy at a dose of 400 mg *once daily*, all patients had laboratory tests performed during treatment with the study therapy. Also, all 24 patients assigned to receive *all other doses* of Vorinostat monotherapy had 1 or more post-baseline laboratory tests.

- Patients in both treatment groups had similar laboratory abnormality profiles.
- The most common laboratory abnormalities seen in the patients assigned to Vorinostat monotherapy at a dose of 400 mg once daily, when *all grades* are included:
 - Increased serum glucose 69.0%
 - Increased serum creatinine 44.8%
 - Decreased hemoglobin 58.6%
 - Decreased platelets 46.0%
 - Decreased lymphocyte count 34.5%
 - Decreased WBC count 24.1%
 - Increased INR 33.3%
 - Increased urine protein 51.4%
- These were also the most common laboratory abnormalities *regardless of the grade*, in the population of patients who received all other doses of Vorinostat monotherapy.
- The majority of these laboratory abnormalities were Grade 1 or Grade 2.
- *Clinically meaningful shifts* in laboratory abnormalities were seen most commonly for increased serum glucose, increased serum creatinine, decreased hemoglobin, and decreased platelets in the patients who were assigned to receive Vorinostat at 400 mg once daily. Similar findings were evident in the patients who were assigned to receive all other doses of Vorinostat monotherapy in this population.
- Clinically meaningful grade shifts in increased urine protein were seen in only 3 patients who received Vorinostat at 400 mg once daily

Evaluation of Laboratory Abnormalities by the Highest CTCAE Grade – Vorinostat Monotherapy – CTCL

In the following table, laboratory abnormalities by highest grade for each test are shown and the *number of patients who had a graded abnormality during treatment (n)* are compared to the *number of patients who had the test performed post-baseline (N)*.

The patients assigned to the treatment group of Vorinostat monotherapy 400 mg once daily (the clinically recommended dose and schedule) were the primary treatment group in the CTCL population. The small numbers of patients in this population who were assigned to other treatment groups (24) and received other doses of Vorinostat monotherapy were combined into one second group for these data analyses.

400 mg Once Daily

The most common laboratory abnormalities, *regardless of grade*, occurring in at least 10% of the patients, listed in order of decreasing frequency were:

- Increased serum glucose in 60 of 87 patients 69.0%
- Increased serum cholesterol in 49 of 74 patients 66.2%
- Increased serum triglycerides in 49 of 74 patients 66.2%
- Increased serum creatinine in 39 of 87 patients 44.8%
- Decreased total serum carbon dioxide in 28 of 74 patients 37.8%
- Increased serum alkaline phosphate in 18 of 87 patients 20.7%
- Decreased serum phosphorus in 17 of 87 patients 19.5%
- Increased serum aspartate aminotransferase in 14 of 87 patients 16.1%
- Decreased serum potassium in 14 of 87 patients 16.1%
- Increased serum alanine aminotransferase in 13 of 87 patients 14.9%
- Decreased serum calcium in 13 of 87 patients 14.9%
- Decreased glucose in 10 of 87 patients 11.5%

The most common **hematology** abnormalities, *regardless of grade*, occurring in at least 10% of patients, listed in decreasing order of frequency, at this dose were:

- Decreased hemoglobin in 51 of 87 patients 58.6%
- Decreased platelet count in 40 of 87 patients 46.0%
- Decreased lymphocyte count in 30 of 87 patients 34.5%
- Decreased WBC count in 21 of 87 patients 24.1%

- Of the 18 patients with INR test, 6 of the 18 patients (33.3%) had increased INR
- The most common urinalysis abnormality was increased urine protein in 38 of 74 patients (51.4%)

The laboratory abnormalities (chemistry and hematology) that were *Grade 3* included:

- Decreased lymphocytes in 9 patients 10.3%
- Increased glucose in 5 patients 5.7%
- Decreased platelets in 4 patients 4.5%
- Decreased potassium in 3 patients 3.4%
- Increased INR in 3 patients 3.4%
- Increased serum creatinine, decreased serum phosphorus, increased serum triglycerides, decreased absolute lymphocyte count, and decreased hemoglobin—each in 2 patients

- Decreased serum glucose, decreased serum sodium, increased serum potassium, increased serum aspartate aminotransferase, increased serum cholesterol, and decreased WBC—each in 1 patient

Laboratory abnormalities (chemistry and hematology) that were *Grade 4* included:

- Increased uric acid in 3 patients (3.4%)
- Decreased *absolute* lymphocyte count in 2 patients (2.2%)
- Decreased absolute neutrophil count, decreased neutrophils, decreased lymphocytes and decreased platelets—each occurred in one patient

- Majority of the laboratory abnormalities were Grade 1 and Grade 2
- Only grade 3 laboratory abnormality > 10% was decreased lymphocytes
- The only *serious* laboratory adverse experience considered by the Investigator to be *related* to Vorinostat in this population was Grade 3 increased serum creatinine. These laboratory adverse experiences occurred in patients dosed above MTD.
- The three laboratory abnormalities with the highest frequency (regardless of the grade) were increased serum glucose, increased serum cholesterol and increased serum triglycerides. The evaluation of glucose and lipids was not necessarily done in the fasted state for all measurements as this was not mandated by study protocol.

All Other Doses of Vorinostat Monotherapy in CTCL Population

The number of patients for each test category was determined by the number of patients who had a post-baseline value for the laboratory test.

The most common *serum chemistry* abnormalities occurring in at least 10% of patients, *regardless of grade*, in descending order of frequency:

- | | |
|--|-------|
| ○ Increased serum glucose in 19 of 24 patients | 79.2% |
| ○ Decreased serum albumin in 12 of 24 patients | 50.0% |
| ○ Increased serum alkaline phosphatase in 11 of 24 patients | 45.8% |
| ○ Decreased serum calcium in 9 of 24 patients | 37.5% |
| ○ Increased serum aspartate aminotransferase in 8 of 24 patients | 33.3% |
| ○ Decreased serum phosphorus in 8 of 24 patients | 33.3% |
| ○ Increased serum uric acid in 6 of 24 patients | 25.0% |
| ○ Increased serum creatinine in 5 of 24 patients | 20.8% |
| ○ Decreased serum potassium in 5 of 24 patients | 20.8% |
| ○ Decreased serum sodium in 5 of 24 patients | 20.8% |
| ○ Increased total serum bilirubin in 5 of 24 patients | 20.8% |
| ○ Increased serum potassium in 3 of 24 patients | 12.5% |

The most common *hematology* abnormalities:

- | | |
|---|-------|
| ○ Decreased hemoglobin in 23 of 24 patients | 95.8% |
|---|-------|

- Decreased platelet count in 16 of 24 patients 66.7%
- Decreased absolute lymphocyte count in 13 of 24 patients 54.2%
- Decreased WBC in 9 of 24 patients 37.5%
- Decreased absolute neutrophil count in 5 of 24 patients 20.8%

- Of the 3 patients with hemostatic function tests, 2 patients (66.7%) had increased INR.

Grade 3 or Grade 4 laboratory abnormalities, each in 3 (12.5%) or fewer patients:

- Decreased platelets, decreased hemoglobin, decreased absolute lymphocyte count, decreased potassium, decreased phosphorus, increased INR and prolonged prothrombin time.

In the two treatment groups in this population, the laboratory safety profiles are similar in that **increased serum glucose** occurs with the highest frequency in both groups.

- Sixty (60) of 87 patients (Vorinostat 400 mg once daily group) had increased glucose, 27 patients had an increased glucose reported as Grade 1, 28 patients had Grade 2 increased serum glucose and 5 patients experienced an increased glucose level of Grade 3.
- These glucose elevations may not have been evaluated in the fasted state. Comparing the serum glucose abnormalities to the adverse experience reports, there is consistency with the observation that the most of the laboratory abnormalities of increased serum glucose were Grade 1 or Grade 2 and were not reported as adverse experiences.
- The patients in all the other monotherapy groups who had increased serum glucose had reported laboratory values of Grade 1 or Grade 2. No patient had increased serum glucose levels of Grade 3 or Grade 4.

Increased serum creatinine was also present in both treatment groups.

- Thirty-nine (39) of 87 patients administered Vorinostat at a dose of 400 mg once daily had increased creatinine: 32 of these increased values were Grade 1; 5 were Grade 2; and 2 were Grade 3.
- Comparison of the laboratory abnormalities to the Clinical and Laboratory adverse experiences (discussed earlier in this review) shows the consistency of the finding that majority of the laboratory abnormalities of increased serum creatinine were Grade 1 or 2.

The difference in the serum chemistry profiles between the two treatment groups in this population occurs because the patients administered Vorinostat at a dose of 400 mg once daily treatment group had **increased cholesterol and increased triglycerides** (49 of 74 or 66% of the patients) and these laboratory tests were not performed in the 24 patients in the other monotherapy groups.

- Evaluation of lipids was not necessarily done in the fasted state for all measurements, as this was not mandated by the study protocol.

The **hematology and hemostatic function** safety profiles in the two treatment groups were similar.

Thirty-eight (38) patients in this population experienced **increased urine protein**. Thirty-one of these were Grade 1 and 7 were Grade 2. The increased urine protein that is present in the patients administered Vorinostat at a dose of 400 mg once daily group is not noted in the other monotherapy treatment groups because no patients in the other groups had a urinalysis test performed while on the study therapy. However, in none of these cases the Investigator considered proteinuria as an adverse experience, i.e., as a clinically significant laboratory abnormality.

Table 141. Laboratory Abnormalities by Highest Grade (Vorinostat Monotherapy – CTCL) (Applicant's Table)

Laboratory Test	400mg qd 7d/wk						all other monotherapies					
	N	Grades				Total n (%)	N	Grades				Total n (%)
		1	2	3	4			1	2	3	4	
blood chemistry test												
decreased serum calcium	87	11	2	0	0	13 (14.9)	24	6	2	1	0	9 (37.5)
decreased serum glucose	87	8	1	1	0	10 (11.5)	24	0	0	0	0	0 (0.0)
decreased serum potassium	87	11	0	3	0	14 (16.1)	24	4	0	1	0	5 (20.8)
decreased serum sodium	87	6	0	1	0	7 (8.0)	24	5	0	0	0	5 (20.8)
increased serum glucose	87	27	28	5	0	60 (69.0)	24	13	6	0	0	19 (79.2)
increased serum magnesium	7	5	0	0	0	5 (71.4)	0	0	0	0	0	0 (0.0)
increased serum potassium	87	1	3	1	0	5 (5.7)	24	0	3	0	0	3 (12.5)
increased serum sodium	87	1	0	0	0	1 (1.1)	24	2	0	0	0	2 (8.3)
serum alanine aminotransferase	87	12	1	0	0	13 (14.9)	24	2	0	0	0	2 (8.3)
serum albumin	87	7	3	0	0	10 (11.5)	24	6	6	0	0	12 (50.0)
serum alkaline phosphatase	87	16	2	0	0	18 (20.7)	24	10	1	0	0	11 (45.8)
serum aspartate aminotransferase	87	11	3	0	0	14 (16.1)	24	7	1	0	0	8 (33.3)
serum bicarbonate	13	1	0	0	0	1 (7.7)	24	2	1	0	0	3 (12.5)
serum cholesterol	74	43	5	1	0	49 (66.1)	0	0	0	0	0	0 (0.0)
serum creatine kinase	3	3	0	0	0	3 (100.0)	0	0	0	0	0	0 (0.0)
serum creatinine	87	32	5	2	0	39 (44.8)	24	4	1	0	0	5 (20.8)
serum phosphorus	87	6	9	2	0	17 (19.5)	24	2	4	2	0	8 (33.3)
serum triglyceride	74	39	8	2	0	49 (66.2)	0	0	0	0	0	0 (0.0)
serum uric acid	87	6	0	0	3	9 (10.3)	24	5	0	0	1	6 (25.0)
total serum bilirubin	87	4	3	0	0	7 (8.0)	24	4	0	1	0	5 (20.8)
total serum carbon dioxide	74	23	5	0	0	28 (37.8)	0	0	0	0	0	0 (0.0)
endocrine test												
total serum thyroxine	1	0	1	0	0	1 (100.0)	0	0	0	0	0	0 (0.0)
hematology laboratory test												
WBC count	87	13	7	1	0	21 (24.1)	24	7	2	0	0	9 (37.5)
absolute lymphocyte count	14	0	1	2	2	5 (35.7)	24	4	5	2	2	13 (54.2)
absolute monocyte count	4	1	0	0	0	1 (25.0)	0	0	0	0	0	0 (0.0)
absolute neutrophil count	17	2	3	0	1	5 (29.4)	24	1	3	0	1	5 (20.8)
hemoglobin	87	41	8	2	0	51 (58.6)	24	16	5	2	0	23 (95.8)
lymphocyte count	87	4	16	9	1	30 (34.5)	24	0	0	0	0	0 (0.0)
mean corpuscular volume	25	2	0	0	0	2 (8.0)	24	0	0	0	0	0 (0.0)
neutrophil count	87	1	8	0	1	10 (11.5)	24	0	0	0	0	0 (0.0)
platelet count	87	32	3	4	1	40 (46.0)	24	3	2	3	3	11 (45.8)
hemostatic function test												
APTT	21	2	1	0	0	3 (14.3)	8	2	0	0	0	2 (22.2)
INR	18	3	0	3	0	6 (33.3)	3	1	0	1	0	2 (66.7)
prothrombin time	21	0	1	0	0	1 (4.8)	8	0	0	1	0	1 (12.5)
urinalysis test												
calcium oxalate crystal	5	3	0	0	0	3 (60.0)	0	0	0	0	0	0 (0.0)
urine protein	74	31	7	0	0	38 (51.4)	6	0	0	0	0	0 (0.0)

N: number of patients who had the lab test during treatment.
 If a patient had more than one graded abnormalities for a lab test, only the highest grade is counted.

[Ref. 3.3.5.2: P061, P065]

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Evaluation of Clinical Laboratory Abnormalities by Clinical Laboratory Shift Analysis – Vorinostat Monotherapy – CTCL

The laboratory shift data is summarized in the following table. The number of patients (M) who had a change in at least 1 post-baseline value is compared to the number of all patients who had at least 1 post-baseline value for the laboratory test (N). It also includes data for laboratory values for the test.

400 mg Once Daily

Serum glucose

Sixty (60) of the 87 patients (69%) in this treatment group had serum glucose post-baseline.

- Forty-six (46) of these 60 patients (67.6%) experienced a worsening of the grade value.
- In thirty-eight (38) of the 46 patients (77%) grade changes improved at subsequent serum glucose tests—8 improved to Grade 1 and 30 improved to Grade 0—however, in the other 8 of the 46 patients (17.4%) there were no further changes in serum glucose with subsequent serum glucose tests.
- In 28 patients increased serum glucose improved without any action taken in regard to Vorinostat treatment, in 6 patients it improved after dose interruption or dose modification, and in 4 after discontinuation of Vorinostat therapy.

- Twenty-one (21) of the 46 patients (45.7%) experienced clinically meaningful shifts in their increased serum glucose levels.
- Fourteen (14) of these 21 patients (30.4%) worsened and then improved with subsequent tests, and 7 (15.2%) showed no further changes.
- Seven (7) of the 21 patients (15.2%) improved to Grade 1, and 7 (15.2%) improved to Grade 0. Nine (9) of the 21 patients (19.6%) who improved to Grade 1 or Grade 0, improved with no action taken in regard to Vorinostat treatment, 3 improved after dose interruption or dose modification of Vorinostat treatment, and 2 improved after discontinuation of Vorinostat treatment.

Serum creatinine

All of the 87 patients assigned to this treatment group had serum creatinine tests performed post-baseline.

- Thirty-six (36) of these 87 patients (41.4%) who had post-baseline serum creatinine tests, experienced changes from baseline values of increased serum creatinine (worsened); four (4) of these 36 (11.1%) had clinically meaningful shifts.
- Fourteen (14) of the 36 patients (38.9%) worsened and then improved at subsequent serum creatinine tests—2 (5.6%) improved to Grade 1, and 11 (30.6%) improved to Grade 0.

- Eight (8) patients improved to Grade 0 or Grade 1 with no action taken in regard to Vorinostat treatment, 4 improved to Grade 0 or Grade 1 after dose interruption or dose modification of Vorinostat therapy, and 1 after discontinuation of Vorinostat therapy.
- Four (4) of the 36 patients (11.1%) had clinically meaningful shifts.
- One patient improved to Grade 1, and 2 patients improved to Grade 0.
- One patient improved to Grade 1 or Grade 0 with no action taken in regard to Vorinostat treatment, and 2 patients improved to Grade 1 or Grade 0 after dose interruption or dose modification of Vorinostat treatment.

Serum potassium

All of the 87 patients in this treatment group had post-baseline serum potassium values.

- Thirteen (13) patients experienced post-baseline change in serum potassium values: 12 of the 13 patients had a worsening of grade level from the baseline (decreased serum potassium), and 1 improved.
- Ten 10 patients with decreased serum potassium worsened and then improved: 5 improved to Grade 1 or Grade 0 without any action in regard to Vorinostat treatment, 4 after dose interruption or dose modification, and 1 after discontinuation of Vorinostat treatment.
- 3 of 13 patients (23.1%) had a clinically meaningful shift, however, all 3 improved to Grade 0 with no action taken in regard to Vorinostat treatment.

Hemoglobin

All 87 patients assigned to this treatment group had post-baseline hemoglobin values

- Thirty-four (34) patients (39%) experienced changes in the post-baseline values—33 of the 34 patients experienced worsening of their hemoglobin values.
- Twelve (12) of the 34 patients (35.3%) worsened and then improved: 9 improved to Grade 0 and 3 improved to Grade 1.
- Eight (8) improved with no action taken in regard to Vorinostat treatment, 3 after dose interruption or dose modification, and 1 patient improved with discontinuation of Vorinostat treatment. Twenty-one (21) patients had no further change in the later hemoglobin test results.
- 5 patients (14.7%) had *clinically meaningful* shifts. One (1) patient had no further changes with subsequent tests, 2 patients improved to Grade 1, and two (2) to Grade 0.
- One patient improved to Grade 1 or Grade 0 with no action taken in regard to Vorinostat treatment, and 3 after dose interruption or dose modification of Vorinostat treatment.

Reviewer Comments: *Usage of blood transfusions could not be ascertained from the applicant's data.*

Platelet count

All 87 patient assigned to this treatment group had post-baseline platelet counts.

- Thirty-nine (39) of the 87 patients (44.8%) experienced post-baseline changes in platelet counts. All 39 patients experienced a worsening (decreased platelet counts). Seven (7) of the 39 patients (17.9%) with post-baseline decreased platelet counts had *clinically meaningful* shifts.
- Twenty-nine (29) of the 39 patients (74.4%) with post-baseline decreased platelet count worsened and then improved at later test results—27 improved to Grade 0 and 2 improved to Grade 1, and 10 patients showed no change in subsequent test results.
 - Eighteen (18) patients with decreased platelets improved with no action taken in regard to Vorinostat treatment, 8 improved after dose interruption or dose modification, and 3 after discontinuation of Vorinostat treatment.
- Seven (7) patients had *clinically meaningful* shifts. One (1) patient showed no further change with subsequent tests, 2 patients improved to Grade 1, and 4 improved to Grade 0.
 - One (1) patient improved with no action taken in regard to Vorinostat treatment, and 5 improved to Grade 1 or Grade 0 after dose interruption or dose modification of Vorinostat treatment.

Urine protein

Of the 87 patients assigned to this treatment group, 74 (85.1%) had post-baseline urinalysis tests performed

- Thirty (30) of the 74 patients (40.5%) experienced a post-baseline change in urine protein; 29 experienced worsening of increased urine protein values, in 3 patients the shifts were considered clinically meaningful.
- 18 patients worsened and then improved on subsequent tests, and 11 patients showed no change in the increased urine protein values on subsequent testing.
- 16 patients improved to Grade 0 and 3 improved to Grade 1.
- 14 patients improved with no action taken in regard to Vorinostat treatment, 4 improved after dose interruption or dose modification of Vorinostat treatment.

- 3 patients had clinically meaningful shifts: 1 patient showed no further changes, and 2 patients improved to Grade 1 with no action taken in regard to Vorinostat treatment.

Lymphocyte count

Eighty-seven (87) patients assigned to this treatment group had post-baseline lymphocyte count values.

- Twenty-four (24) of the 87 patients (27.6%) experienced changes in their post-baseline values. Two (2) of the 24 patients (8.3%) improved at subsequent tests and 22 worsened at subsequent tests.
- Nineteen (19) of the 24 lymphocyte count changes were clinically meaningful shifts.
- One (1) of the 24 patients (4.2%) who had post-baseline changes in lymphocyte counts, showed a consistent improvement from baseline on the subsequent tests, 11 of the 24 patients experienced no change in subsequent tests, and another 11 of the 24 patients worsened and then improved—1 patient improved to Grade 1, and 10 to Grade 0.
- Eleven (11) patients improved with no action taken in regard to Vorinostat treatment

Serum uric acid

Eighty-seven (87) patients assigned to this treatment group had post-baseline uric acid values, and 6 of these patients (33.3%) had post-baseline changes; however, none of the patients was determined to have clinically meaningful shifts.

300 mg Twice Daily (n = 12)

For comparison, the laboratory tests identified in the 400 mg once daily treatment group are also reviewed in this treatment group.

Serum glucose

Nine (9) of the patients assigned to this treatment group had post-baseline serum glucose values, and 7 of these 9 patients (77.8%) experienced a worsening of grade level—in 2 of these 7 patients (28.6%) grade shifts were clinically meaningful.

- Six (6) of the 7 patients (85.7%) had grade changes that worsened and then improved with subsequent serum glucose tests and 1 of the 7 patients (14.3%) had no further change in serum glucose on subsequent testing.
- In 2 of the 6 patients improved to Grade 1, and 4 improved to Grade 0.
- Three (3) patients improved with no action taken in regard to Vorinostat treatment, 1 improved after dose interruption or dose modification of Vorinostat, and 2 improved after discontinuation of Vorinostat therapy.
- Two (2) patients had clinically meaningful shifts. These two patients later improved to Grade 1 with no action taken in regard to Vorinostat treatment.

Serum creatinine

Post-baseline serum creatinine values were available in 12 patients in this treatment group. Two (2) of these 12 patients (16.7%) experienced a worsening (from the baseline) of serum creatinine values, and in 1 of these 2 patients had a grade shift was clinically meaningful.

- Both patients worsened and then improved on subsequent serum creatinine tests. One patient improved to Grade 1 and 1 improved to within normal laboratory range.
- One patient improved after dose interruption or dose modification and 1 patient improved after discontinuation of Vorinostat therapy.
- 1 patient had a clinically meaningful shift. This patient improved to Grade 1 after dose interruption or dose modification of Vorinostat treatment.

Serum potassium

Of the 11 patients who had post-baseline serum potassium values in this treatment group, 1 patient had decreased serum potassium; however, the shift was not clinically meaningful.

Hemoglobin

Twelve (12) patients in this treatment group had post-baseline hemoglobin values. Three of the 12 patients (25.0%) had worsening of their hemoglobin level, however, only 1 patient had a clinically meaningful grade shift.

- Two (2) of the 3 patients (66.7%) worsened and then improved with subsequent tests, and one (1) of the 3 patients (33.3%) had no change with subsequent tests.
- Two (2) of the 3 patients (66.7%) improved to Grade 1; one patient improved with no action taken in regard to Vorinostat treatment, and 1 patient improved after dose interruption or dose modification of Vorinostat treatment.
- One patient had a clinically meaningful shift, this patient improved to Grade 1 after dose interruption or dose modification of Vorinostat treatment.

Platelet count

Twelve (12) patients in this treatment group had post-baseline platelet counts, 6 patients (50.0%) experienced a worsening of the platelet count, and in 2 patients the post-baseline changes in platelet counts were clinically meaningful.

- Four (4) of the 6 patients (66.7%) worsened and later improved at subsequent tests to Grade 0, and 2 patients showed no change in decreased platelet counts.
- One (1) patient improved with no action taken in regard to Vorinostat treatment, 1 patient improved after dose interruption or dose modification, and 2 patients improved after discontinuation of Vorinostat treatment.
- Two (2) patients had clinically meaningful shifts, both patients improved to Grade 0; 1 patient improved to Grade 0 after dose interruption or dose modification and 1 patient improved to Grade 0 after discontinuation of Vorinostat treatment.

Proteinuria

- Post-baseline urine protein results were not reported in this treatment group.

Other Laboratory Parameters

In contrast to the 400 mg once daily treatment group, clinically meaningful shifts were seen in the following laboratory parameters; however they occurred in small numbers of patients in this treatment group:

- Increased serum potassium in 2 patients with post-baseline tests
- Decreased absolute neutrophil count in 2 patients with post-baseline tests
- Decreased serum phosphorus in 3 of 12 patients with post-baseline tests
- Decreased serum albumin in 2 of 4 patients with post-baseline tests

Doses above the MTD

For comparison, the laboratory parameters reviewed in the 400 mg once daily treatment group are also reviewed in this treatment group.

Serum glucose

Two (2) patients in this treatment group had serum glucose tests performed post-baseline; 1 of these patients had a worsening of the grade level, but the serum glucose shift in this patient was not considered clinically meaningful. The patient did not have any subsequent changes in serum glucose values at subsequent tests.

Serum creatinine

12 patients had post-baseline serum creatinine tests, 1 patient (8.3%) had a change in the post-baseline serum creatinine values—it was a worsening of grade level from the baseline that was not considered a clinically meaningful shift. The patient did not have any subsequent changes in the serum creatinine values.

Hemoglobin

Twelve (12) patients in this treatment group had post-baseline hemoglobin values, 3 (25.0%) worsened.

None of the changes were considered clinically meaningful.

Platelet count

Twelve (12) patients in this treatment group had post-baseline platelet counts, 5 of these 12 patients had post-baseline values that were worse; 4 of the 5 patients (80.0%) with post-baseline changes had clinically meaningful shifts.

- Three (3) of the 5 patients with post-baseline shifts, worsened and then improved with subsequent tests, and two showed no subsequent change.
- Two (2) of the 5 patients improved to Grade 1 or Grade 0 with no action taken in regard to Vorinostat therapy.

Other laboratory parameters

Post-baseline test results were not reported in this treatment group for decreased serum potassium and urinalysis.

In contrast to the 400 mg once daily treatment group, clinically meaningful shifts were seen in the following laboratory parameters; however they occurred in small numbers of patients in this treatment group:

- Absolute neutrophil count in 1 patient with post-baseline changes
- Increased total serum bilirubin in 1 of 3 patients with post-baseline changes

Table 142. Summary of Shift in Laboratory Parameters from Baseline to Worst Post-baseline Value to Last Value Vorinostat Monotherapy – CTCL (Applicant's Table)

Parameter and Treatment Group	N ¹¹	M ¹²	Number (%) of Subjects											
			Change in CTCAE Grade ¹ from Baseline to Worst Value Postbaseline			Change in CTCAE Grade from Worst Value Postbaseline to Last Value Postbaseline								
			Improved ¹³	Worsened	Clinically Meaningful Shift ¹⁴	Consistent Improvement from Baseline ¹⁵	Worsened and then Improved ¹⁶	No Change ¹⁷	Grade 1	Grade 0	Improved to Grade 0 or Grade 1 ¹⁸ Without Any Change in Therapy	With Dose Interruption or Modification	Associated With Stopping Therapy	
absolute neutrophil count														
300mg BID 3:7	12	2	0(0.0)	2(16.7)	2(16.7)	0(0.0)	1(8.3)	1(8.3)	0(0.0)	0(0.0)	1(8.3)	0(0.0)	0(0.0)	1(8.3)
400mg QD continuous	17	3	0(0.0)	3(17.6)	3(17.6)	0(0.0)	3(17.6)	0(0.0)	0(0.0)	0(0.0)	3(17.6)	0(0.0)	0(0.0)	3(17.6)
Doses above MTD	12	1	0(0.0)	1(8.3)	1(8.3)	0(0.0)	0(0.0)	0(0.0)	1(8.3)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(8.3)
hemoglobin														
300mg BID 3:7	12	2	0(0.0)	3(25.0)	1(8.3)	0(0.0)	2(16.7)	1(8.3)	2(16.7)	0(0.0)	1(8.3)	1(8.3)	1(8.3)	0(0.0)
400mg QD continuous	17	3	1(5.9)	13(77.1)	5(29.4)	0(0.0)	12(70.6)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Doses above MTD	12	1	0(0.0)	3(25.0)	0(0.0)	0(0.0)	2(16.7)	1(8.3)	0(0.0)	2(16.7)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
lymphocyte count														
400mg QD continuous	17	3	2(11.8)	15(88.2)	1(5.9)	0(0.0)	15(88.2)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
platelet count														
300mg BID 3:7	12	2	0(0.0)	4(33.3)	2(16.7)	0(0.0)	4(33.3)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
400mg QD continuous	17	3	0(0.0)	13(76.5)	7(41.2)	0(0.0)	13(76.5)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Doses above MTD	12	1	0(0.0)	3(25.0)	4(33.3)	0(0.0)	3(25.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
serum albumin														
300mg BID 3:7	12	4	1(8.3)	3(25.0)	2(16.7)	0(0.0)	2(16.7)	1(8.3)	0(0.0)	2(16.7)	1(8.3)	0(0.0)	0(0.0)	1(8.3)
400mg QD continuous	17	10	2(11.8)	15(88.2)	4(23.5)	0(0.0)	15(88.2)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Doses above MTD	12	1	1(8.3)	3(25.0)	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)
serum creatinine														
300mg BID 3:7	12	2	0(0.0)	2(16.7)	1(8.3)	0(0.0)	2(16.7)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(8.3)
400mg QD continuous	17	5	0(0.0)	16(94.1)	4(23.5)	0(0.0)	16(94.1)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Doses above MTD	12	1	0(0.0)	1(8.3)	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)
serum glucose - increased														
300mg BID 3:7	8	7	0(0.0)	7(87.5)	2(25.0)	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)
400mg QD continuous	68	46	0(0.0)	68(100.0)	21(30.9)	0(0.0)	38(55.9)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Doses above MTD	2	1	0(0.0)	1(50.0)	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)
serum phosphorus														
300mg BID 3:7	12	5	1(8.3)	4(33.3)	3(25.0)	0(0.0)	4(33.3)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
400mg QD continuous	17	17	0(0.0)	17(100.0)	11(64.7)	0(0.0)	15(88.2)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Doses above MTD	12	3	1(8.3)	1(8.3)	1(8.3)	0(0.0)	1(8.3)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
serum potassium - decreased														
300mg BID 3:7	7	1	0(0.0)	1(14.3)	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)
400mg QD continuous	47	13	1(2.1)	12(25.5)	3(6.4)	0(0.0)	10(21.3)	2(4.3)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
serum potassium - increased														
300mg BID 3:7	4	2	0(0.0)	2(50.0)	2(50.0)	0(0.0)	1(25.0)	1(25.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
400mg QD continuous	34	5	0(0.0)	5(14.7)	4(11.8)	0(0.0)	5(14.7)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Doses above MTD	3	1	0(0.0)	1(33.3)	0(0.0)	0(0.0)	1(33.3)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
serum uric acid														
300mg BID 3:7	12	2	1(8.3)	1(8.3)	0(0.0)	0(0.0)	1(8.3)	0(0.0)	0(0.0)	0(0.0)	1(8.3)	0(0.0)	0(0.0)	0(0.0)
400mg QD continuous	17	6	2(11.8)	4(23.5)	0(0.0)	0(0.0)	2(11.8)	0(0.0)	0(0.0)	0(0.0)	2(11.8)	0(0.0)	0(0.0)	0(0.0)
Doses above MTD	12	1	0(0.0)	1(8.3)	0(0.0)	0(0.0)	1(8.3)	0(0.0)	0(0.0)	0(0.0)	1(8.3)	0(0.0)	0(0.0)	0(0.0)
urine protein														
400mg QD continuous	54	50	1(1.9)	29(53.7)	3(5.6)	1(1.9)	18(33.3)	11(20.4)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(1.9)

¹¹Based on NCI CTCAE, Version 3.0
¹²A clinically meaningful shift in CTCAE grade was defined as a shift from less than Grade 3 to Grade 3 or 4 or 5 OR a shift from Grade 0 to Grade 2
¹³Includes subjects from the column labeled "Improved".
¹⁴Includes subjects from the column labeled "Worsened".
¹⁵Includes subjects from the column labeled "Consistent improvement from baseline" and "Worsened and then improved".
¹⁶Number of patients who improved from baseline based on worst postbaseline.
¹⁷Number of patients with at least 1 postbaseline value. Patients without any changes from baseline are included.
¹⁸Denominator for each parameter = number of patients with at least 1 postbaseline value. Patients without any changes from baseline are excluded. A missing baseline value was set Grade 0.
 Ref: 3.3.S.2.P001.P003

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Vorinostat Monotherapy – CTCL Stage IIB and Higher

Summary Comparison of Clinical Laboratory Evaluations – Vorinostat Monotherapy CTCL Stage IIB or Higher

Reviewer Comments: This population is a subset of the Vorinostat Monotherapy – CTCL population.

Of the 72 patients assigned to the treatment group of Vorinostat monotherapy 400 mg once daily, all patients had at least one laboratory test done post-baseline. Of the 21 patients who were assigned to receive all other doses of Vorinostat monotherapy in the stage IIB or higher population, all had 1 or more post-baseline laboratory tests.

- Evaluation of laboratory values by the highest CTCAE Grade showed similar results for the patients assigned to receive Vorinostat at 400 mg once daily dose and the patients assigned to receive all other doses of Vorinostat monotherapy in the CTCL Stage IIB or higher population.

When **all grades** are included, the most common serum *chemistry* abnormalities occurring in at least 10% of patients in 400 mg once daily dose group:

- Increased serum glucose 70.8%
- Increased serum creatinine 47.2%

The most common *hematology* abnormalities:

- Decreased hemoglobin 59.7%
- Decreased platelet count 45.8%
- Decreased lymphocyte count 33.3%
- Increased INR 31.3%
- Increased urine protein in 33 of 61 patients 54.1%

These were also the most common laboratory abnormalities, regardless of grade, in the population of patients assigned to all other doses of Vorinostat monotherapy in this population. The majority of these laboratory abnormalities were Grade 1 and Grade 2.

Clinically meaningful shifts in laboratory abnormalities were seen most commonly for:

- Increased serum glucose
- Increased serum creatinine
- Decreased hemoglobin
- Decreased platelet counts
- Increased urine protein

Findings were similar in the patients who were assigned to receive 400 mg once daily and all other doses of Vorinostat monotherapy in this population.

Evaluation by Highest CTCAE Grade – Vorinostat Monotherapy CTCL Stage IIB or Higher

The table below lists the laboratory abnormalities by the highest grade for each test: the numbers of patients *who had a graded abnormality* during treatment (n) are compared to the number of patients *who had the test performed* post-baseline (N).

- The patients assigned to Vorinostat monotherapy 400 mg once daily were the primary treatment group in the CTCL Stage IIB or Higher population. The patients in this population who were assigned to receive all other doses of Vorinostat monotherapy (21) were combined into a second group for these data analyses.
- All 72 patients in the Vorinostat monotherapy group of 400 mg once daily and all 21 patients in all other Vorinostat monotherapy doses groups had 1 or more post-baseline laboratory tests.

400 mg Once Daily

The most common laboratory abnormalities, *regardless of grade*, occurring in at least 10% of patients, listed in order of decreasing frequency:

- | | |
|---|-------|
| ○ Increased serum glucose in 51 of 72 patients | 70.8% |
| ○ Increased serum triglycerides in 42 of 61 patients | 68.9% |
| ○ Increased serum cholesterol in 41 of 61 patients | 67.2% |
| ○ Increased serum creatinine in 34 of 72 patients | 47.2% |
| ○ Total serum carbon dioxide in 23 of 61 patients | 37.7% |
| ○ Increased alkaline phosphatase in 17 of 72 patients | 23.6% |
| ○ Increased serum aspartate aminotransferase in 13 of 72 patients | 18.1% |
| ○ Decreased serum potassium in 12 of 72 patients | 16.7% |
| ○ Decreased calcium in 12 of 72 patients | 16.7% |
| ○ Increased serum alanine aminotransferase in 12 of 72 patients | 16.7% |
| ○ Decreased serum phosphorus in 10 of 72 patients | 13.9% |
| ○ Decreased serum albumin in 10 of 72 patients | 13.9% |
| ○ Increased uric acid in 8 of 72 patients | 11.1% |

The most common hematology abnormalities, *regardless of grade*, occurring in at least 10% of patients, listed in order of descending frequency:

- | | |
|---|-------|
| ○ Decreased hemoglobin in 43 of 72 patients | 59.7% |
| ○ Decreased platelet count in 33 of 72 patients | 45.8% |
| ○ Decreased lymphocyte count in 24 of 72 patients | 33.3% |

Of the 18 patients with hemostatic function tests, 16 patients had INR tests and 5 of 16 patients (31.3%) had increased INR.

The most common urinalysis abnormality was urine protein in 33 of 61 patients (54.1%).

Grade 3 laboratory abnormalities:

- Decreased lymphocyte count 9 patients
- Increased serum glucose 4 patients
- Decreased platelet count 4 patients
- Decreased potassium 2 patients
- Increased serum creatinine 2 patients
- Increased triglycerides 2 patients,
- Decreased absolute lymphocytes 2 patients
- Decreased hemoglobin 2 patients,
- Increased INR 2 patients
- Increased potassium 1 patient
- Increased cholesterol 1 patient
- Decreased sodium 1 patient
- Decreased white blood cell count 1 patient

Grade 4 laboratory abnormalities:

- Increased uric acid 3 patients
- Decreased lymphocyte count 1 patient
- Decreased neutrophil count 1 patient
- Decreased platelet count 1 patient

Again, increased serum glucose, increased serum cholesterol and increased serum triglycerides were among the most common laboratory abnormalities in this group of patients, however, the evaluation of these were not necessarily done in the fasted state as this was not mandated by study protocols.

All Other Doses of Vorinostat Monotherapy

The most common *serum chemistry* abnormalities in patients assigned to all other doses of Vorinostat monotherapy in the CTCL Stage IIB or higher population, *regardless of grade*, occurring in at least 10% of patients, listed in order of decreasing frequency:

- Increased serum glucose in 16 of 21 patients 76.2%
- Decreased albumin in 11 of 21 patients 52.4%
- Increased serum alkaline phosphatase in 11 of 21 patients 52.3%
- Decreased serum calcium in 9 of 21 patients 42.9%
- Increased serum aspartate aminotransferase in 8 of 21 patients 38.1%
- Decreased phosphorus in 7 of 21 patients 33.3%
- Increased uric acid in 6 of 21 patients 28.6%
- Increased serum creatinine in 5 of 21 patients 23.8%

- Decreased serum sodium in 5 of 21 patients 23.8%
- Decreased serum potassium in 5 of 21 patients 23.8%
- Increased total serum bilirubin in 4 of 21 patients 19.0%
- Decreased serum bicarbonate in 3 of 21 patients 14.3%
- Increased serum potassium in 3 of 21 patients 14.3%

The most common *hematology* abnormalities:

- Decreased hemoglobin in 21 of 21 patients 100.0%
- Decreased platelet count in 13 of 21 patients 61.9%
- Decreased absolute lymphocyte count in 12 of 21 patients 57.1%
- Decreased WBC in 8 of 21 patients 38.1%
- Absolute neutrophil count in 5 of 21 patients 23.8%

Of the 7 patients with *hemostatic* function tests, 3 patients had INR tests and 2 of 3 patients (66.7%) had increased INR.

- The majority of laboratory abnormalities were Grade 1 and Grade 2
- Only one (1) Grade 3 laboratory abnormality (decreased lymphocyte count) occurred in > 10% of the patients.
- No Grade 4 laboratory abnormalities occurred in >5% of the patient population.

- The safety profiles for the two treatment groups of patients were similar: increased serum glucose occurred with the highest frequency in both groups. Increased serum creatinine was also present in both treatment groups.
- Hematology tests that were similar in both treatment groups: decreased hemoglobin, decreased platelets, decreased lymphocytes, and decreased WBC count.
- Increased INR in the hemostatic function category was also present in both treatment groups.

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Table 143. Laboratory Abnormality by Highest Grade (Vorinostat Monotherapy – CTCL Stage IIB and Higher) (Applicant's Table)

Laboratory Test	400mg qd 7d/wk						all other monotherapies					
	N	Grades				Total n (%)	N	Grades				Total n (%)
		1	2	3	4			1	2	3	4	
blood chemistry test												
decreased serum calcium	72	10	2	0	0	12 (16.7)	21	6	2	1	0	9 (42.9)
decreased serum glucose	72	6	1	0	0	7 (9.7)	21	0	0	0	0	0 (0.0)
decreased serum potassium	72	10	0	2	0	12 (16.7)	21	4	0	1	0	5 (23.8)
decreased serum sodium	72	6	0	1	0	7 (9.7)	21	5	0	0	0	5 (23.8)
increased serum calcium	72	4	0	0	0	4 (5.6)	21	0	0	0	0	0 (0.0)
increased serum glucose	72	23	24	4	0	51 (70.8)	21	10	6	0	0	16 (76.2)
increased serum magnesium	5	5	0	0	0	5 (60.0)	6	0	0	0	0	0 (0.0)
increased serum potassium	72	1	3	1	0	5 (6.9)	21	0	3	0	0	3 (14.3)
increased serum sodium	72	0	0	0	0	0 (0.0)	21	2	0	0	0	2 (9.5)
serum alanine aminotransferase	72	11	1	0	0	12 (16.7)	21	2	0	0	0	2 (9.5)
serum albumin	72	7	3	0	0	10 (13.9)	21	5	6	0	0	11 (52.4)
serum alkaline phosphatase	72	15	2	0	0	17 (23.6)	21	10	1	0	0	11 (52.4)
serum aspartate aminotransferase	72	10	3	0	0	13 (18.1)	21	7	1	0	0	8 (38.1)
serum bicarbonate*	11	1	0	0	0	1 (9.1)	21	2	1	0	0	3 (14.3)
serum cholesterol	61	36	4	1	0	41 (67.2)	6	0	0	0	0	0 (0.0)
serum creatine kinase	2	2	0	0	0	2 (100.0)	0	0	0	0	0	0 (0.0)
serum creatinine	72	17	5	1	0	24 (47.2)	21	4	1	0	0	5 (23.8)
serum phosphorus	72	5	5	0	0	10 (13.9)	21	1	4	2	0	7 (33.3)
serum triglyceride	61	32	8	2	0	42 (68.8)	6	0	0	0	0	0 (0.0)
serum uric acid	72	5	0	0	2	7 (9.7)	21	5	0	0	1	6 (28.6)
total serum bilirubin	72	1	3	0	0	4 (5.6)	21	4	0	0	0	4 (19.0)
total serum carbon dioxide*	61	19	4	0	0	23 (37.7)	6	0	0	0	0	0 (0.0)
endocrine test												
total serum thyroxine		1	0	1	0	1 (100.0)	0	0	0	0	0	0 (0.0)
hematology laboratory test												
WBC count	72	33	4	1	0	38 (52.8)	21	6	2	0	0	8 (38.1)
absolute lymphocyte count	12	6	1	2	1	10 (83.3)	21	4	4	2	2	12 (57.1)
absolute monocyte count	2	1	0	0	0	1 (50.0)	0	0	0	0	0	0 (0.0)
absolute neutrophil count	14	1	2	0	0	3 (21.4)	21	1	3	0	1	5 (23.8)
hemoglobin	72	33	8	2	0	43 (59.7)	21	14	5	2	0	21 (100.0)
lymphocyte count	72	4	10	9	1	24 (33.3)	21	0	0	0	0	0 (0.0)
mean corpuscular hemoglobin conc	26	1	0	0	0	1 (5.0)	21	0	0	0	0	0 (0.0)
neutrophil count	72	1	5	0	1	7 (9.7)	21	0	0	0	0	0 (0.0)
platelet count	72	25	3	4	1	33 (45.8)	21	5	2	3	3	13 (61.9)
hemostatic function test												
APTT	18	2	0	0	0	2 (11.1)	7	2	0	0	0	2 (28.6)
INR	16	3	0	2	0	5 (31.3)	3	1	0	1	0	2 (66.7)
prothrombin time	18	0	1	0	0	1 (5.6)	6	0	0	1	0	1 (16.7)
urinalysis test												
calcium oxalate crystal	4	2	0	0	0	2 (50.0)	0	0	0	0	0	0 (0.0)
urine protein	61	16	7	0	0	23 (37.7)	5	0	0	0	0	0 (0.0)

N = number of patients who had the lab test during treatment.
 *If a patient had more than one graded abnormalities for a lab test, only the highest grade is counted.
 (Ref: 5.3.5.2: P061, P065)

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Evaluation by Clinical Laboratory Shift Analysis (Vorinostat Monotherapy – CTCL Stage IIB or Higher)

- The laboratory shift data summary is shown in the following table.
- Data from the laboratory results from the patients who *had a change in at least 1 post-baseline value (M)* are compared to the data from all the patients *who had at least 1 post-baseline value for the laboratory test (N)*.

400 mg Once Daily

Serum glucose

- Fifty-eight (58) patients in this dose group had post-baseline serum glucose values, 39 of these 58 (67.3%) experienced worsening of the grade level from the baseline, and in 19 of these 39 patients (48.7%) grade shifts were clinically meaningful.
- Thirty-one (31) patients who had post-baseline increased serum glucose tests worsened and then improved: in 6 patients increased serum glucose improved to Grade 1 and in 25 it improved to Grade 0. In 8 patients there was no change in the post-baseline increased serum glucose tests.
- In 22 patients, increased serum glucose tests improved with no action taken in regard to Vorinostat treatment, in 6 serum glucose tests improved after dose interruption or dose modification, and in 3 patients after discontinuation of Vorinostat therapy.

Serum creatinine

- Seventy-two (72) patients in this treatment group had post-baseline serum creatinine values and 31 patients (43.1%) experienced post-baseline changes: all 31 experienced worsening of grade level from the baseline, and in 4 patients grade shifts were clinically meaningful.
- Thirteen (13) of the 31 patients (41.9%) who had post-baseline changes, worsened and then improved, 2 (6.5%) improved to Grade 1, and 10 (32.3%) to Grade 0.
- Seven (7) patients (22.6%) improved without any action taken in regard to Vorinostat treatment, 4 improved after dose interruption or dose modification, and 1 improved after discontinuation.

Hemoglobin

- Seventy-two (72) patients had post-baseline hemoglobin and 28 (38.9%) experienced changes in the post-baseline hemoglobin values.
- One (1) of the 28 patients (3.6%) who had post-baseline hemoglobin changes improved at subsequent testing, but 27 (96.4%) experienced a worsening in their decreased hemoglobin—5 of these were clinically meaningful grade shifts.
- In 10 patients hemoglobin changes worsened and then improved at subsequent testing: in 7 to Grade 0 and in 3 to Grade 1; 17 patients showed no change with subsequent tests.

- Seven (7) patients who had post-baseline hemoglobin worsening improved with no action taken in regard to Vorinostat treatment and 3 patients improved after dose interruption or dose modification of Vorinostat.

Platelet count

- Seventy-two (72) patients in this treatment group had post-baseline platelet counts and 32 of them experienced changes: all changes were a decreased platelet count; in 7 patients these were clinically meaningful.
- Twenty-three (23) of 32 patients worsened and then improved at subsequent testing; in 2 patients the decreased platelet counts improved to Grade 1 and in 21 to Grade 0, and 9 patients showed no change.
- Thirteen (13) patients improved with no action taken in regard to Vorinostat treatment, 8 improved with dose interruption or dose modification, and 2 improved with discontinuation of Vorinostat.

Proteinuria

- Sixty-one (61) patients had post-baseline urinalysis tests, 25 (41.0%) had worsening—increased urine protein, and in 3 of these 25 patients the shifts were clinically meaningful.
- Fifteen (15) of the 25 patients (60.0%) who had post-baseline change of increased urine protein worsened and then improved on subsequent testing: 12 patients improved to Grade 0 and 3 to Grade 1, and 10 patients showed no change.
- Ten (10) of the 25 patients (40%) improved with no action taken in regard to Vorinostat treatment, 4 (16%) improved after dose interruption or dose modification of Vorinostat treatment, and 1 (4%) improved after discontinuation of Vorinostat treatment.

Lymphocyte count

- Seventy-two (72) patients in this treatment group had post-baseline lymphocyte counts and 20 (27.8%) had changes in the post-baseline values: 1 of the 20 patients (5.0%) had an improvement in the lymphocyte count at subsequent testing but 19 (95.0%) showed worsening at subsequent testing, 16 (80.0%) had clinically meaningful shifts.
- Lymphocyte count in 9 of the 20 patients (45.0%) worsened and then improved with subsequent tests, in 10 patients there was no change; in 1 patient the count improved to Grade 1 and in 7 to Grade 0; in 8 patients the lymphocyte count improved with no action taken in regard to Vorinostat treatment.

300 mg Twice Daily

For comparison, the laboratory abnormalities identified in the 400 mg once daily treatment group are also reviewed in this dose group.

Serum glucose

- Eight (8) patients in this treatment group had post-baseline serum glucose values and 6 of the 8 patients (75%) showed a worsening of grade level from the baseline, in 2 patients the grade shifts were clinically meaningful.
- Five (5) of the 6 patients (83.3%) who had post-baseline serum glucose changes worsened and then improved at subsequent tests, 2 improved to Grade 1 and 3 improved to Grade 0.
- Three (3) improved with no action taken in regard to Vorinostat treatment, 1 improved after dose interruption or dose modification, and 1 improved after discontinuation.

Serum creatinine

- Eleven (11) patients had post-baseline serum creatinine values and 2 (18%) experienced changes—both patients had worsening of serum creatinine, in one patient the shift in serum creatinine was clinically meaningful.
- Both patients at first worsened and subsequently improved, 1 improved to Grade 1 and 1 to Grade 0; one improved after dose interruption or dose modification of Vorinostat and one improved after discontinuation of Vorinostat treatment.

Hemoglobin

- Eleven patients in this treatment group had post-baseline hemoglobin values and 3 (27%) experienced post-baseline changes—all 3 showed a decrease in hemoglobin, in one patient this was clinically meaningful.
- Two (2) of the 3 patients (67%) who had worsened, improved at subsequent tests to Grade 1, and 1 showed no further changes.
- One (1) patient improved with no action taken in regard to Vorinostat treatment and one improved after dose interruption or dose modification.

Platelet count

- Eleven (11) patients in this treatment group had post-baseline platelet counts and 5 (45%) experienced changes—all had a post-baseline decrease in platelet counts, in 2 this was clinically meaningful.
- Three (3) of the 5 patients improved at subsequent tests to grade 0 and 2 showed no change. One (1) patient improved with no action taken in regard to Vorinostat treatment, 1 improved after dose interruption or dose modification, and 1 after discontinuation.

Post-baseline test results were not reported in this treatment group for **lymphocyte counts** and **urinalysis**.

Vorinostat Monotherapy – Solid Tumors

Summary Comparison of Clinical Laboratory Evaluations (Vorinostat Monotherapy – Solid Tumors)

Analysis of clinical laboratory testing by toxicity grades shows similar results whether the patients received Vorinostat at 400 mg once daily or other doses of Vorinostat in the solid tumor population.

400 mg once daily group

The most common *serum chemistry* abnormalities *regardless of grade* listed in descending order of frequencies:

- Decreased serum albumin 74%
- Decreased serum sodium 64%
- Increased serum creatinine 54%
- Increased serum alkaline phosphatase 49%
- Increased serum glucose 41%
- Decreased serum bicarbonate 37%
- Decreased serum calcium 33%
- Increased serum magnesium 26%
- Increased serum potassium 15%

The most common hematology abnormalities were:

- Decreased hemoglobin 87%
- Decreased platelet count 58%

The most common hemostatic function abnormality:

- Increased INR 44%

The most common *Grade 3* laboratory abnormalities (a higher frequency noted in the group of patients who were included in the all other monotherapy group):

- Decreased lymphocyte count
- Decreased platelet counts

All other doses group

The most common serum chemistry abnormalities, *regardless of grade*, in patients who received *all other doses of Vorinostat monotherapy* in the solid tumors population, listed in order of decreasing frequencies:

○ Increased serum glucose	95.6%
○ Decreased serum albumin	70.5%
○ Increased serum alkaline phosphatase	62.3%
○ Increased serum creatinine	62.3%
○ Increased serum aspartate aminotransferase	45.9%
○ Decreased serum calcium	44.3%
○ Decreased serum sodium	39.3%
○ Increased serum alanine aminotransferase	37.7%
○ Decreased serum potassium	27.9%

The most common *hematology* abnormalities in patients who received all other doses of Vorinostat monotherapy:

○ Decreased hemoglobin	91.8%
○ Decreased platelet count	50.8%

Of the 45 patients with *hemostatic function* test, (51%) had increased INR.

Of the 16 patients who had *urinalysis* for proteinuria 1 (6.3%) experienced Grade 1 and 1 (6.3%) experienced Grade 2 proteinuria.

Clinically meaningful laboratory shifts were similar across all treatment groups in this population and were:

- Increased serum creatinine
 - Increased serum glucose
 - Increased serum alkaline phosphatase
 - Decreased hemoglobin
 - Decreased platelet counts
-
- Serum Chemistry abnormalities in the two treatment groups in this population were similar, however, increased serum glucose was seen at a higher frequency in the group of patients who received *all other doses* of Vorinostat than in the group of patients who received 400 mg once daily.
 - Clinically meaningful shifts were similar across all treatment groups in this population except for decreased platelet counts which occurred with a much higher frequency in the group of patients who received Vorinostat at doses above MTD in this population.
 - Similar to the CTCL population, clinically meaningful shifts occurred in increased serum creatinine, increased serum glucose, decreased hemoglobin and decreased platelets; however, in the solid tumor population, increased serum alkaline phosphatase and increased serum aspartate aminotransferase also had clinically meaningful shifts.
(*Reviewer Comments: likely to be metastatic disease effects and disease progression*)

Evaluation by the Highest CTCAE Grade (Vorinostat Monotherapy – Solid Tumors)

- The following table shows laboratory abnormalities by grade: the number of patients *who had an abnormality (n)* is compared to the number of patients *who had the test performed post-baseline (N)*.
- The patients who received Vorinostat monotherapy 400 mg once daily were the primary treatment group. All other patients in this population who received all other doses of Vorinostat monotherapy were combined into a second group for these data analyses.

400 mg Once Daily

The most common *serum chemistry* laboratory abnormalities, *regardless of grade*, occurring in at least 10% of patients, in order of decreasing frequency:

- Decreased serum albumin in 29 of 39 patients 74.4%
- Decreased serum sodium in 25 of 39 patients 64.1%
- Increased serum creatinine in 21 of 39 patients 53.8%
- Decreased serum alkaline phosphatase in 19 of 39 patients 48.7%
- Increased serum glucose in 16 of 39 patients 41.0%
- Decreased serum bicarbonate in 13 of 35 patients 37.1%
- Decreased serum calcium in 13 of 39 patients 33.3%
- Increased serum magnesium in 7 of 27 patients 25.9%
- Increased serum potassium 15.4%

The most common *hematology* abnormalities:

- Decreased hemoglobin in 33 of 38 patients 86.8%
- Decreased platelet count in 22 of 38 patients 57.9%

The most common *hemostatic function* abnormality:

- Increased INR in 11 of 25 patients 44.0%

There were *no Grade 4* serum chemistry laboratory abnormalities in this treatment group

Grade 3 laboratory abnormalities occurred in the following tests:

- Decreased serum sodium in 5 patients
- Increased magnesium in 3 patients
- Increased serum glucose in 2 patients
- Decreased serum albumin in 1 patient
- Increased serum alkaline phosphatase in 1 patient
- Increased serum aspartate aminotransferase in 1 patient
- Increased serum creatinine in 1 patient

Hematology laboratory tests:

Grade 4 abnormalities

- Decreased hemoglobin in 1 patient
- Decreased platelet count in 1 patient
- Decreased lymphocyte count in 1 patient

Grade 3 abnormalities:

- Decreased absolute lymphocyte counts in 5 patients
- Decreased lymphocyte count in 4 patients
- Decreased hemoglobin in 1 patient

There were no *Grade 3* or *Grade 4 hemostatic* function laboratory abnormalities in this treatment group.

All Other Doses of Vorinostat Monotherapy

The most common *serum chemistry* laboratory abnormalities, *regardless of grade*, occurring in at least

10% of patients, in order of decreasing frequency:

- | | |
|---|-------|
| ○ Increased serum glucose in 43 of 45 patients | 95.6% |
| ○ Decreased serum albumin in 43 of 61 patients | 70.5% |
| ○ Increased serum alkaline phosphatase in 38 of 61 patients | 62.3% |
| ○ Increased serum creatinine in 38 of 61 patients | 62.3% |
| ○ Increased serum aspartate aminotransferase in 28 of 61 patients | 45.9% |
| ○ Decreased serum calcium in 27 of 61 patients | 44.3% |
| ○ Decreased in serum sodium in 24 of 61 patients | 39.3% |
| ○ Increased serum alanine aminotransferase in 23 of 61 patients | 37.7% |
| ○ Decreased serum potassium in 17 of 61 patients | 27.9% |

The most common *hematology* abnormalities in patients who received all other doses of Vorinostat monotherapy:

- | | |
|---|-------|
| ○ Decreased hemoglobin in 56 of 61 patients | 91.8% |
| ○ Decreased platelet count in 31 of 61 patients | 50.8% |

Of the 45 patients with *hemostatic function test*, 23 (51.1%) had increased INR.

Of the 50 patients with *urinalysis test*, 7 (14.0%) had urine RBC, one of 16 patients (6.3%) experienced *Grade 1* increased urine protein and one of 16 patients (6.3%) experienced *Grade 2* increased urine protein.

Grade 4 serum *chemistry* laboratory abnormalities:

- Increased serum creatinine kinase in 2 patients
- Decreased serum sodium in 1 patient

Grade 3 serum chemistry abnormalities:

- Increased serum alkaline phosphatase in 8 patients
- Decreased serum sodium in 6 patients
- Increased serum glucose in 6 patients
- Increased fasting glucose in 2 patients
- Increased serum calcium in 2 patients
- Increased serum potassium in 2 patients
- Increased serum aspartate aminotransferase in 2 patients
- Increased serum creatine kinase isoenzyme MM test in 2 patients
- Decreased serum calcium in 1 patient
- Decreased serum glucose in 1 patient
- Decreased serum albumin in 1 patient
- Increased serum creatine kinase isoenzyme BB test in 1 patient
- Increased serum creatinine in 1 patient

Grade 4 hematology laboratory abnormalities:

- Decreased absolute lymphocytes in 11 patients
- Decreased platelet counts in 9 patients
- Decreased hemoglobin in 3 patients

Grade 3 hemostatic function abnormalities included: prolonged aPTT in 2 patients and increased INR in 1 patient.

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Table 145. Laboratory Abnormalities by Grade (Vorinostat Monotherapy – Solid Tumors) (Applicant's Table)

Laboratory Test	400mg qd 7d/wk						all other monotherapies							
	N	Grades					Total n (%)	N	Grades					Total n (%)
		1	2	3	4	5			1	2	3	4		
blood chemistry test														
decreased serum calcium	39	11	2	0	0	13 (33.3)	61	21	5	1	0	27 (44.3)		
decreased serum glucose	39	1	0	0	0	1 (2.6)	45	3	0	1	0	4 (8.9)		
decreased serum magnesium	27	0	0	0	0	0 (0.0)	38	0	0	0	0	0 (0.0)		
decreased serum potassium	39	4	0	0	0	4 (10.3)	61	14	0	3	0	17 (27.9)		
decreased serum sodium	39	20	0	5	0	25 (64.1)	61	17	0	6	1	24 (39.3)		
fasting serum glucose	0	0	0	0	0	0 (0.0)	18	11	3	2	0	16 (100.0)		
increased serum calcium	39	2	0	0	0	2 (5.1)	61	3	0	2	0	5 (8.2)		
increased serum glucose	39	7	7	2	0	16 (41.0)	45	25	14	6	0	45 (100.0)		
increased serum magnesium	27	4	0	3	0	7 (25.9)	38	9	0	0	0	9 (23.5)		
increased serum potassium	39	6	0	0	0	6 (15.4)	61	8	6	2	0	16 (26.2)		
increased serum sodium	39	0	0	0	0	0 (0.0)	61	10	0	0	0	10 (16.4)		
serum alanine aminotransferase	39	3	0	0	0	3 (7.7)	61	20	1	3	0	23 (37.7)		
serum albumin	39	18	6	1	0	24 (61.5)	61	31	11	1	0	43 (70.5)		
serum alkaline phosphatase	39	15	3	1	0	19 (48.7)	61	21	9	8	0	38 (62.3)		
serum aspartate aminotransferase	39	5	0	1	0	6 (15.4)	61	25	1	2	0	28 (45.9)		
serum bicarbonate	39	13	0	0	0	13 (33.1)	17	3	0	0	0	3 (17.6)		
serum creatine kinase	0	0	0	0	0	0 (0.0)	7	5	0	2	2	7 (100.0)		
serum creatine kinase isoenzyme	0	0	0	0	0	0 (0.0)	1	0	1	0	0	1 (100.0)		
serum creatine kinase isoenzyme BB test	0	0	0	0	0	0 (0.0)	1	0	0	1	0	1 (100.0)		
serum creatine kinase isoenzyme MM test	0	0	0	0	0	0 (0.0)	1	0	2	0	0	2 (100.0)		
serum creatinine	39	11	9	1	0	21 (53.8)	61	29	8	1	0	38 (62.3)		
serum phosphorus	14	2	0	0	0	2 (14.3)	25	0	4	2	0	6 (24.0)		
serum uric acid	39	3	0	0	0	3 (7.7)	15	1	0	0	0	2 (13.3)		
total serum bilirubin	39	3	3	1	0	7 (17.9)	61	16	2	0	1	19 (31.1)		
total serum protein	39	7	0	0	0	7 (17.9)	61	0	0	0	0	0 (0.0)		
hematology laboratory test														
WBC count	38	10	2	0	0	12 (31.6)	61	11	5	0	0	16 (26.2)		
absolute lymphocyte count	17	1	3	5	0	9 (52.9)	60	9	3	11	0	23 (38.3)		
absolute neutrophil count	17	0	0	0	0	0 (0.0)	61	1	4	0	0	5 (8.2)		
hemoglobin	38	20	11	1	1	33 (86.8)	61	30	22	3	1	56 (91.8)		
lymphocyte count	37	1	4	4	1	10 (27.0)	45	0	0	0	0	0 (0.0)		
platelet count	38	16	0	5	1	22 (57.9)	61	11	8	9	3	31 (50.8)		
hemostatic function test														
APTT	26	6	0	0	0	6 (23.1)	60	21	3	2	0	26 (43.3)		
INR	25	2	2	0	0	4 (16.0)	45	20	2	1	0	23 (51.1)		
plasma fibrinogen test	1	1	0	0	0	1 (100.0)	0	0	0	0	0	0 (0.0)		
prothrombin time	25	10	0	0	0	10 (40.0)	60	2	0	0	0	2 (3.3)		
urinalysis test														
urine RBC count	25	0	0	0	0	0 (0.0)	50	7	0	0	0	7 (14.0)		
urine protein	21	0	0	0	0	0 (0.0)	16	1	1	0	0	2 (12.5)		

N: number of patients who had the lab test during treatment.
 If a patient had more than one graded abnormality for a lab test, only the highest grade is counted.
 [Ref. 5.3.3.2: P008] [Ref. 5.3.3.4: P002, P006, P011V1]

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Evaluation by Clinical Laboratory Shift Analysis (Vorinostat Monotherapy – Solid Tumors)

The following table summarizes the laboratory shift data. The number of patients (M) *who had a change in at least 1 post-baseline value* is compared to the number of all patients *who had at least 1 post-baseline value* for the laboratory test (N).

400 mg Once Daily

Serum creatinine

- Thirty-nine (39) patients in this treatment group had post-baseline serum creatinine values, 19 (49%) developed worsening of grade level—increased serum creatinine from the baseline, and in 2 patients grade shifts were clinically meaningful.
- Four (4) of the 19 patients (21%) worsened and then improved on subsequent laboratory testing, 2 to Grade 1 and 1 to Grade 0, and 15 showed no change.
- Three (3) patients who had improved post-baseline serum creatinine changes did so without any action taken in regard to Vorinostat treatment.

Serum glucose

- Post-baseline serum glucose tests were performed in 27 patients in this treatment group, 10 (37%) had changes in their post-baseline serum glucose that were worse, and in 3 of these 10 patients the changes were clinically meaningful.
- Five (5) of the 10 patients worsened and then improved on subsequent testing, 3 improved to Grade 1, one improved to Grade 0, and 5 showed no further change.
- Four (4) patients improved without any action taken in regard to Vorinostat treatment.

Hemoglobin

- Thirty-eight (38) patients in this treatment group had post-baseline hemoglobin tests and 23 (60%) experienced worsening of grade level from the baseline, in 3 patients the grade shifts were clinically meaningful.
- Fourteen (14) of the 23 patients who had post-baseline changes in hemoglobin values, worsened and then improved with subsequent tests, 3 improved to Grade 1 and 10 improved to Grade 0, and 9 showed no additional post-baseline changes.
- Twelve (12) patients improved without any action taken in regard to Vorinostat therapy, and one improved after dose interruption or dose modification of Vorinostat treatment.

Platelets

- Thirty-eight (38) patients in this treatment group had post-baseline platelet counts, 19 (50%) experienced worsening of grade level from the baseline, and in 6 grade shifts were clinically meaningful.

- Eight (8) of the 19 patients worsened and then improved at subsequent testing, 2 improved to Grade 1, and 6 improved to Grade 0, and 11 showed no further changes.
- Seven (7) patients improved with no action taken in regard to Vorinostat treatment, and 1 improved after dose interruption or dose modification of Vorinostat treatment.

Serum potassium

- Hyperkalemia was reported under adverse experiences for this population in the safety section

Serum calcium

- Eleven (11) patients had post-baseline increased serum calcium values; however, there were no clinically meaningful shifts.

AST

- 39 patients had post-baseline serum AST and 5 (13%) had increased post-baseline AST values: 1 of the 5 patients improved and 4 patients worsened, but only 1 patient had a clinically meaningful shift.
- Two patients worsened and then improved on later testing to grade 0, and 2 showed no change. These 2 patients improved with no action taken in regard to Vorinostat therapy.

300 mg Twice Daily 3 Out of 7 Days

Serum glucose

- Eleven (11) patients had post-baseline serum glucose values, 8 (73%) had increased levels, and in 3 these were clinically meaningful shifts.
- Seven (7) of the 8 patients worsened and then improved with subsequent tests, and 1 showed no further change.
- Six (6) patients improved to Grade 0 with no action taken in regard to Vorinostat treatment.

Hemoglobin

- Thirteen (13) patients in this treatment group had post-baseline hemoglobin tests, 8 (61.5%) experienced a worsening of grade level, and 3 patients had clinically meaningful grade shifts.
- Three (3) patients worsened and then improved with subsequent tests, 2 improved to Grade 1 and 1 improved to Grade 0, and 5 showed no change.
- Two (2) patients improved with no action taken in regard to Vorinostat treatment and 1 patient improved with dose interruption or dose modification.

Serum creatinine, AST, platelet count

- Thirteen (13) patients had post-baseline serum creatinine values, serum aspartate aminotransferase, and platelet counts. Four (4) of the 13 patients (31%) had post-baseline changes that showed worsening; however, there were no clinically meaningful shifts.

200 mg Twice Daily

Serum creatinine

- Four (4) patients in this treatment group had post-baseline serum creatinine values, 2 showed worsening, and 1 of these 2 patients had a clinically meaningful shift.
- One (1) of the 2 patients improved to grade 1 with subsequent tests and 1 showed no change. The patient improved did so with no action taken in regard to Vorinostat treatment.

Serum glucose

- Three (3) patients in this treatment group had post-baseline serum glucose values, all were patients worsened from the baseline, and 1 had a clinically meaningful shift.
- Two (2) of 3 patients worsened and then improved to grade 1 with no action taken in regard to study therapy at subsequent tests, and 1 showed no change.

Hemoglobin

- Four (4) patients in this treatment group had post-baseline hemoglobin values, 1 worsened compared to the baseline; however, a clinically meaningful shift did not occur.

Platelets

- Four (4) patients in this treatment group had post-baseline platelet counts, 2 had worsening in their post-baseline values and had clinically meaningful shifts.
- One (1) of the 2 patients worsened and then improved to grade 1 with no action taken in regard to Vorinostat treatment at subsequent testing, and 1 showed no further change.

AST

- Four patients in this treatment group had post-baseline increased serum aspartate aminotransferase values. One (1) of the 4 patients had changes that were worse from the baseline; however, a clinically meaningful shift did not occur.

Doses above the MTD

Serum creatinine

- Thirty-eight (38) patients at this dose had post-baseline serum creatinine values, 15 (40%) had post-baseline values that were worse, and 4 of these 15 patients had clinically meaningful grade shifts.
- Nine (9) worsened and then improved with subsequent tests, 2 improved to Grade 1 and 6 improved to Grade 0, and 6 showed no additional change.
- Six (6) patients improved with no action taken in regard to Vorinostat treatment, and 2 improved after dose interruption or dose modification of Vorinostat treatment.

Serum glucose

- Fifteen (15) patients at this dose level had post-baseline serum glucose values, 12 (80%) experienced worsening of grade level from the baseline, and 3 had clinically meaningful grade shifts.
- Six (6) of the 12 patients worsened and then improved with subsequent tests, and 6 showed no further change.
- Two (2) of the 12 patients improved to Grade 1, and 3 improved to Grade 0.
- Three (3) of the 12 patients improved with no action taken in regard to Vorinostat treatment, and 2 after dose interruption or dose modification of Vorinostat treatment.

Hemoglobin

- Thirty-eight (38) patients in this treatment group had post-baseline hemoglobin values, 16 (42%) had changes, and in 15 there was worsening of grade level from the baseline. Four (4) of the 16 patients who had post-baseline hemoglobin changes had clinically meaningful grade shifts.
- Six (6) patients worsened and then improved on subsequent testing, 1 improved to Grade 1 and 3 improved to Grade 0, and 9 patients showed no further changes.
- Three (3) patients improved with no action taken in regard to Vorinostat therapy and 1 patient improved with dose interruption or dose modification of Vorinostat treatment.

Platelets

- Thirty-eight (38) patients in this treatment group had post-baseline platelet counts, 20 (53%) experienced changes in their post-baseline platelet values; in 19 patients the platelet change was worse, and 14 had clinically meaningful grade shifts.
- Fourteen (14) patients worsened and then improved with subsequent tests, 1 improved to Grade 1 and 10 improved to Grade 0, and 5 showed no further change.
- Nine (9) patients improved with no action taken in regard to Vorinostat treatment and 2 improved after dose interruption or dose modification of Vorinostat treatment.

Table 146. Summary of Shifts in Laboratory Parameters from the Baseline to the Worst Post-baseline Value to Last Value (Vorinostat Monotherapy – Solid Tumor) (Applicant's Table)

Parameter and Treatment Group	N ¹¹	M ¹¹	Number(%) of Subjects										
			Change in CTCAE Grade ¹ from Baseline to Worst Value Postbaseline			Change in CTCAE Grade from Worst Value Postbaseline to Last Value Postbaseline							
			Improved ²	Worsened	Clinically Meaningful Shift ³	Consistent Improvement from Baseline ⁴	Worsened and then Improved ⁴	No Change ⁴	Grade 1	Grade 0	Improved to Grade 0 or Grade 1 ⁵ Without Any Change in Therapy	With Dose Interruption or Modification	Associated With Stopping Therapy
fasting serum glucose													
Doses above MTD	16	15	2(12.5)	13(81.3)	5(31.3)	0(0.0)	5(31.3)	8(50.0)	3(18.8)	3(20.0)	5(31.3)	0(0.0)	0(0.0)
hemoglobin													
200mg BID continuous	4	1	0(0.0)	3(100.0)	0(0.0)	0(0.0)	3(100.0)	0(0.0)	0(0.0)	3(100.0)	1(33.3)	0(0.0)	0(0.0)
300mg BID 3-7	13	8	0(0.0)	8(100.0)	3(37.5)	0(0.0)	3(37.5)	5(62.5)	2(25.0)	1(12.5)	2(25.0)	1(12.5)	0(0.0)
400mg QD continuous	38	23	0(0.0)	23(100.0)	3(13.6)	0(0.0)	14(60.9)	9(39.1)	3(13.0)	10(43.5)	12(52.2)	1(4.3)	0(0.0)
Doses above MTD	38	18	1(2.6)	15(39.5)	4(25.0)	0(0.0)	9(56.5)	1(6.3)	3(18.8)	3(18.8)	1(6.3)	0(0.0)	0(0.0)
platelet count													
200mg BID continuous	4	2	0(0.0)	2(100.0)	2(100.0)	0(0.0)	1(50.0)	1(50.0)	1(50.0)	0(0.0)	1(50.0)	0(0.0)	0(0.0)
300mg BID 3-7	13	4	0(0.0)	4(100.0)	0(0.0)	0(0.0)	1(25.0)	3(75.0)	0(0.0)	1(25.0)	1(25.0)	0(0.0)	0(0.0)
400mg QD continuous	38	19	0(0.0)	19(100.0)	6(31.6)	0(0.0)	8(42.1)	11(57.9)	2(10.5)	6(31.6)	7(36.8)	1(5.3)	0(0.0)
Doses above MTD	38	20	1(2.6)	19(95.0)	14(70.0)	0(0.0)	14(70.0)	5(25.0)	1(5.0)	10(50.0)	8(40.0)	2(10.0)	0(0.0)
serum aspartate aminotransferase													
200mg BID continuous	4	1	0(0.0)	3(100.0)	0(0.0)	0(0.0)	3(100.0)	0(0.0)	0(0.0)	3(100.0)	1(100.0)	0(0.0)	0(0.0)
300mg BID 3-7	13	4	0(0.0)	4(100.0)	0(0.0)	0(0.0)	4(100.0)	0(0.0)	0(0.0)	4(100.0)	4(100.0)	0(0.0)	0(0.0)
400mg QD continuous	38	5	1(20.0)	4(80.0)	1(20.0)	0(0.0)	2(40.0)	2(40.0)	0(0.0)	2(40.0)	2(40.0)	0(0.0)	0(0.0)
Doses above MTD	38	10	1(10.0)	9(90.0)	3(30.0)	0(0.0)	4(40.0)	5(50.0)	0(0.0)	3(30.0)	3(30.0)	0(0.0)	0(0.0)
Doses below MTD	6	1	0(0.0)	5(100.0)	0(0.0)	0(0.0)	0(0.0)	5(100.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
serum calcium - decreased													
200mg BID continuous	4	2	0(0.0)	2(100.0)	0(0.0)	0(0.0)	2(100.0)	0(0.0)	0(0.0)	2(100.0)	2(100.0)	0(0.0)	0(0.0)
300mg BID 3-7	11	6	0(0.0)	6(100.0)	0(0.0)	0(0.0)	4(66.7)	2(33.3)	0(0.0)	4(66.7)	3(50.0)	1(16.7)	0(0.0)
400mg QD continuous	27	11	1(9.1)	10(90.9)	2(18.2)	0(0.0)	6(54.5)	4(36.4)	0(0.0)	6(54.5)	6(54.5)	0(0.0)	0(0.0)
Doses above MTD	31	11	0(0.0)	11(100.0)	4(36.4)	0(0.0)	6(54.5)	5(45.5)	1(9.1)	5(45.5)	5(45.5)	1(9.1)	0(0.0)
serum calcium - increased													
400mg QD continuous	11	1	0(0.0)	1(100.0)	0(0.0)	0(0.0)	1(100.0)	0(0.0)	0(0.0)	1(100.0)	1(100.0)	0(0.0)	0(0.0)
Doses above MTD	7	2	0(0.0)	2(100.0)	1(50.0)	0(0.0)	1(50.0)	1(50.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Doses below MTD	1	1	0(0.0)	1(100.0)	0(0.0)	0(0.0)	1(100.0)	0(0.0)	0(0.0)	1(100.0)	1(100.0)	0(0.0)	0(0.0)
serum creatinine													
200mg BID continuous	4	2	0(0.0)	2(100.0)	1(50.0)	0(0.0)	1(50.0)	1(50.0)	1(50.0)	0(0.0)	1(50.0)	0(0.0)	0(0.0)
300mg BID 3-7	13	4	0(0.0)	4(100.0)	0(0.0)	0(0.0)	1(25.0)	3(75.0)	1(25.0)	0(0.0)	1(25.0)	0(0.0)	0(0.0)
400mg QD continuous	38	19	0(0.0)	19(100.0)	2(10.5)	0(0.0)	4(21.1)	15(78.5)	2(10.5)	15(78.5)	3(15.8)	0(0.0)	0(0.0)
Doses above MTD	38	15	0(0.0)	15(100.0)	4(26.7)	0(0.0)	5(60.0)	6(40.0)	2(13.3)	8(40.0)	6(40.0)	2(13.3)	0(0.0)
Doses below MTD	4	1	0(0.0)	1(100.0)	0(0.0)	0(0.0)	1(100.0)	0(0.0)	0(0.0)	1(100.0)	1(100.0)	0(0.0)	0(0.0)
serum glucose - decreased													
300mg BID 3-7	2	1	0(0.0)	1(100.0)	0(0.0)	0(0.0)	1(100.0)	0(0.0)	0(0.0)	1(100.0)	1(100.0)	0(0.0)	0(0.0)
400mg QD continuous	11	1	0(0.0)	1(100.0)	0(0.0)	0(0.0)	0(0.0)	1(100.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
serum glucose - increased													
200mg BID continuous	5	5	0(0.0)	5(100.0)	1(20.0)	0(0.0)	2(40.0)	1(20.0)	2(40.0)	0(0.0)	2(40.0)	0(0.0)	0(0.0)
300mg BID 3-7	11	5	0(0.0)	5(100.0)	3(60.0)	0(0.0)	3(60.0)	2(40.0)	1(20.0)	0(0.0)	2(40.0)	0(0.0)	0(0.0)
400mg QD continuous	27	10	0(0.0)	10(100.0)	3(30.0)	0(0.0)	5(50.0)	5(50.0)	3(30.0)	3(30.0)	4(40.0)	0(0.0)	0(0.0)
Doses above MTD	15	12	0(0.0)	12(100.0)	3(25.0)	0(0.0)	4(50.0)	6(50.0)	2(16.7)	3(25.0)	3(25.0)	0(0.0)	0(0.0)
Doses below MTD	3	2	0(0.0)	2(100.0)	0(0.0)	0(0.0)	1(50.0)	1(50.0)	1(50.0)	0(0.0)	1(50.0)	0(0.0)	0(0.0)

¹ Based on NCI CTCAE, Version 3.0
² A clinically meaningful shift in CTCAE grade was defined as a shift from less than Grade 3 to Grade 3 or 4 or 5 OR a shift from Grade 0 to Grade 2.
³ Includes subjects from the column labeled "Improved".
⁴ Includes subjects from the column labeled "Worsened".
⁵ Includes subjects from the column labeled "Consistent improvement from baseline" and "Worsened and then improved".
¹¹ Number of patients who improved from baseline based on worst postbaseline.
¹² Number of patients with at least 1 postbaseline value. Patients without any changes from baseline are included.

[Ref. 5.3.3.2; P008] [Ref. 5.3.5.4; P002; P006; P011V1]

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Vorinostat Monotherapy – Hematologic Malignancies

Summary Comparison of Clinical Laboratory Evaluations (Vorinostat Monotherapy – Hematologic Malignancies)

- Analysis of clinical laboratory tests, regardless of grade, showed similar results for patients in the Hematologic Malignancies population that received Vorinostat at 400 mg once daily and that received all the other doses of Vorinostat.
- **Similar** to the CTCL population, *clinically meaningful grade shifts* in laboratory abnormalities were seen in increased serum glucose, increased serum creatinine, decreased hemoglobin, and decreased platelets.
- However, *clinically meaningful grade shifts* in laboratory abnormalities were seen at a **higher frequency** for decreased white blood cell counts, absolute neutrophil count, increased serum alanine aminotransferase, decreased albumin, decreased calcium, decreased phosphorus, decreased potassium, decreased sodium and decreased total bilirubin in the patients in the hematologic malignancies population who received Vorinostat at doses above the MTD.

Evaluation by Highest CTCAE Grade (Vorinostat Monotherapy – Hematologic Malignancies)

The following table summarizes laboratory abnormalities by the highest grade for patients in this population.

400 mg Once Daily

The most common *serum chemistry* abnormalities, *regardless of grade*, listed in order of decreasing frequency, in patients in this treatment group were:

- | | |
|--|-------|
| ○ Decreased serum albumin in 10 of 11 patients | 90.9% |
| ○ Increased serum glucose in 10 of 11 patients | 90.9% |
| ○ Increased serum creatinine in 10 of 11 patients | 90.9% |
| ○ Increased serum aspartate aminotransferase in 6 of 11 patients | 54.5% |
| ○ Decreased serum sodium in 6 of 11 patients | 54.5% |
| ○ Decreased serum calcium in 6 of 11 patients | 54.5% |
| ○ Increased serum alkaline phosphatase in 5 of 11 patients | 45.5% |
| ○ Increased serum alanine aminotransferase in 5 of 11 patients | 45.5% |

The most common *hematology* abnormalities:

- | | |
|--|-------|
| ○ Decreased hemoglobin in all patients | 100% |
| ○ Decreased platelet count in 9 of 11 patients | 81.8% |
| ○ Decreased white blood cell count in 7 of 11 patients | 63.6% |

Of the 11 patients with *hemostatic function* test, 9 patients (81.8%) had increased INR.

There was no *urine abnormality* reported at this dose in this population.

No *Grade 3 or Grade 4 serum chemistry* laboratory abnormalities were seen in this treatment group.

Grade 4 hematology abnormalities include:

- Decreased platelet count in 2 patients
- Decreased WBC in 1 patient
- Decreased absolute neutrophil count in 1 patient
- Decreased hemoglobin in 1 patient

One (1) patient experienced *Grade 3 hemostatic function* test of increased INR.

Vorinostat Therapy at All Other Doses

The most common *serum chemistry* abnormalities, *regardless of grade*, in the patient population that received all other doses of Vorinostat:

- | | |
|---|-------|
| ○ Increased serum glucose in 72 of 76 patients | 94.7% |
| ○ Decreased serum albumin in 46 of 76 patients | 60.5% |
| ○ Decreased serum calcium in 38 of 76 patients | 50.0% |
| ○ Increased serum alkaline phosphatase in 35 of 76 patients | 46.1% |
| ○ Increased serum creatinine in 34 of 76 patients | 44.7% |
| ○ Decreased serum potassium in 34 of 76 patients | 44.7% |
| ○ Increased serum aspartate aminotransferase in 30 of 75 patients | 40.0% |
| ○ Increased serum alanine aminotransferase in 27 of 76 patients | 35.5% |
| ○ Decreased serum sodium in 27 of 76 patients | 35.5% |
| ○ Decreased serum phosphorus in 24 of 73 patients | 32.9% |

The most common *hematology* abnormalities in this population:

- | | |
|---|-------|
| ○ Decreased hemoglobin in 75 of 76 patients | 98.7% |
| ○ Decreased platelet count in 67 of 76 patients | 88.2% |

Grade 4 serum chemistry laboratory abnormalities:

- Decreased serum potassium in 2 patients
- Decreased serum phosphorus in 1 patient

Grade 3 serum chemistry laboratory abnormalities in order of decreasing frequency:

- Increased serum glucose in 11 patients
- Decreased serum phosphorus in 11 patients

- Decreased serum potassium in 10 patients
- Decreased serum sodium in 10 patients
- Increased serum alanine aminotransferase in 2 patients
- Increased serum aspartate aminotransferase in 2 patients
- Decreased serum calcium in 1 patient
- Increased serum uric acid in 1 patient
- Increased total serum bilirubin in 1 patient

Grade 3 and 4 hematology laboratory abnormalities occurred at a higher frequency in this treatment group.

Grade 4 abnormalities included:

- Decreased platelet count in 44 patients
- Decreased absolute neutrophil count in 35 patients
- Decreased WBC in 12 patients
- Decreased hemoglobin in 6 patients

Grade 3 abnormalities included:

- Decreased absolute lymphocyte count in 23 patients
- Decreased hemoglobin in 22 patients
- Decreased WBC in 19 patients
- Decreased absolute neutrophil count in 7 patients
- Decreased platelet count in 4 patients
- Decreased lymphocyte count in 3 patients
- Decreased neutrophil count in 3 patients

Two patients experienced *Grade 3 hemostatic function* test of increased INR.

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Table 147. Laboratory Abnormalities by Grade (Vorinostat Monotherapy – Hematologic malignancies) (Applicant's Table)

Laboratory Test	400mg qd 7d/wk					Total n (%)	all other monotherapies					Total n (%)
	N	Grades					N	Grades				
		1	2	3	4		1	2	3	4		
blood chemistry test												
decreased serum calcium	11	3	3	0	0	6 (54.5)	76	19	18	1	0	38 (50.0)
decreased serum glucose	11	1	0	0	0	1 (9.1)	76	3	0	0	0	3 (3.9)
decreased serum magnesium	11	0	2	0	0	2 (18.2)	31	9	0	0	0	9 (29.0)
decreased serum potassium	11	3	0	0	0	3 (27.3)	76	22	0	10	2	34 (44.7)
decreased serum sodium	11	6	0	0	0	6 (54.5)	76	19	0	8	0	27 (35.5)
increased serum calcium	11	0	1	0	0	1 (9.1)	76	4	1	0	0	5 (6.6)
increased serum glucose	11	5	5	0	0	10 (90.9)	76	29	33	11	0	73 (94.7)
increased serum magnesium	11	1	0	0	0	1 (9.1)	31	8	0	0	0	8 (25.8)
increased serum potassium	11	0	0	0	0	0 (0.0)	76	7	2	0	0	9 (11.8)
increased serum sodium	11	0	0	0	0	0 (0.0)	76	5	1	0	0	6 (7.9)
serum alanine aminotransferase	11	2	3	0	0	5 (45.5)	76	20	5	2	0	27 (35.5)
serum albumin	11	9	1	0	0	10 (90.9)	76	28	18	0	0	46 (60.5)
serum alkaline phosphatase	11	5	0	0	0	5 (45.5)	76	29	5	0	0	35 (46.1)
serum aspartate aminotransferase	11	6	0	0	0	6 (54.5)	76	23	3	2	0	30 (40.0)
serum creatinine	11	8	2	0	0	10 (90.9)	76	33	11	0	0	44 (44.7)
serum gamma glutamyl transferase	6	0	0	0	0	0 (0.0)	10	2	0	0	0	2 (20.0)
serum phosphorus	6	0	3	0	0	3 (50.0)	73	3	10	11	1	24 (32.9)
serum uric acid	3	0	0	0	0	0 (0.0)	68	3	0	1	0	4 (5.9)
total serum bilirubin	11	3	0	0	0	3 (27.3)	76	11	10	1	0	22 (28.9)
total serum carbon dioxide	11	0	0	0	0	0 (0.0)	76	16	3	0	0	19 (25.0)
clinical microbiology test												
blood culture	0	0	0	0	0	0 (0.0)	1	0	0	1	0	1 (100.0)
hematology laboratory test												
WBC count	11	2	3	1	1	7 (63.6)	76	9	13	16	12	50 (65.7)
absolute lymphocyte count	11	0	0	5	0	5 (45.5)	51	6	6	23	1	36 (70.6)
absolute neutrophil count	11	0	1	0	1	2 (18.2)	59	2	5	7	55	69 (83.1)
hemoglobin	11	4	3	3	1	11 (100.0)	76	19	18	23	6	75 (98.7)
lymphocyte count	11	0	0	0	0	0 (0.0)	76	0	2	3	0	5 (6.6)
mean corpuscular hemoglobin conc	0	0	0	0	0	0 (0.0)	9	1	0	0	0	1 (11.1)
neutrophil count	11	0	0	0	0	0 (0.0)	76	2	0	3	0	5 (6.6)
platelet count	11	5	1	1	2	9 (81.8)	76	9	10	4	4	67 (88.2)
hemostatic function test												
APTT	11	5	2	0	0	7 (63.6)	66	7	0	2	0	9 (13.6)
INR	11	7	1	1	0	9 (81.8)	26	7	1	0	0	8 (30.8)
laboratory test												
hemostatic function test	0	0	0	0	0	0 (0.0)	1	1	0	0	0	1 (100.0)

N: number of patients who had the lab test during treatment.
 If a patient had more than one graded abnormalities for a lab test, only the highest grade is counted.
 [Ref: S.3.S.4; P063V1, P064V1, P066, P013V1]

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Evaluation by Clinical Laboratory Shift Analysis (Vorinostat Monotherapy – Hematologic Malignancies)

The following table is a summary of the shift in laboratory parameters from the baseline compared to the worst post-baseline value in the Vorinostat Monotherapy – Hematologic Malignancies Population.

400 mg Once Daily

Serum glucose

- Six (6) patients at this dose level had post-baseline serum glucose values and all 6 experienced a worsening of the grade level from the baseline. However, only 2 of the 6 patients had *clinically significant* grade shifts.
- Five (5) of the 6 patients worsened and then improved with subsequent tests, all 5 improved to Grade 0, and 1 showed no further change.
- Four (4) patients improved with no action taken in regard to Vorinostat treatment, and 1 patient improved with dose interruption or dose modification of Vorinostat treatment.

Serum creatinine

- Eleven (11) patients in this treatment group had post-baseline serum creatinine values, 5 (45.5%) had a worsening of the grade level; however, there were no *clinically significant* grade shifts. Three patients worsened and then improved with subsequent tests to grade 0, and 2 showed no further changes.
- Two (2) patients improved with no action taken in regard to Vorinostat treatment, and 1 with dose interruption or dose modification of Vorinostat treatment.

Hemoglobin

- Eleven (11) patients in this treatment group had post-baseline hemoglobin values and 5 (45.5%) had worsening of the grade level from the baseline values—in 4 patients there were *clinically meaningful* grade shifts.
- Four (4) patients worsened and then improved with subsequent tests, 2 improved to Grade 1, one patient showed no further change.
- One patient improved with no action taken in regard to Vorinostat treatment, and 1 patient improved with dose interruption or dose modification of Vorinostat treatment.

Platelet count

- Eleven (11) patients in this treatment group had post-baseline platelet counts and 6 patients (54.5%) experienced changes, all 6 had a worsening from the baseline, 2 of these 6 had *clinically meaningful* grade shifts.
- One (1) of the 6 patients worsened and then improved with subsequent tests to grade 0 after dose modification of Vorinostat, and 5 patients showed no change.

300 mg Twice Daily, 3 of 7 Days

- Three (3) patients in this treatment group had post-baseline **hemoglobin** values and 2 had worsening of the hemoglobin values, 1 of these was a clinically meaningful shift.
- One (1) of the 2 patients worsened and then improved with subsequent tests to grade 1, without any action taken in regard to Vorinostat treatment, and 1 patient showed no further change..

200 mg Twice Daily

- Six (6) patients in this treatment group had post-baseline **platelet counts**, 4 had worsening in the platelet counts, and all were considered clinically meaningful shifts.
- All 4 of the patients worsened and then improved, 3 improved to CTCAE Grade 1, two (2) without any action taken in regard to Vorinostat therapy.

200 mg Twice Daily, 14 Out Of 21 Days

Serum glucose

- Nine patients at this dose level had post-baseline serum glucose levels, 8 patients had changes from the baseline—all were worse, and in 3 of the 8 these were *clinically meaningful* grade shifts.
- Six (6) of the 8 patients worsened and then improved with subsequent tests, 2 improved to Grade 1 and 2 improved to Grade 0, and 2 showed no further change.
- Three (3) patients improved with no action taken in regard to Vorinostat treatment and 1 with discontinuation of Vorinostat treatment.

Serum creatinine

- Ten (10) patients in this treatment group had post-baseline serum creatinine levels, 3 of the 10 patients (30%) had post-baseline increase in serum creatinine values, and 1 of these 3 patients had a clinically meaningful grade shift.
- One (1) of 3 patients improved to Grade 1, and 2 patients improved to Grade 0.
- Two (2) patients improved with no action taken in regard to Vorinostat treatment and 1 patient improved with discontinuation of Vorinostat treatment.

Hemoglobin

- Ten (10) patients in this treatment group had post-baseline hemoglobin levels available for comparison and 8 of these 10 patients (80%) had changes in their post-baseline hemoglobin. One (1) of the 8 patients showed improvement and 7 patients had worsening of hemoglobin values, 5 of these were clinically meaningful grade shifts.
- Six (6) patients worsened and then improved with subsequent tests, 3 improved to Grade 1 and one (1) showed no further change.

- Three (3) improved with no action taken in regard to Vorinostat therapy.

Platelets

- Ten (10) patients in this dose level had post-baseline platelet counts and 5 (50%) had worsening in their platelet counts, 1 was a clinically meaningful grade shift.
- Four (4) of the 5 patients with changes in post-baseline platelet counts worsened and then improved at subsequent tests, and 1 showed no further change.
- Two (2) patients improved to Grade 0 with no action taken in regard to Vorinostat treatment.

Doses above the MTD

In contrast to the previous populations, the Hematologic Malignancies group had clinically meaningful grade shifts in laboratory tests that occurred with high frequency in patients who received Vorinostat at doses above MTD. Details of the shifts for WBC, absolute lymphocyte count, absolute neutrophil count, serum alanine aminotransferase, serum albumin, serum calcium, serum phosphorus, serum potassium, serum sodium, total serum bilirubin and total serum carbon dioxide are shown in the table below.

Serum glucose

- Thirty-eight (38) of the 51 patients in this treatment group had post-baseline serum glucose values, 37 of the 38 patients (97%) had post-baseline changes in their serum glucose levels, all 37 had post-baseline worsening, and in 21 of these 37 patients (57%) grade shifts were clinically meaningful.
- Twenty-eight 28 of the 37 (76%) patients who had worsened, improved on subsequent testing, 11 improved to Grade 1 and 14 improved to Grade 0, and 9 showed no further change.
- Sixteen (16) patients improved with no action taken in regard to Vorinostat treatment, 2 patients improved with dose interruption or dose modification, and 7 improved with discontinuation of Vorinostat treatment.

Serum creatinine

- Fifty-one (51) patients in this treatment group had post-baseline serum creatinine values, 16 of the 51 patients (31%) experienced a worsening of grade level from the baseline, and in 1 of these 16 patients (6%) grade shift was clinically significant.
- Six (6) of the 16 patients (37%) showed no further change, 8 (50%) improved to Grade 0, and 2 of 16 (12%) improved to Grade 1.
- Nine (9) of the 16 patients who had post-baseline changes in serum creatinine improved with no action taken in regard to Vorinostat treatment, and 1 patient improved after dose interruption or dose modification of Vorinostat treatment.

Hemoglobin

- Fifty-one (51) patients in this dose level had post-baseline hemoglobin values, 32 of the 51 (63%) had changes post-baseline, thirty (30) of these 32 patients had worsening of grade level; in 17 patients grade shifts were clinically meaningful.
- Eighteen (18) patients worsened and then improved with subsequent tests, 6 improved to Grade 1 and 5 improved to Grade 0.
- Nine patients improved with no action taken in regard to Vorinostat treatment, 1 improved with dose interruption or dose modification, 1 improved with discontinuation of Vorinostat treatment.

Platelet counts

- Thirty-one (31) of 51 the patients who received Vorinostat at doses above MTD had a worsening of grade level from baseline in platelet counts, and in 17 of 31 patients these grade shifts were clinically significant.
- Twenty (20) patients (65%) worsened and then improved, 2 improved to CTCAE Grade 1 and 8 patients improved to within normal laboratory range—these 8 patients had no action taken in regard to Vorinostat therapy.

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Parameter and Treatment Group	N ¹¹	M ¹²	Number(s) of Subjects														
			Change in CTCAE Grade ¹ from Baseline to Worst Value Postbaseline			Change in CTCAE Grade from Worst Value Postbaseline to Last Value Postbaseline											
			Improved ¹³	Worsened	Clinically Meaningful Shift ¹⁴	Consistent Improvement from Baseline ¹⁵	Worsened and then Improved ¹⁶	No Change ¹⁷	Improved to Grade 0 or Grade 1 ¹⁸			Without Any Change in Therapy	With Dose Interruption or Modification	Associated With Stopping Therapy			
									Grade 1	Grade 0	Grade 0						
total serum carbon dioxide																	
100mg BID 14.7	10	2	0(0.0)	2(100.0)	0(0.0)	0(0.0)	2(100.0)	0(0.0)	0(0.0)	2(100.0)	0(0.0)	2(100.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
300mg BID 14.7	3	1	0(0.0)	1(100.0)	1(100.0)	0(0.0)	0(0.0)	0(0.0)	1(100.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Dose: above MID	51	14	0(0.0)	14(100.0)	1(7.1)	0(0.0)	1(64.3)	5(35.7)	1(7.1)	8(57.1)	6(42.9)	2(14.3)	0(0.0)	1(7.1)	0(0.0)	0(0.0)	1(7.1)

¹¹Based on NCI CTCAE, Version 3.0
¹²A clinically meaningful shift in CTCAE grade was defined as a shift from less than Grade 3 to Grade 3 or 4 or 5 OR a shift from Grade 0 to Grade 1.
¹³Includes subjects from the column labeled "Improved".
¹⁴Includes subjects from the column labeled "Worsened".
¹⁵Includes subjects from the column labeled "Consistent improvement from baseline" and "Worsened and then improved".
¹⁶Number of patients who improved from baseline based on worst postbaseline.
¹⁷Number of patients with at least 1 postbaseline value. Patients without any changes from baseline are included.
¹⁸Denominator for each parameter = number of patients with at least 1 postbaseline value. Patients without any changes from baseline are excluded. A missing baseline value was set Grade 0.
 [Ref. 5.3.5.4: P003V1, P004V1, P006, P013V1]

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Vorinostat Monotherapy – Combination Therapies

Summary Comparison of Clinical Laboratory Evaluations (Vorinostat Combination Therapies)

A small number of patients (10) in this population limits the comparisons with the other populations. Evaluation of the laboratory values by shift analysis showed clinically meaningful shifts in platelet counts, serum creatinine, and increased serum glucose

Evaluation by CTCAE Grade (Vorinostat – Combination Therapies)

The following table summarizes the laboratory abnormalities by grade for patients at all doses in this population. The most common *serum chemistry* abnormalities, *regardless of grade*, listed in descending order of frequency:

- Increased serum glucose in 7 of 10 patients 70%
- Increased serum creatinine in 5 of 10 patients 50%
- Decreased serum sodium in 5 of 10 patients 50%
- Decreased serum calcium in 3 of the 10 patients 30%
- Decreased serum potassium in 3 of the 10 patients 30%
- Increased serum ALT in 3 of the 10 patients 30%
- Decreased serum albumin in 3 of the 10 patients 30%
- Decreased serum phosphorus in 3 of the 10 patients 30%
- Increased serum triglyceride in 3 of the 10 patients 30%
- Increased uric acid in 3 of the 10 patients 30%
- Total serum carbon dioxide in 3 of the 10 patients 30%
- Increased total bilirubin in 3 of the 10 patients 30%

The most common *hematology* abnormalities:

- Decreased hemoglobin in all patients 100%
- Decreased white blood cell count in 9 of 10 patients 90%
- Decreased absolute neutrophil count in 8 of 10 patients 80%

Urine protein was reported in 3 of 10 patients (30%).

There are no *Grade 4* laboratory abnormalities in this patient population.

Grade 3 laboratory abnormalities:

- Decreased serum sodium 2 patients
- Increased serum glucose 2 patients
- Decreased neutrophil count 2 patients
- Increased INR 2 patients
- Decreased WBC 1 patient

- o Prolonged APTT 1 patient

**Table 149. Laboratory Abnormality by Grade (Vorinostat Combination Therapies)
 (Applicant's Table)**

Laboratory Test	N	Overall Grades				Total n (%)
		1	2	3	4	
blood chemistry test						
decreased serum calcium	10	2	1	0	0	3 (30.0)
decreased serum glucose	10	1	0	0	0	1 (10.0)
decreased serum magnesium	5	4	0	0	0	4 (80.0)
decreased serum potassium	10	3	0	0	0	3 (30.0)
decreased serum sodium	10	3	0	2	0	5 (50.0)
increased serum calcium	10	1	0	0	0	1 (10.0)
increased serum glucose	10	2	3	2	0	7 (70.0)
increased serum potassium	10	1	0	0	0	1 (10.0)
serum alanine aminotransferase	10	3	0	0	0	3 (30.0)
serum albumin	10	2	1	0	0	3 (30.0)
serum alkaline phosphatase	10	4	0	0	0	4 (40.0)
serum aspartate aminotransferase	10	2	0	0	0	2 (20.0)
serum bicarbonate	3	2	0	0	0	2 (66.7)
serum cholesterol	3	2	0	0	0	2 (66.7)
serum creatinine	10	4	1	0	0	5 (50.0)
serum gamma glutamyl transferase	1	1	0	0	0	1 (100.0)
serum phosphorus	9	3	0	0	0	3 (33.3)
serum triglyceride	3	2	1	0	0	3 (100.0)
serum uric acid	9	3	0	0	0	3 (33.3)
total serum bilirubin	10	1	0	0	0	1 (10.0)
total serum carbon dioxide	7	3	0	0	0	3 (42.9)
total serum protein	10	3	0	0	0	3 (30.0)
hematology laboratory test						
WBC count	10	1	7	1	0	9 (90.0)
absolute neutrophil count	10	3	3	2	0	8 (80.0)
hemoglobin	10	5	5	0	0	10 (100.0)
lymphocyte count	10	0	2	0	0	2 (20.0)
neutrophil count	10	2	0	0	0	2 (20.0)
platelet count	10	4	2	0	0	6 (60.0)
red blood cell count	10	1	0	0	0	1 (10.0)
hemostatic function test						
APTT	10	5	0	1	0	6 (60.0)
ENR	9	0	0	2	0	2 (22.2)
urinalysis test						
urine protein	10	2	1	0	0	3 (30.0)

N: number of patients who had the lab test during treatment.
 If a patient had more than one graded abnormalities for a lab test, only the highest grade is counted.

[Ref. 5.3.5.4: P012V1, P015V1, P016V1]

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Evaluation by Clinical Laboratory Shift Analysis (Vorinostat – Combination Therapies)

The following table is a summary of the shift in laboratory parameters from the baseline to the worst post-baseline value to the last value for the Vorinostat Combination Therapies Population.

Serum creatinine

- Ten (10) patients in this population had post-baseline serum creatinine values and 5 of the 10 (50%) experienced changes—all were a worsening of the grade level, however, only 1 patient had post-baseline change that was a clinically meaningful grade shift.
- Two (2) of 5 patients worsened and then improved with subsequent tests, both improved to Grade 0.
- One (1) patient improved with no action taken in regard to Vorinostat treatment, and 1 improved with dose interruption or dose modification of Vorinostat.

Serum glucose

- Eight (8) patients in this population had post-baseline serum glucose values and 7 (88%) experienced a worsening of grade level from the baseline; however, in only 2 of the 7 patients the grade shifts were clinically significant.
- Six (6) of the 7 patients worsened and later improved at subsequent tests, 2 improved to Grade 1 and 4 improved to Grade 0, and 1 patient showed no further changes.
- Five (5) patients improved with no action taken in regard to Vorinostat treatment.
- Five of the 10 patients (50%) were receiving dexamethasone which can cause increases in blood glucose levels, and 2 patients (20%) had entered the study with a previous diagnosis of non-insulin dependent diabetes mellitus.

Platelet counts

- Ten (10) patients in this population had post-baseline platelet counts, 5 of the 10 (50%) had changes in the post-baseline values—all changes were a worsening of grade level, and in 1 patient the grade shift was clinically meaningful.
- Four (4) of 5 patients worsened and then improved with subsequent tests to grade 0 and 1 patient showed no change
- Three (3) patients improved with no action taken in regard to Vorinostat treatment and 1 patient improved with dose interruption or dose modification of Vorinostat treatment.

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Table 150. Summary of Shift in Laboratory Parameters from the Baseline to the Worst Post-baseline Value to Last Value (Vorinostat Combination Therapies) (Applicant's Table)

Parameter and Treatment Group	N ¹¹	M ¹²	Number(s) of Subjects										
			Change in CTCAE Grade ¹ from Baseline to Worst Value Postbaseline			Change in CTCAE Grade from Worst Value Postbaseline to Last Value Postbaseline							
			Improved ¹³	Worsened	Clinically Meaningful Shift ¹⁴	Consistent Improvement from Baseline ¹⁵	Worsened and then Improved ¹⁶	No Change ¹⁷	Grade 1	Grade 0	Without Any Change in Therapy	With Dose Interruption or Modification	Associated With Stopping Therapy
hemoglobin													
Combination Therapies	13	7	0(0.0)	7(100.0)	0(0.0)	0(0.0)	2(26.8)	5(71.4)	1(14.3)	1(14.3)	2(28.6)	0(0.0)	0(0.0)
platelet count													
Combination Therapies	10	5	0(0.0)	5(100.0)	1(20.0)	0(0.0)	4(80.0)	1(20.0)	0(0.0)	4(80.0)	3(60.0)	1(20.0)	0(0.0)
serum creatinine													
Combination Therapies	10	5	0(0.0)	5(100.0)	1(20.0)	0(0.0)	2(40.0)	3(60.0)	0(0.0)	2(40.0)	1(20.0)	1(20.0)	0(0.0)
serum glucose - increased													
Combination Therapies	8	7	0(0.0)	7(100.0)	2(28.6)	0(0.0)	0(0.0)	1(12.5)	1(12.5)	2(25.0)	4(50.0)	1(12.5)	0(0.0)

¹Based on NCI CTCAE, Version 3.0

²A clinically meaningful shift in CTCAE grade was defined as a shift from less than Grade 3 to Grade 3 or 4 or 5 OR a shift from Grade 0 to Grade 2.

³Includes subjects from the column labeled "Improved"

⁴Includes subjects from the column labeled "Worsened"

⁵Includes subjects from the column labeled "Consistent improvement from baseline" and "Worsened and then improved".

⁶Number of patients who improved from baseline based on worst postbaseline.

⁷Number of patients with at least 1 postbaseline value. Patients without any changes from baseline are included.

⁸Denominator for each parameter = number of patients with at least 1 postbaseline value. Patients without any changes from baseline are excluded. A missing baseline value was set Grade 0.

[Ref. 5.3.5.4: P012V1, P015V1, P016V1]

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7.1.7.4 Additional analyses and explorations

- See subsection 7.1.3 Dropouts and Other Significant Adverse Events (Further analyses of serum glucose, serum creatinine, and platelet counts are detailed)

7.1.7.5 Special assessments

- See above

***Reviewer Comments:** Due to the limited duration of exposure of the patients to Vorinostat in all the study populations (commonly due to lack of efficacy), the small number of the patients, and due to the lack of a control arm, only limited analysis of the data was possible in this safety analysis.*

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7.1.8 Vital Signs

Vital Signs, Physical Findings, and Other Observations Related to Safety

7.1.8.1 Overview of vital signs testing in the development program

Patients were seen prior to enrollment into the studies and had scheduled follow-up visits. Their physical condition was assessed and weight, vital signs, ECOG performance status, treatment and disease related AEs were recorded, along with any tumor responses. The data for this section comes from these visits.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Data from the studies in CTCL population, solid tumors population, and hematologic malignancies population were used in this analysis. A list of the studies is provided in Section 7 Subsection 7.1 METHODS AND FINDINGS

7.1.8.3 Standard analyses and explorations of vital signs data

Descriptive statistics summarizing performance status scores (Eastern Cooperative Oncology Group: ECOG), body weight, and vital signs for each of the 5 study populations are provided in the following five tables.

Week 17 was chosen as the cut-off period for evaluation as overall exposure fell to less than 50% of the study populations after this time point.

- No clinically meaningful changes or trends in the safety measurements were noted in any population. However, a decrease in mean weight in the CTCL population was observed over time.
- A wide variation in data was noted in the Vorinostat Combination Therapies population. This variation is likely due to the small sample size and limited follow-up in these ongoing studies.
 - The marked decrease in mean weight from baseline (-16.9 kg) noted at Week 3 was due in part to a missing data point from 1 patient (AN3151) in Protocol 012. This patient was particularly obese, with a baseline weight of 145 kg. The patient missed the Week 3 visit, resulting in a lowering of the mean weight for that time point.
- When clinical safety measurements are compared across populations, the mean ECOG performance status scores were lower (better) in the CTCL population than in the other populations. This suggests that the non-CTCL population may have been more debilitated than the CTCL population.

Table 151. Mean (Standard Deviation) of Clinical Safety Measurements during the Studies: Vorinostat Monotherapy – CTCL (Applicant's Table)

Treatment Visit	N ¹	ECOG	Temperature (C)	DBP (mmHg)	SBP (mmHg)	Heart Rate (beats/min)	Weight (kg)
Baseline	111	0.6 (0.6)	36.5 (0.4)	76.4 (10.9)	132.1 (14.8)	77.3 (12.1)	78.6 (15.1)
Week 3	97	0.6 (0.7)	36.5 (0.5)	78.1 (11.2)	135.3 (17.9)	76.7 (11.5)	78.6 (15.7)
Week 5	99	0.6 (0.7)	36.5 (0.5)	75.9 (11.3)	133.4 (19.4)	80.1 (12.4)	77.7 (15.8)
Week 7	92	0.6 (0.7)	36.5 (0.5)	76.5 (10.6)	135.2 (18.7)	76.8 (12.6)	77.3 (16.1)
Week 9	81	0.6 (0.6)	36.4 (0.5)	75.7 (10.0)	132.4 (15.8)	78.0 (12.0)	77.5 (15.8)
Week 13	68	0.5 (0.6)	36.5 (0.5)	74.7 (9.5)	130.5 (15.4)	76.2 (11.0)	76.9 (14.2)
Week 17	50	0.4 (0.6)	36.5 (0.5)	75.3 (8.8)	126.9 (16.5)	75.4 (10.3)	75.5 (13.1)

¹Number of patients with at least one clinical safety measurement. The last-value-carried-forward approach is used to impute missing measurements for those with incomplete data.
 DBP = Diastolic Blood Pressure
 SBP = Systolic Blood Pressure

[Ref. 5.3.5.2: P001, P005]

Table 152. Mean (Standard Deviation) of Clinical Safety Measurements during the Studies: Vorinostat Monotherapy – CTCL Stage IIB or Higher (Applicant's Table)

Treatment Visit	N ¹	ECOG	Temperature (C)	DBP (mmHg)	SBP (mmHg)	Heart Rate (beats/min)	Weight (kg)
Baseline	93	0.6 (0.7)	36.5 (0.4)	75.7 (10.2)	132.4 (14.6)	77.2 (12.6)	78.6 (15.3)
Week 3	81	0.7 (0.7)	36.4 (0.6)	77.4 (11.0)	136.5 (18.1)	76.3 (11.2)	78.0 (16.2)
Week 5	83	0.7 (0.8)	36.5 (0.5)	75.0 (11.2)	133.6 (20.4)	80.2 (12.6)	77.1 (16.3)
Week 7	75	0.7 (0.7)	36.5 (0.5)	75.7 (11.0)	136.1 (19.0)	76.6 (12.1)	77.4 (16.6)
Week 9	64	0.6 (0.7)	36.4 (0.5)	75.5 (9.7)	133.2 (15.2)	78.1 (12.3)	77.3 (16.4)
Week 13	51	0.6 (0.6)	36.5 (0.5)	74.2 (9.9)	131.1 (16.0)	76.9 (10.0)	76.5 (14.3)
Week 17	39	0.5 (0.6)	36.5 (0.5)	76.3 (8.5)	129.8 (15.3)	74.9 (10.1)	75.2 (13.8)

¹Number of patients with at least one clinical safety measurement. The last-value-carried-forward approach is used to impute missing measurements for those with incomplete data.
 DBP = Diastolic Blood Pressure
 SBP = Systolic Blood Pressure

[Ref. 5.3.5.2: P001, P005]

Table 153. Mean (Standard Deviation) of Clinical Safety Measurements during the Studies: Vorinostat Monotherapy – Solid Tumor (Applicant's Table)

Treatment Visit	N ¹	ECOG	Temperature (C)	DBP (mmHg)	SBP (mmHg)	Heart Rate (beats/min)	Weight (kg)
Baseline	101	1.0 (0.4)	36.6 (0.5)	71.1 (10.3)	123.9 (18.4)	86.2 (13.3)	77.7 (18.4)
Week 3	91	1.1 (0.5)	36.5 (0.4)	74.2 (10.6)	130.2 (20.6)	84.1 (16.3)	77.1 (19.1)
Week 5	84	1.3 (0.7)	36.5 (0.5)	72.1 (9.4)	126.6 (19.4)	82.7 (15.8)	75.5 (18.9)
Week 7	69	1.4 (0.7)	36.5 (0.5)	69.5 (9.6)	121.7 (20.3)	84.9 (19.6)	73.6 (18.0)
Week 9	59	1.4 (0.7)	36.5 (0.5)	70.9 (9.5)	125.8 (20.4)	85.7 (19.5)	75.1 (18.4)
Week 13	52	1.0 (0.6)	36.5 (0.4)	71.5 (9.0)	123.3 (19.4)	79.4 (15.7)	75.8 (20.6)
Week 17	26	1.0 (0.6)	36.5 (0.3)	71.2 (7.8)	123.4 (15.1)	81.1 (16.3)	76.0 (19.6)

¹Number of patients with at least one clinical safety measurement. The last-value-carried-forward approach is used to impute missing measurements for those with incomplete data.
 DBP = Diastolic Blood Pressure
 SBP = Systolic Blood Pressure

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

Table 154. Mean (Standard Deviation) of Clinical Safety Measurements during the Studies: Vorinostat Monotherapy – Hematologic Malignancies (Applicant's Table)

Treatment Visit	N ¹	ECOG	Temperature (C)	DBP (mmHg)	SBP (mmHg)	Heart Rate (beats/min)	Weight (kg)
Baseline	87	0.9 (0.6)	36.7 (0.6)	69.3 (10.7)	125.4 (20.0)	82.8 (17.4)	79.5 (19.5)
Week 3	79	1.2 (0.8)	36.6 (0.7)	68.2 (9.9)	122.4 (19.3)	86.1 (16.5)	77.1 (19.4)
Week 5	69	1.2 (0.9)	36.6 (0.7)	67.9 (10.8)	119.3 (22.9)	83.7 (16.5)	78.9 (19.0)
Week 7	55	1.0 (0.9)	36.7 (0.8)	70.9 (11.8)	126.8 (20.1)	85.1 (16.7)	78.5 (18.4)
Week 9	43	1.0 (0.7)	36.5 (0.7)	71.4 (11.5)	123.8 (18.9)	86.0 (13.9)	78.4 (18.4)
Week 13	25	0.7 (0.6)	36.3 (0.7)	71.3 (9.6)	121.2 (18.8)	87.6 (13.6)	76.0 (16.3)
Week 17	18	0.8 (0.6)	36.4 (0.5)	73.5 (9.0)	120.6 (13.7)	84.0 (13.8)	77.7 (16.1)

¹Number of patients with at least one clinical safety measurement. The last-value-carried-forward approach is used to impute missing measurements for those with incomplete data.
 DBP = Diastolic Blood Pressure
 SBP = Systolic Blood Pressure

[Ref. 5.3.5.4: P003V1, P004V1, P006, P013V1]

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Table 155. Mean (Standard Deviation) of Clinical Safety Measurements during the Studies: Vorinostat Combination Therapies (Applicant's Table)

Treatment Visit	N ¹	ECOG	Temperature (C)	DBP (mmHg)	SBP (mmHg)	Heart Rate (beats/min)	Weight (kg)
Baseline	10	0.6 (0.5)	36.5 (0.5)	77.5 (5.9)	136.1 (24.0)	71.2 (10.2)	85.8 (28.2)
Week 3	9	1.0 (0.0)	36.4 (0.6)	75.1 (11.5)	123.8 (19.3)	72.9 (15.4)	68.9 (19.5)
Week 5	8	1.0 (1.4)	36.6 (0.4)	76.0 (8.1)	124.1 (18.4)	79.8 (12.6)	85.4 (28.9)
Week 7	6	1.0 (0.0)	36.5 (0.2)	71.2 (10.0)	122.7 (15.1)	81.5 (2.9)	93.3 (26.3)
Week 9	5	0.5 (0.7)	36.6 (0.5)	77.8 (4.5)	130.3 (10.2)	83.0 (14.2)	96.5 (28.5)
Week 13	3	1.0 ()	36.1 (0.1)	76.3 (9.3)	131.0 (9.5)	81.0 (16.0)	98.5 (40.1)
Week 17	2	()	36.1 (0.3)	84.0 (11.3)	148.0 (4.2)	69.5 (2.1)	85.9 (39.3)

¹Number of patients with at least one clinical safety measurement. The last-value-carried-forward approach is used to impute missing measurements for those with incomplete data.
 DBP = Diastolic Blood Pressure
 SBP = Systolic Blood Pressure

[Ref. 5.3.5.4: P012V1, P015V1, P016V1]

7.1.8.4 Additional analyses and explorations

- As all the studies were single arm studies, further analysis (comparison to a control) were not possible

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7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program

QTc prolongation was evaluated by:

- Adverse experience reporting in all the studies
- Directed local or central reading of ECGs in Protocols 008, 011, and 013
- Blinded retrospective analysis of ECG data available as of January 2004 from Protocols 002, 003, 005, and 006 performed by an external cardiologist

The following table provides a summary of the ECG time points per protocol. Although ECGs were performed at screening in all protocols, subsequent time points for ECG testing varied by the protocol.

Table 156. Summary of ECG Time Points per Protocol (Applicant's Table)

Protocol No.	Time Points	Evaluation
001	Screening, every 4 weeks, and off-study	Local
002	Screening, Week 1, Week 4, Week 8, every 4 weeks thereafter, and off-study	Local
003	Screening, C1D8, C2D22, C2D29, C3D43, and off-study	Local
004	Screening, C1D8, C1D15, C1D22, C2D1, D1 of each cycle thereafter, and off-study	Local
005	Screening, Week 1, Week 2, Week 3, Week 6, every 3 weeks thereafter, and off-study	Local
006	Screening and every 4 weeks	Local
008	Screening, C1D1 (pre-dose ad 2 hours), C1D2, C1D5 (2 hours), C1D15, C1D28 (2 hours), and C1D29	Local
011	Screening and C1D15	Local
012	Screening, C1D1, C1D11, and post-treatment	Local
013	Screening and C1D15	Central
015	Screening, C1D1, C1D11, and post-treatment	Local
016	Screening, every 30 days, and post-treatment	Local

"Off-study" also indicates post-treatment visits.

[Ref. 5.3.3.2: P008] [Ref. 5.3.5.2: P001, P005] [Ref. 5.3.5.4: P002, P003V1, P004V1, P006, P011V1, P012V1, P013V1, P015V1, P016V1]

CTCL Population

Prolonged QT intervals were reported as *clinical* adverse experiences in 3 of 107 patients (2.8%) patients in the Vorinostat Monotherapy – CTCL population.

- These events occurred in 3 patients in Protocol 001 (AN1012, 1043, and 1079).
- All were CTCAE Grade 2 or less – no patient had **QTc interval** greater than 500 msec.
- By manual reading the **changes from the baseline QTc intervals** were 31, 55, and 105 msec for patients AN 1079, AN1043, and AN1012, respectively.
- Two (2) of the 3 QTc prolongations (patients AN1012 and AN1079) were considered *possibly related* to the study drug.
 - Patient AN 1012 had medical history of cardiac murmur and other ECG abnormalities (T-wave changes and left atrial enlargement) prior to enrollment. This patient also had a concurrent Grade 1 hyponatremia reported as an adverse experience that was possibly related to the study drug.
- One (1) patient recovered by the time of data cut-off date (30-Nov-2005), 1 day after initial diagnosis.
- The mean time for these events was 69.7 days with a range of 33 – 120 days. None of the 3 patients were taking prior or concomitant therapies known to be associated with QTc prolongation.

Solid Tumor, Hematologic Malignancies, or the Combination Therapies population

- No QTc prolongation adverse experience was reported for patients in the solid tumor, hematologic malignancies, or the combination therapies population.

Protocols 008, 011, and 013

In protocols (008, 011, and 013) with capturing of QTc measurements, 8 ECG QTc prolonged abnormalities were reported for 8 patients: AN0001, AN0005, AN0007, AN0009, and AN0014 in Protocol 008; AN0003 and AN0032 in Protocol 011; and AN0422 in Protocol 013.

- The **increases in QTc** for all patients except the one patient in Protocol 013 were less than 50 msec.
- For patient AN0422 in Protocol 013, there was an ECG abnormality of a Grade 2 prolonged QTc on Day 15, at 2-hour post-dose follow-up ECG; however, the pre-treatment baseline value was higher than the value reported as abnormal even though it was not listed in the patient's medical history. The **baseline QTc value** was 486 msec and the Day 15, 2-hour **post-dose QTc value** was 473 msec, thus a 13 msec decrease from baseline.
- There were no **absolute QTc intervals** greater than 500 msec.
- None of these QTc abnormalities were considered the Investigators to be adverse experiences. Seven (7) of 8 patients had prior cardiac history.

Of the 165 patients enrolled in the 4 early Vorinostat protocols (002, 003, 005, and 006) whose ECG data were analyzed in the blinded retrospective study by an outside cardiologist, 118 patients had at least 1 post-baseline ECG.

- Of these 118 patients, 12 had ECG tracings with > 30 msec **QTc interval prolongation** from the baseline, and/or greater than 500 msec **absolute QT or QTc**.
- Of these 12 patients, 10 patients had **baseline QTc** values of less 450 msec, 9 of which had **changes in QTc** interval of 60 msec or less.
- One (1) of 12 patients had QTc intervals in subsequent ECG measurements that were less than the baseline value resulting in negative deltas. Patient AN1001 in Protocol 005 had a baseline QTc value of 575 msec. The QTc changes from baseline were between -87 and -7 msec, thus the longest QTc interval was measured at the baseline. This patient whose relevant medical history included diabetes, hypertension, hypothyroidism, and hyperlipidemia was being treated prophylactically with levofloxacin for a concomitant infection possibly related to the uncontrolled diabetes. Levofloxacin has been associated with QTc prolongation. Concomitant medical conditions may also have predisposed him to prolonged QTc. However, this patient's subsequent QTc intervals decreased in value from the first post-baseline to the last post-baseline measurement with the last read being less than that of the baseline value: 568, 501, 508, 488, 509, and 496 msec.

Two other patients (AN1054 and AN1036 in Protocol 006) exhibited a pattern in which **subsequent QTc** measurements returned to **baseline** or to near baseline reading:

- AN1054's **baseline QTc** interval was 423 msec and **subsequent** readings were 517, 419, and 428 msec.
- AN1036's **baseline QTc** interval was 435 msec and **subsequent** readings were 529, 429, 401, and 491 msec.
- QTc interval for these patients initially increased after starting study drug then eventually returned to baseline or normal to near normal while still on treatment.
- AN1054 had a history of hypertriglyceridemia. Neither patient was taking medications associated with prolonged QTc interval.
- As the retrospective evaluation of the available data from the 4 clinical trials (described above) did not indicate a significant effect of Vorinostat on the QTc interval, the applicant concluded that Vorinostat did not exert a substantial effect on cardiac repolarization.

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Table 157. Summary of QTc Interval Changes from the Baseline (Applicant's Table)

Protocol	Allocation Number	Dose Level	Baseline Heart Rate and QTc	Post-Baseline Heart Rate and QTc	Maximum Changes in QTc
006	1054	400 mg once daily x 7d/wk	HR 73, QTc 423	HR 109, QTc 517 HR 71, QTc 419 HR 71, QTc 428	94 msec
006	1019	400 mg once daily x 7d/wk	HR 51, QTc 327	HR 90, QTc 527 HR 91, QTc 541 HR 85, QTc 599 HR 82, QTc 506 HR 76, QTc 550 HR 83, QTc 502	75 msec
006	1057	400 mg once daily x 7d/wk	HR 64, QTc 406	HR 78, QTc 453 HR 65, QTc 422	45 msec
006	1011	400 mg once daily x 7d/wk	HR 80, QTc 406	HR 100, QTc 438 HR 78, QTc 435 HR 88, QTc 411	32 msec
006	1022	600 mg once daily x 7d/wk	HR 84, QTc 411	HR 115, QTc 442 HR 128, QTc 408	31 msec
006	1036	200 mg twice daily x 7d/wk	HR 67, QTc 435	HR 73, QTc 529 HR 72, QTc 429 HR 78, QTc 401 HR 75, QTc 491	50 msec
006	1042	200 mg twice daily x 7d/wk	HR 43, QTc 372	HR 51, QTc 418 HR 60, QTc 400 HR 58, QTc 409 HR 60, QTc 414 HR 55, QTc 403 HR 90, QTc 425	54 msec 46 msec 42 msec 34 msec
006	1050	300 mg twice daily x 7d/wk	HR 64, QTc 396	HR 73, QTc 429 HR 85, QTc 433	37 msec 33 msec
002	1009	400 mg once daily, continuous	HR 78, QTc 405	HR 83, QTc 465 HR 83, QTc 393	60 msec
005	1016	300 mg twice daily, 3/7 days	HR 127, QTc 397	HR 133, QTc 393 HR 77, QTc 454	57 msec
005	1015	300 mg twice daily, 3/7 days	HR 58, QTc 424	HR 60, QTc 395 HR 65, QTc 416 HR 60, QTc 398 HR 54, QTc 367 HR 48, QTc 449	25 msec
005	1061	500 mg once daily for first 12 days, then 350 mg once daily	HR 86, QTc 575	HR 84, QTc 568 HR 78, QTc 501 HR 77, QTc 508 HR 73, QTc 488 HR 73, QTc 509 HR 66, QTc 496	QTc values all less than baseline.

[Ref. 5.4: 45]

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7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

Following is a list of individual clinical trials for each study population. Patients for ECG studies and analysis were drawn from these studies.

- Vorinostat Monotherapy – CTCL: Protocols 001, 005
- Vorinostat Monotherapy – CTCL Stage IIB and Higher: Protocols 001, 005
- Vorinostat Monotherapy – Solid Tumors: Protocol 002, 008 (Part I), 011, 006 (solid tumors patients only)
- Vorinostat Monotherapy – Hematologic Malignancies: Protocols 003, 004, 013, 006 (hematologic patients only)
- Vorinostat Combination Therapies – Protocols 012, 015, 016

Protocol 008

Protocol 008 specifically looked at the baseline and the post-baseline QTc measurements and is detailed below.

- An analysis of changes in QTc intervals using baseline and post-baseline QT/QTc measurements was done on ECG data collected in Protocol 008.
- **Baseline** was defined as the **pre-dose QTc interval**. In the event a pre-dose ECG was not available, the *pre-study* QTc interval was used.
- Unscheduled measurements were not included in the mean analysis of QTc intervals; however, unscheduled visits were included in the **absolute maximum QTc interval** analysis and **change from baseline** analysis.

Baseline QTc Intervals and Change from Baseline at Prescribed Times in Protocol 008

The following table provides an overall summary of QTc intervals at each of the protocol specified time points.

- Evaluation of the prescribed QTc measurements suggests that Vorinostat does not increase the QTc interval to a clinically meaningful extent.

Table 158. Analysis of QTc Intervals (in msec) at Prescribed Times for Patients in Vorinostat Protocol 008 (Applicant's Table)

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Time	Summary Statistics			Change from Baseline		
	N	Mean (SD)	Median (Range)	Mean (Std Err)	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 (23.6)	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.

[Ref. 5.3.3.2: P008]

- Similar analysis comparing QTc interval changes across all populations was not done due to wide variation of time points for ECG acquisition across protocols and due to the absence of ECG raw data collection for the early Vorinostat clinical trials (Protocols 001, 002, 003, 005, and 006).
- A subset of study patients who entered Vorinostat clinical trails prior to January 2004 in Protocols 002, 003, 005, and 006 underwent blinded review by an external cardiologist and the results of that are discussed later in this section. Protocols 008, 011, and 013 mandated formal collection of all ECG data. In all other studies, ECG abnormalities were to be reported as adverse experiences.

Absolute Maximum QTc Intervals in Protocol 008

The following table provides a categorical summary of the absolute maximum QTc intervals for patients participating in Protocol 008:

- No patient had a QTc interval greater than or equal to 500 msec.
- Two (2) patients (AN0002 and AN0005) had a maximum QTc interval between 481 and 499 msec.
 - A maximum QTc interval of 482 msec was observed in AN0002 on Day 1, at 6 hours post-dose (approximately 2 hours after peak Vorinostat plasma concentration). The patient's pre-study and pre-dose QTc intervals were 477 and 457 msec, respectively. Two (2) hours after a single dose of Vorinostat on Day 5, a QTc interval of 477 msec was noted. On Day 15, a pre-dose QTc interval of 475 msec was recorded.
 - A maximum QTc interval of 492 msec was observed in AN0005 on Day 1, at 6 hours post-dose (approximately 4 hours before peak Vorinostat plasma concentration). The patient's pre-study and pre-dose QTc intervals were 470 and 457 msec, respectively. This patient received only 1 dose of study drug before being discontinued from the study. No cardiac-related adverse experiences were reported in these patients.

- Six (6) patients had a maximum QTc interval between 451 and 480 msec. The respective maximum QTc intervals for AN0001, AN0008, AN0009, AN0014, AN0019, and AN0020 were 466 msec, 466 msec, 473 msec, 476 msec, 454 msec, and 451 msec.

Table 159. Categorical Analysis of Absolute Maximum QTc for Patients in Vorinostat Protocol 008 (Applicant's Table)

Treatment	N	Maximum QTc			
		Count (%)			
		≤450 msec	451 to 480 msec	481 to 499 msec	≥ 500 msec
400 mg	23	15 (65.2%)	6 (26.1%)	2 (8.7%)	0 (0.0%)

N= Number of patients

[Ref. 5.3.3.2: P008]

Maximum QTc Change from the Baseline in Protocol 008

The following table provides a categorical summary of QTc maximum *change from the baseline*:

- Baseline was defined as the QTc interval taken most recent to the first dose of Vorinostat.
- Of the 23 patients enrolled in the study, 18 experienced a ≤30 msec increase from the baseline, 5 had a >30 and <60 msec increase from baseline, and no patient experienced a greater than 60 msec increase from baseline.

Table 160. Categorical Analysis of Maximum QTc Change from the Baseline in Vorinostat Protocol 008 (Applicant's Table)

Treatment	N [†]	Number (Percent) of Patients in Each Category		
		≤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 post-dose measurement.
[‡] AN 0001, AN 0005, AN 0007, AN 0009, AN 0014
 N = Number of patients; qd = Once daily; d = Days; wk = Week.

[Ref. 5.3.3.2: P008]

Five (5) patients had >30 and ≤60 msec increases from baseline in QTc interval: AN0001, AN0005, AN0007, AN0009, and AN0014. The following table summarizes their individual QTc values.

- AN0001 had Day 5, 2-hour post-dose QTc interval of 466 msec: a 32 msec increase from the baseline. All subsequent QTc measurements reported for this patient were at least 19 msec lower than this.
- Patient AN0005 had Day 1, 6-hour post-dose QTc interval of 492 msec: a 35 msec increase from his pre-dose baseline measurement. The patient had taken only 1 dose of the study drug before being admitted to the hospital for serious adverse experiences of

- fever, abdominal pain, and ankle edema. No additional ECG was performed beyond 6 hours.
- AN0007 had Day 1, 2-hour post dose QTc interval of 439 msec: a 34 msec increase from the pre-dose baseline measurement. All other QTc measurements for this patient were within 10 msec of baseline (405 msec).
 - AN0009 had Day 1, 24-hour post-dose QTc interval of 473 msec: a 34 msec increase from the baseline. This maximum increase occurred approximately 22.5 hours after Vorinostat peak plasma concentration. All other QTc measurements taken during the study for this patient were within 12 msec of the pre-dose baseline (439 msec).
 - AN0014 had an unscheduled Day 15 QTc interval of 476: a 42 msec increase over the patient's unscheduled pre-dose baseline measurement. This measurement occurred at least 24 hours after the patient's last dose of Vorinostat.

Table 161. Individual Listing of QTc Values for Selected Patients (>30 and ≤60 msec increases from baseline in QTc interval) in Vorinostat Protocol 008 (Applicant's Table)

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AN	Prescribed Time	QTc (msec)	Change From Baseline [†] (msec)
0001	Prestudy	434	--
	D1, 2 hr	400	-34
	D1, 6 hr	398	-36
	D1, 24 hr	451	17
	D5, 2 hr	466	32
	D15	445	11
	D28, 2 hr	438	4
	D28, 24 hr	447	13
0005	Prestudy	470	--
	Predose	457	--
	D1, 2 hr	401	-56
	Unscheduled	461	4
	Unscheduled	460	3
	D1, 6 hr	492	35
0007	Predose	405	--
	D1, 2 hr	439	34
	Unscheduled	401	-4
	D1, 6 hr	406	1
	D1, 24 hr	408	3
	D5, 2 hr	415	10
	D15	407	2
	D28, 2 hr	403	-2
D28, 24 hr	411	6	
0009	Prestudy	420	--
	Predose	439	--
	D1, 2 hr	451	12
	D1, 6 hr	443	4
	D1, 24 hr	473	34
	D5, 2 hr	422	-17
	D15	398	-41
	Unscheduled	416	-23
	D28, 2 hr	427	-12
D28, 24 hr	419	-20	
0014	Prestudy	440	--
	Predose	415	--
	Unscheduled	434	--
	D1, 2 hr	418	-16
	D1, 6 hr	462	44
	D1, 24 hr	430	-32
	D5, 2 hr	424	-6
	D15	476	52
	Unscheduled	457	-19
[†] Baseline is defined as the QTc closest to dosing. An unscheduled value can be considered baseline if the ECG was taken after the prescribed predose measurement and before dosing. AN = Allocation number.			

[Ref. 5.3.3.2: P008]

Adverse Experience: Abnormal ECG

The following five tables summarize the number of patients with abnormal ECG adverse experiences in each of the 5 populations:

- Of the 309 total patients in all 5 populations, 39 patients (12.6%) had 1 or more abnormal ECG adverse experiences, 18 (5.8%) were considered drug-related, and 1 patient (0.3%) had serious abnormal ECG adverse experience.
- Nineteen (19) patients were from the CTCL population and the rest (20) from the non-CTCL population.
- Of the 87 patients who received Vorinostat at doses of 400 mg once daily in the CTCL population, 17 (19.5%) patients had abnormal ECG adverse experiences as compared to 3 of 40 (7.5%) patients with solid tumors and no patients with hematologic malignancies. Vorinostat at doses of 400 mg once daily was not studied in the trials with combination therapies.
- The majority of the 17 CTCL patients had cardiac risk factors that may influence the development of conduction abnormalities in these patients.

Table 162. Number (%) Of Patients with Abnormal ECG Adverse Experiences (Vorinostat Monotherapy – CTCL) (Applicant's Table)

	400 mg QD Continuous (N=87)		300 mg BID 3/7 (N=12)		Doses Above MTD (N=12)		Total (N=111)	
	n	(%)	n	(%)	n	(%)	n	(%)
Patients With One Or More Abnormal ECG Adverse Experience	17	19.5	1	8.3	1	8.3	19	17.1
Patients With One Or More Drug-related Abnormal ECG Adverse Experience	11	12.6	0	0.0	1	8.3	12	10.8
Patients With One Or More Serious Abnormal ECG Adverse Experience	1	1.1	0	0.0	0	0.0	1	0.9

Although a patient may have had two or more clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.

[Ref. 5.3.5.2: P001, P005]

Table 163. Number (%) Of Patients with Abnormal ECG Adverse Experiences (Vorinostat Monotherapy – CTCL Stage IIB and Higher) (Applicant's Table)

	400 mg QD Continuous (N=72)		300 mg BID 3/7 (N=11)		Doses Above MTD (N=10)		Total (N=93)	
	n	(%)	n	(%)	n	(%)	n	(%)
Patients With One Or More Abnormal ECG Adverse Experience	14	19.4	1	9.1	1	10.0	16	17.2
Patients With One Or More Drug-related Abnormal ECG Adverse Experience	9	12.5	0	0.0	1	10.0	10	10.8
Patients With One Or More Serious Abnormal ECG Adverse Experience	0	0.0	0	0.0	0	0.0	0	0.0

Although a patient may have had two or more clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.

[Ref. 5.3.5.2: P001, P005]

Table 164. Number (%) Of Patients with Abnormal ECG Adverse Experiences (Vorinostat Monotherapy – Solid Tumor) (Applicant's Table)

	400 mg QD Continuous (N=40)		300 mg BID 3/7 (N=13)		200 mg BID Continuous (N=4)		Doses Above MTD (N=38)		Doses Below MTD (N=6)		Total (N=101)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients With One Or More Abnormal ECG Adverse Experience	3	7.5	0	0.0	0	0.0	2	5.3	1	16.7	6	5.9
Patients With One Or More Drug-related Abnormal ECG Adverse Experience	0	0.0	0	0.0	0	0.0	1	2.6	0	0.0	1	1.0
Patients With One Or More Serious Abnormal ECG Adverse Experience	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

Although a patient may have had two or more clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.

[Ref. 5.3.3.2: P003] [Ref. 5.3.5.4: P002, P006, P011V1]

Table 165. Number (%) Of Patients with Abnormal ECG Adverse Experiences (Vorinostat Monotherapy – Hematologic Malignancies) (Applicant's Table)

	400 mg QD Continuous (N=11)		300 mg BID 3/7 (N=3)		200 mg BID Continuous (N=6)		200 mg BID 14/21 (N=10)		Doses Above MTD (N=51)		Doses Below MTD (N=6)		Total (N=87)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients With One Or More Abnormal ECG Adverse Experience	0	0.0	0	0.0	0	0.0	2	20.0	9	17.6	0	0.0	11	12.6
Patients With One Or More Drug-related Abnormal ECG Adverse Experience	0	0.0	0	0.0	0	0.0	1	10.0	2	3.9	0	0.0	3	3.4
Patients With One Or More Serious Abnormal ECG Adverse Experience	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

Although a patient may have had two or more clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.

[Ref. 5.3.5.4: P003V1, P004V1, P006, P013V1]

Table 166. Number (%) Of Patients with Abnormal ECG Adverse Experiences (Vorinostat Combination Therapies) (Applicant's Table)

	Combination Therapies (N=10)	
	n	(%)
Patients With One Or More Abnormal ECG Adverse Experience	3	30.0
Patients With One Or More Drug-related Abnormal ECG Adverse Experience	2	20.0
Patients With One Or More Serious Abnormal ECG Adverse Experience	0	0.0

Although a patient may have had two or more clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.

[Ref. 5.3.5.4: P012V1, P015V1, P016V1]

ECG Abnormalities by Type and Study Drug Association

The following table summarizes ECG abnormalities by type and study drug relationship for the 49 ECG adverse experiences in the overall safety population.

- Six (6) of the 39 patients who had ECG abnormalities experienced more than one ECG abnormality for a total of 49 ECG adverse experiences
- Within this group, there were 21 drug-related abnormal ECG adverse experiences reported for 18 patients.

Breakdown of ECG abnormalities by type and study drug relationship:

Thirty-eight (38) arrhythmias:

- Tachycardia 14
- Sinus tachycardia 6
- Supraventricular tachycardia 2
- Sinus arrhythmia 2
- Bradycardia 2
- Sinus bradycardia 2
- Electrocardiogram QT prolonged 2
- Ventricular extrasystoles 2
- Supraventricular extrasystoles 2
- Atrial fibrillation 1
- Bundle branch block 1
- QT corrected interval prolonged 1
- Cardiac flutter 1

The following 14 arrhythmias considered by the Investigator to be *related* to Vorinostat:

- Tachycardia 9
- Sinus bradycardia 2
- Ventricular extrasystoles 1
- Electrocardiogram QT prolonged 1
- QT corrected interval prolonged 1

Five (5) non-arrhythmias:

- T wave abnormal 3
- P wave abnormal 1
- Ventricular hypertrophy 1

The 3 non-arrhythmias considered by the Investigator to be *related* to Vorinostat:

- T-wave abnormal 1
- P-wave abnormal 1
- Ventricular hypertrophy 1

Six (6) ischemic events:

- ST-T segment abnormal 2
- ST segment abnormal 3
- Myocardial infarction 1

The 2 types of ischemic events considered by the Investigator to be *related* to Vorinostat:

- ST-T segment abnormal 2
- ST segment abnormal 2

Within the **Vorinostat Monotherapy – CTCL population**, the following ECG adverse experiences were reported:

- There were 15 arrhythmic adverse experiences and 8 were considered by the Investigator to be related to the study drug. These drug-related arrhythmic adverse experiences were experienced by 7 patients, one of whom experienced 2 of these 8 arrhythmic events. The majority of these 7 CTCL patients had risk factors that could predispose them to developing arrhythmias.
- There were 5 non-arrhythmic adverse experiences, 3 were experienced by 1 patient in this population and were considered by the Investigator to be related to study drug. This patient had a prior history of ECG abnormality specifically abnormal P-wave changes.
- There were 6 ischemic adverse experiences, all occurred in 6 individual patients and 4 were considered by the Investigator to be related to the study drug.

Other safety populations:

- There were 6 arrhythmic adverse experiences in the **solid tumor population**, 1 considered related to the study drug; 13 in the **hematologic malignancies**, 3 considered to be drug-related; and 4 in the **combination therapies population**, 2 of which were considered to be drug-related.

There was 1 *serious* ECG adverse experience reported for the overall population. This serious adverse experience was a Grade 4 myocardial infarction which was considered by the investigator to be *not related to the study drug* and was reported for a patient in the Vorinostat Monotherapy – CTCL population.

- With the exception of this Grade 4 myocardial infarction, all of the ECG adverse experiences were Grade 2 or less.

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Table 167. Abnormal ECG Adverse Experiences Overall Population (Applicant's Table)

	Arrhythmias		Non-arrhythmias		Ischemia	
	Not Related to Study Drug	Drug-related	Not Related to Study Drug	Drug-related	Not Related to Study Drug	Drug-related
Vorinostat Monotherapy – CTCL ^{††}	7	8	2	3	2	4
Vorinostat Monotherapy – Solid Tumors	5	1	0	0	0	0
Vorinostat Monotherapy – Hematologic Malignancies [‡]	10	3	0	0	0	0
Vorinostat Monotherapy - Combined Therapies ^{‡‡}	2	2	0	0	0	0
Sub-totals	24	14	2	3	2	4
Total –49 events	38 arrhythmias		5 Non-arrhythmias		6 Ischemia	

[†] Patients in the Vorinostat Monotherapy – CTCL Stage IIB and Higher population are not included in this table because it is a subset of the Vorinostat Monotherapy – CTCL population
[‡] AN 1039, AN1043 and AN1047 in Protocol 001 had multiple abnormal ECG adverse experiences.
^{‡‡} AN 1008 and AN 1005 in Protocol 004 each had 2 abnormal ECG adverse experiences.
^{‡‡‡} AN 4001 in Protocol 012 had 2 abnormal ECG adverse experiences.

[Ref. 5.3.3.2: P008] [Ref. 5.3.5.2: P001, P005] [Ref. 5.3.5.4: P002, P003V1, P004V1, P006, P011V1, P012V1, P013V1, P015V1, P016V1]

Details of ECG AEs

The following table provides a listing of patients with abnormal ECG adverse experiences for the overall population:

- There were 49 abnormal ECG adverse experiences reported for all 5 populations
- Twenty-one (21) events were considered by the Investigator to be related to study therapy, all of which were Grade 2 or less. None of these drug-related adverse experiences met serious criteria. There was only 1 serious ECG adverse experience, a Grade 4 myocardial infarction, which was considered by the Investigator to be not related to study drug.
- Intensity was not collected in all studies, but abnormal ECG adverse experiences were graded using the appropriate NCI Criteria.
- ECG events, regardless of drug relationship, tended to occur within the first two months on study drug.

Patient AN1004 participating in Protocol 001 experienced a serious adverse experience that was considered to be not related to study drug by the Investigator. AN1004 was a 50-year-old Black woman with Stage IV CTCL who experienced a Grade 4 myocardial infarction 31 days after starting study drug. This patient’s medical history included coronary artery disease and cardiac risk factors such as uncontrolled hypertension and uncontrolled hypercholesterolemia. (Medical history, prior/concomitant therapies, and treatment-related information for this patient can be found in the narratives section Sec. 2.7.4.11 of the original study safety report)

Table 168. Listing Of Patients with Abnormal ECG Adverse Experiences (Overall Population) (Applicant's Table)

Protocol	Site	AN	Baseline	Adverse Experience	Serious	Causality	Intensity	Relative Start Day	NCI Toxicity Grade
001	0008	1004	8004	Myocardial infarction	Y	def not		31	4
001	0009	1008	9008	Electrocardiogram: ST-T segment abnormal	N	poss	mild	28	1
001	0004	1010	4010	Sinus bradycardia	N	poss	mild	28	1
001	0010	1012	10012	Electrocardiogram: QT prolonged	N	poss	mod	56	2
001	0010	1014	10014	Ventricular extrasystoles	N	poss	mild	30	1
001	0002	1019	2019	Sinus arrhythmia	N	prob not	mild	113	1
001	0010	1020	10020	Electrocardiogram: ST-T segment abnormal	N	poss	mild	58	1
001	0010	1027	10027	Electrocardiogram: T wave abnormal	N	prob not	mild	30	1
001	0008	1037	8037	Tachycardia	N	poss	mod	6	2
001	0009	1039	9039	Electrocardiogram: P wave abnormal	N	poss	mild	29	1
001	0009	1039	9039	Electrocardiogram: T wave abnormal	N	poss	mild	29	1
001	0009	1039	9039	Ventricular hypertrophy	N	poss	mild	61	1
001	0009	1041	9041	Electrocardiogram: ST segment abnormal	N	poss	mild	29	1
001	0009	1043	9043	Bundie branch block	N	prob not	mild	120	1
001	0009	1043	9043	Electrocardiogram: QT prolonged	N	prob not	mild	120	1
001	0009	1043	9043	Electrocardiogram: ST segment abnormal	N	prob not	mild	120	1
001	0009	1043	9043	Electrocardiogram: T wave abnormal	N	prob not	mild	120	1
001	0009	1043	9043	Ventricular extrasystoles	N	prob not	mild	66	1
001	0002	1047	2047	Tachycardia	N	poss	mild	25	1
001	0002	1047	2047	Tachycardia	N	poss	mod	8	2
001	0015	1058	15058	Sinus bradycardia	N	poss	mild	114	1
001	0020	1079	20079	Electrocardiogram: QT corrected interval prolonged	N	poss	mild	33	1
002	0002	1011	2011	Sinus tachycardia	N	def not		42	1
003	0002	1005	2005	Supraventricular tachycardia	N	def not		34	2
003	0002	1010	2010	Sinus tachycardia	N	def not		21	1
003	0002	1011	2011	Supraventricular extrasystoles	N	def not		1	1
003	0002	1014	2014	Bradycardia	N	def not		12	1
003	0002	1024	2024	Tachycardia	N	poss		15	1
003	0002	1029	2029	Tachycardia	N	def not		14	1
003	0002	1034	2034	Tachycardia	N	poss	mild	3	1
003	0002	1035	2035	Tachycardia	N	prob not	mild	15	1
004	0003	1005	3005	Sinus tachycardia	N	def not		14	1
004	0003	1005	3005	Tachycardia	N	poss		14	1
004	0003	1008	3008	Sinus tachycardia	N	def not		8	1
004	0003	1008	3008	Sinus tachycardia	N	def not		85	1
005	0002	1007	2007	Cardiac flutter	N	def not		3	1
005	0002	1013	2013	Tachycardia	N	def not		6	1
005	0002	1021	2021	Supraventricular extrasystoles	N	def not		7	1
005	0002	1035	2035	Electrocardiogram: ST segment abnormal	N	poss		8	1
006	0001	1003	1003	Sinus tachycardia	N	prob not		8	1
006	0001	1032	1032	Sinus tachycardia	N	prob not		30	2
008	0001	13	1014	Bradycardia	N	prob not		15	1
008	0001	16	1017	Tachycardia	N	prob not		16	0
011	0003	35	3005	Tachycardia	N	poss	mild	98	1
011	0003	38	3008	Supraventricular tachycardia	N	prob not	mod	43	2
012	0004	3151	4001	Atrial fibrillation	N	prob not	mod	29	2
012	0004	3151	4001	Tachycardia	N	prob	mod	108	2
012	0004	3153	4003	Sinus arrhythmia	N	prob not	mod	9	2
012	0004	3156	4006	Tachycardia	N	prob	mild	9	1

[Ref. 5.3.3.1: P008] [Ref. 5.3.5.2: P001, P005] [Ref. 5.3.5.4: P002, P003V1, P004V1, P006, P011V1, P012V1, P013V1, P015V1, P016V1]

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7.1.9.3 Standard analyses and explorations of ECG data

Interdisciplinary Review Team for QT Studies was consulted to assess the impact of vorinostat on QT interval based on information provided in the submission; a summary of their findings is shown below. (Complete consult is available in the DFS.)

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. 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.

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.

7.1.9.4 Additional analyses and explorations

Based on an exposure-response analysis (performed by the Interdisciplinary Review Team for QT Studies reviewer) on the 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 interval from the baseline for vorinostat at 400 mg daily dose level. But, this result is based on data from a Phase 1 study and has a number of limitations: (1) few subjects were studied, (2) no placebo or positive control was used, (3) ECGs were not taken at C_{max} 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.

- See the complete consult of Interdisciplinary Review Team for QT Studies

7.1.10 Immunogenicity

- Not applicable (Vorinostat is a small non-protein molecule)

7.1.11 Human Carcinogenicity

Neoplasms (Benign, Malignant, and Unspecified; including Cysts and Polyps) are reported as serious adverse events (SAEs). Among the 107 patients on Vorinostat monotherapy for CTCL, there were 8 patients who reported **neoplasms**. However, in 5 patients the reported neoplasm was a worsening of the primary disease/indication (advanced Cutaneous T-Cell Lymphoma), and the remaining patients had squamous cell carcinomas (skin) or lung neoplasm.

400 mg once daily dose level

- Three (3) of 86 (3.5%) CTCL patients who received Vorinostat at a dose of 400 mg once daily were reported to have squamous cell carcinomas as a serious AE.

Other dose levels

- One of 10 patients (10%) in the 200 mg twice daily dose group was reported to have T-cell lymphoma as a serious AE.
- 1 of 20 patients in the doses above the MTD group was reported with to have T-cell lymphoma as a serious AE.
- One (1) of 12 patients in the doses below the MTD group was reported to have squamous cell carcinoma and lung neoplasm.

Reviewer Comments: Cutaneous squamous cell cancers are common in patients with CTCL—this is one of the delayed adverse effects of topical treatments administered over long times to these patients. The patient with lung neoplasm was on a below the MTD dose of Vorinostat—the tumor is unlikely to be due to short exposure to Vorinostat. However, due to a short duration of treatment with Vorinostat, and a lack of control arm in all the available studies, the human carcinogenicity of Vorinostat cannot be estimated reliably.

7.1.12 Special Safety Studies

- Please see Subsection 7.1.9 Electrocardiograms for the available studies to characterize the effect on the QT interval
- As Vorinostat is the first drug in its pharmacological class (histone deacetylase inhibitor), other human studies on this class of agents are not available.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

- No formal studies have been conducted on the effects of withdrawal of Vorinostat
- The effect of withdrawal of Vorinostat is unknown.

- There is no evidence to suggest that Vorinostat produces physical or psychological dependence.
- In clinical trials, no behavioral or central nervous system adverse experiences occurred to suggest that Vorinostat has any potential for drug addiction or abuse.

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7.1.14 Human Reproduction and Pregnancy Data

Use of Vorinostat in Pregnancy and Lactation

- No human safety data are available for the use of Vorinostat during pregnancy—pregnant women were excluded from participating in studies with Vorinostat.
- Animal data suggests that Vorinostat crosses the placenta and may have adverse effects on fetal development.
- Women of child-bearing potential were advised to avoid becoming pregnant while receiving treatment with Vorinostat and to inform the treating physician immediately should pregnancy occur.
- It is unknown whether Vorinostat is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reaction in the nursing infant, breast-feeding was discontinued for the duration of therapy.

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7.1.15 Assessment of Effect on Growth

- No data to assess the effect of Vorinostat on growth is available

Reviewer Comments: *CTCL lymphoma is a disease of older adults—the median ages in the submitted studies ranged around 60 years.*

7.1.16 Overdose Experience

Four (4) patients reported an accidental overdose of Vorinostat:

- Patient AN3152 (Protocol 012) was taking 300 mg once daily 14 out of 21 days, supplied as 100 mg capsules, and inadvertently took 3 extra capsules of Vorinostat for a total daily dose of 600 mg. Study therapy was not interrupted and no adverse experiences were reported related to this episode.
- Patient AN11323 (Protocol 014) was on blinded therapy receiving Vorinostat (or matching placebo) 300 mg twice daily 3 out of 7 days, supplied as 100 mg capsules. During a scheduled off-drug period the patient inadvertently took a 300 mg dose of study therapy. The study blind was continued and the patient continued on study therapy as scheduled. No adverse experiences related to the episode of accidental overdose were reported.
- Patient AN3332 (Protocol 012) was taking 400 mg once daily, supplied as 100 mg capsules, and inadvertently took 400 mg twice daily on 1 day. Study therapy was continued and no adverse experiences were reported related to this episode.
- Patient AN10008 (Protocol 014) was on blinded therapy receiving Vorinostat (or matching placebo) 300 mg twice daily 3 out of 7 days, supplied as 100 mg capsules. During a scheduled off-drug period the patient inadvertently took a 300 mg dose of study therapy. The study blind was continued and study therapy was discontinued 2 days after this episode for complications related to underlying disease. No adverse experiences related to the episode of accidental overdose were reported.

7.1.17 Postmarketing Experience

- Post-marketing data are not available for Vorinostat.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

- Primary data sources for the evaluation of safety of Vorinostat were the data on clinical and laboratory adverse events from 74 patients in the pivotal trial (protocol 001), 33 patients in the supportive study (Protocol 005), and the patients with solid tumors and hematologic malignancies in 10 other studies that enrolled diverse other tumor types: a total of 305 patients.
- See Sub-section 7.1 METHODS AND FINDINGS in Section 7 INTEGRATED REVIEW OF SAFETY for details.

7.2.1.1 Study type and design/patient enumeration

- For details of the studies reviewed for Vorinostat safety evaluation, including the study types and designs, and numbers and characteristics of the patients and the diseases, please see the Tables xxx in Sub-section 4.2 Tables of Clinical Studies.
- These tables define different patient populations and the clinical studies by protocol numbers, the numbers of total patients in each population, and the total patient exposures per population.

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7.2.1.2 Demographics

Demographic characteristics of different patient populations are shown here in a series of tables in the following pages. Further details are available in Sub-section 7.1 METHODS AND FINDINGS in Section 7 INTEGRATED REVIEW OF SAFETY. Briefly:

- Median ages of these diverse patient populations in different studies ranged from 41 years to 78 years. In the CTCL population cohorts the median ages ranged from 60 to 69 years.
- Majority of the patients were White.

Reviewer Comments: Demographics of the patients in different studies in this NDA are representative of the CTCL patient demographics.

Table 169. Demographic characteristics of the CTCL patients in the pivotal trial (Protocols 001) and the supportive trial (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				
CTCL = Cutaneous T-cell Lymphoma				

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

Demographics of the patients in the solid tumors population that received Vorinostat monotherapy:

Table 170. Baseline Patient Characteristics of the Vorinostat Monotherapy – Solid Tumors Population (The first part of the table lists subsets by Vorinostat doses, and second part of the table lists all the patients) (Applicant's Table) (Applicant's Table)

		400mg once daily continuous (N = 40)		300mg twice daily 3/7 (N = 13)		200mg twice daily continuous (N = 4)		Doses above MID (N = 38)		Doses below MID (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		19.29
	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. 5.3.5.4: P002, P006, P011V1]

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Demographics of the patients in the hematologic malignancies population that received Vorinostat monotherapy:

Table 171. Baseline Patient Characteristics (Vorinostat Monotherapy – Hematologic Malignancies) (The first part of the table lists subsets by Vorinostat doses, and the second part of the table lists all patients) (Applicant's Table)

		400mg once daily continuous (N = 11)		300mg twice daily 3x7 (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]

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Demographics of the patients in the Vorinostat combination therapy population:

**Table 172. 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	1	(10.0)	1	(10.0)
	American				
	White	9	(90.0)	9	(90.0)

[Ref. 5.3.5.4: P012V1, P015V1, P016V1]

7.2.1.3 Extent of exposure (dose/duration)

All CTCL patients (n = 107)

The overall extent of exposure for all CTCL patients who received Vorinostat Monotherapy on Protocols 001 (n = 74) and 005 (n = 33):

- Ninety-six (96) of 111 (86.5%) exposures were to Vorinostat 400 mg total daily dose (initial or modified). *(This is the recommended dose for the label).*
- The mean number of days on Vorinostat at 400 mg total daily dose was 109 days (Range: 2 to 365 days).
- At any Vorinostat dose, the mean number of days was 110 days (Range: 2 to 365 days).

CTCL Stage IIB and Higher patients (n = 89)

As this population is a subset of the Vorinostat Monotherapy – CTCL Population, the duration of exposure is similar. The overall extent of exposure for CTCL Stage IIB and Higher patients who received Vorinostat Monotherapy on Protocols 001 (n = 61) and 005 (n = 28):

- Seventy-nine (79) of 93 (84.9%) exposures to Vorinostat in patients who had CTCL Stage IIB or Higher were to a 400 mg total daily dose of Vorinostat.
- The mean number of days on this dose was 106 days (Range: 2 to 365 days).
- At any dose, the mean number of days on treatment was 108 days with a range of 2 to 365 days.

Patients with Solid Tumors on Vorinostat Monotherapy (n = 101)

The overall extent of exposure to Vorinostat in patients with solid tumors:

- At any dose, the overall mean number of days on treatment was 104 days with a range of 1 to 1311 days.
- Seventy-one (71) of 101 patients (70%) 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: 92 days (Range: 1 to 1034 days).

Patients with Hematologic Malignancies on Vorinostat Monotherapy (n = 87)

The overall extent of exposure to Vorinostat for patients with hematologic malignancies:

- At any dose, the mean number of days on drug was 48 days (Range: 1 to 341 days)
- Forty-two (42) of 87 (48%) patients received 400 mg daily dose. The mean number of days on drug was highest at this dose: 53 days (Range: 1 to 319 days).

Patients on combination therapies containing Vorinostat (n = 10)

The overall extent of exposure for patients who received combination therapies containing Vorinostat is summarized below. This patient population is small.

- 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)

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

- No secondary clinical data sources are available at present as Vorinostat has not been marketed for any indication. Moreover, Vorinostat is the first drug in its pharmacological class.

7.2.2.1 Other studies

- No other studies are available at present as Vorinostat has not been marketed for any indication. Moreover, it is the first drug in its pharmacological class.

7.2.2.2 Postmarketing experience

- There is no postmarketing experience with Vorinostat.

7.2.2.3 Literature

- The applicant provided several peer-reviewed publications in the pdf format with this submission. These publications support the claim that CTCL is a rare disease, there is a lack of satisfactory treatments for the advanced CTCL, and conducting a randomized controlled clinical trial of adequate statistical power is not possible.
- For further details please see 8.6 LITERATURE REVIEW and REFERENCES.

7.2.3 Adequacy of Overall Clinical Experience

- The number of patients with advanced CTCL, the study population and the primary data source for this NDA, is relatively small; however, this number is similar to that in the other NDAs (submitted and reviewed in the past) to seek approval for systemic treatment of advanced CTCL: Targretin and Ontak. In the current NDA there are 107 patients with advanced CTCL in the pivotal and the supportive trial and 89 patients have stage IIB or higher disease; the overall safety population, however, also includes patients with other malignancies and the total number of patients for safety evaluation is 305.
- These patients are representative of the CTCL patient population in terms of demographics.
- Majority of the patients in the overall safety population were ≥ 60 years of age and over 30% of them had other medical conditions for which they were on treatment.
- The overall length of exposure to Vorinostat is relatively short (median duration of exposure of approximately 120 days in the pivotal trial)—this is mostly due to a lack of efficacy. Responding patients have longer exposures.
- Overall clinical exposure supports marketing approval of Vorinostat, but post-marketing surveillance is required.
- Further studies to evaluate Vorinostat in patients with hepatic insufficiency are required.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

- The applicant conducted preclinical testing to acquire data on the anticipated toxicities of Vorinostat. This was reviewed and found to be adequate.

- Additional preclinical testing was conducted to study the Vorinostat effect on ECG QT interval. Further studies are required. See 7.1.9 ELECTROCARDIOGRAMS.
- Further details of preclinical testing are summarized in Section 5 CLINICAL PHARMACOLOGY.

7.2.5 Adequacy of Routine Clinical Testing

- Patients enrolled in the studies conducted under Vorinostat clinical development programs were evaluated at the baseline and were regularly monitored clinically and by blood tests (serum chemistries and hematology) according to their specific protocols. Overall these evaluations provide adequate to support a marketing approval for Vorinostat; however, routine postmarketing surveillance is necessary.
- Additional studies are required to study Vorinostat in patients with hepatic insufficiency and to study Vorinostat effects on ECG QT interval.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

- Please see section 5 CLINICAL PHARMACOLOGY

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

- Please see the comments in 7.2.3 and 7.2.4 above.

7.2.8 Assessment of Quality and Completeness of Data

- The applicant conducted 12 Phase 1 and Phase 2 studies in different patient populations to collect data on both the short-term and long-term safety of Vorinostat.
- The patient populations (in terms of demographics) are representative of the advanced CTCL patient population—the patient population for which the marketing approval is being sought.
- However, both due to a modest efficacy ($\leq 30\%$ in advanced CTCL and worse in other cancers) and AEs (in patients who were relatively old and had several co-morbidities) the duration of exposures is relatively short (median approximately 120 days). Some AEs may not manifest until longer exposures to the drug. Therefore routine postmarketing surveillance will be required.
- Please also note the comments in 7.2.3 and 7.2.4 above.

7.2.9 Additional Submissions, Including Safety Update

Vorinostat safety update (dated the 25th of July, 2006) required under 21 CFR 314.50(d)(5)(vi)(b) was submitted to the FDA by the applicant. It was reviewed and is summarized in this section.

Data cut-off dates

The following table shows the data cut-off dates for the submitted Vorinostat safety update report (SUR):

Table 173. Reporting Periods for Safety Data in the Original Application and in the SUR (Applicant's Table)

	Data Cut-off Date for the Original Application	Data Cut-off Date for the SUR
Protocol 001 (Pivotal Study)	23-Nov-2005	01-May-2006
All Other Protocols	24-Oct-2005	01-May-2006
WAES Reporting	30-Nov-2005	01-May-2006

Extent of Exposure

- As of 01-May-2006, the clinical safety of Vorinostat is supported by data from 357 patients and 361 patient exposures. (The additional patient exposures occurred in Protocol 005, the initial supportive study in CTCL—patients enrolled in one cohort were permitted to enroll in a subsequent cohort. As a result, 4 patients participated in 2 cohorts.)

The number of patients and exposures to Vorinostat in each dosing group are shown in the table below:

- Fifty-two (52) additional patients are included in the SUR.
- There are no new patients with CTCL on vorinostat monotherapy. However, there are 10 new patients with solid tumors and 15 new patients with hematologic malignancies on Vorinostat monotherapy; and 27 new patients with various types of cancer, including 7 CTCL patients, in Protocol 016, on various Vorinostat combination therapies.

Table 174. Patient Exposure in the Original Application and the SUR Reporting Period (Applicant's Table)

Dosing Groups	Original Application	SUR Cumulative	Difference in Patient Exposure in the SUR*
400 mg QD continuous	147	148	1
300 mg BID 3/7	33	48	15
200 mg BID continuous	24	33	9
200 mg BID 14/21	27	32	5
Doses above MTD	109	109	0
Doses below MTD	47	74	27
Total Patient Exposure	305	357	
* Five (5) patients were exposed to more than one dose level.			

Duration of Vorinostat Exposure

In the Vorinostat Monotherapy – CTCL population the total number of patients exposures has remained 111; however, the duration of exposure to vorinostat has increased.

- The mean number of days on Vorinostat, *at any dose*, increased from 110 to 128 days.
 - The maximum number of days on Vorinostat increased from 365 to 480 days.
- The mean number of days on Vorinostat, *at 400 mg total daily dose*, increased from 126 to 149 days.
 - The maximum number of days on Vorinostat increased from 365 to 462 days.
- As of 01-May-2006, 13 patients from Protocol 001 were enrolled in the ongoing extension study, Protocol 007.
- Twelve (12) of 13 patients continue to receive 400 mg daily.
- One (1) of the 13 patients discontinued due to progressive disease after 393 days on treatment.

Extension of Vorinostat Monotherapy for patients enrolled in previous studies who continued to derive clinical benefit

Several patients had continued their treatment on Protocol 007, the extension study, and they are listed in the table below.

Table 175. Listing of Patients Enrolled in Protocol 007, Extension Study (Applicant's Table)

No.	Allocation Number	Base Protocol	Base Protocol Start Date	Protocol 007 Start Date	Vorinostat Therapy Stop Date	Reason for Discontinuation
1	0006	008	10-Feb-2005	01-Aug-2005	Continuing	Not Applicable
2	0010	008	17-Mar-2005	01-Aug-2005	Continuing	Not Applicable
3	0012	008	14-Apr-2005	01-Aug-2005	26-Sep-2005	Progressive Disease
4	0007	008	14-Aug-2005	15-Aug-2005	30-Jan-2006	Progressive Disease
5	0016	008	21-Aug-2005	22-Aug-2005	05-Apr-2006	Progressive Disease
6	0021	008	14-Aug-2005	15-Aug-2005	24-Oct-2005	Clinical AE
7	0022	008	16-Aug-2005	17-Aug-2005	17-Oct-2005	Progressive Disease
8	015	006	13-Sep-2005	14-Sep-2005	Continuing	Not Applicable
9	1045	001	02-Mar-2005	17-Aug-2005	18-Nov-2005	Progressive Disease
10	1030	001	30-Dec-2004	17-Nov-2005	Continuing	Not Applicable
11	1050	001	10-Mar-2005	17-Nov-2005	Continuing	Not Applicable
12	0406	013	06-Jun-2005	28-Nov-2005	06-Mar-2006	Progressive Disease
13	1053	001	15-Mar-2005	03-Dec-2005	Continuing	Not Applicable
14	1058	001	22-Mar-2005	21-Dec-2005	Continuing	Not Applicable
15	1078	001	02-Jun-2005	13-Jan-2006	Continuing	Not Applicable
16	1069	001	11-May-2005	20-Jan-2006	Continuing	Not Applicable
17	1014	001	16-Nov-2004	07-Feb-2006	Continuing	Not Applicable
18	3154	012	03-Aug-2005	09-Feb-2006	Continuing	Not Applicable
19	1038	001	08-Feb-2005	15-Feb-0206	Continuing	Not Applicable
20	1068	001	03-May-2005	15-Feb-2006	Continuing	Not Applicable
21	1076	001	31-May-2005	16-Feb-2006	Continuing	Not Applicable
22	1079	001	10-Jun-2006	16-Feb-0206	Continuing	Not Applicable
23	1025	001	28-Dec-2004	11-Apr-2006	Continuing	Not Applicable

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Adverse Experience Profile

The most common clinical adverse experiences, regardless of grade, that occurred in at least 20% of the **CTCL patients** who received vorinostat monotherapy were:

- Fatigue 61.7%
 - Diarrhea 53.3%
 - Nausea 48.6%
 - Dysgeusia 36.4%
 - Thrombocytopenia 31.8%
 - Anorexia 26.2%
 - Weight decreased 24.3%
 - Dry mouth 20.6%
-
- The incidence of thrombocytopenia increased 1% and the incidence for weight loss increased 0.9% in the CTCL population during the SUR reporting period.
 - These adverse events were of limited clinical significance, and generally did not lead to discontinuation of study medication or dose adjustment.
 - Discontinuations and dose modifications due to adverse experiences occurred in 12% and 14%, respectively, of the CTCL patients treated at a dose of 400 mg once daily.
 - Other relevant adverse experiences that were observed in CTCL patients included: dehydration (8%) and increased blood creatinine (18%).
 - Muscle spasms, reported in 16% of the CTCL monotherapy population were reported as severe (Grade 3-4) in a small proportion of the patients (1.9%).
 - Alopecia was noted in 16% of these patients.

Comparison of Vorinostat AEs across different patient populations

A summary of specific clinical or laboratory adverse experiences at any dose level across three major safety populations is presented in the table below: CTCL patients (Population 1), solid tumor patients (Population 3), and hematologic malignancy patients (Population 4). [Population 2 is not presented separately as it is a subset of Population 1]

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ON ORIGINAL**

Table 176. Summary of Specific Clinical or Laboratory Adverse Experiences by Preferred Term in the three patient populations: CTCL (Population 1), solid tumors (Population 3), and hematologic malignancies (Population 4) (Applicant's Table)

	Population 1				Population 3				Population 4			
	400mg QD continuous (N=86)		Total Patients (N=107)		400mg QD continuous (N=46)		Total Patients (N=111)		400mg QD continuous (N=16)		Total Patients (N=102)	
	n	%	n	%	n	%	n	%	n	%	n	%
Diarrhoea	45	(52.3)	57	(53.3)	16	(34.8)	47	(42.3)	9	(56.3)	73	(71.6)
Fatigue	45	(52.3)	66	(61.7)	34	(73.9)	88	(79.3)	12	(75.0)	64	(62.7)
Nausea	35	(40.7)	52	(48.6)	27	(58.7)	78	(70.3)	6	(37.5)	61	(59.8)
Dysgeusia	24	(27.9)	39	(36.4)	9	(19.6)	13	(11.7)	0	(0.0)	10	(9.8)
Thrombocytopenia	22	(25.6)	34	(31.8)	13	(28.3)	24	(21.6)	1	(6.3)	31	(30.4)
Anorexia	21	(24.4)	28	(26.2)	30	(65.2)	70	(63.1)	4	(25.0)	56	(54.9)
Weight Decreased	18	(20.9)	26	(24.3)	14	(30.4)	40	(36.0)	1	(6.3)	22	(21.6)
Muscle Spasms	17	(19.8)	17	(15.9)	6	(13.0)	10	(9.0)	0	(0.0)	7	(6.9)
Alopecia	16	(18.6)	17	(15.9)	6	(13.0)	12	(10.8)	1	(6.3)	8	(7.8)
Blood Creatinine Increased	14	(16.3)	20	(18.7)	17	(37.0)	44	(39.6)	12	(75.0)	34	(33.3)
Chills	14	(16.3)	18	(16.8)	2	(4.3)	8	(7.2)	2	(12.5)	17	(16.7)
Dry Mouth	14	(16.3)	22	(20.6)	5	(10.9)	10	(9.0)	0	(0.0)	9	(8.8)
Constipation	13	(15.1)	15	(14.0)	12	(26.1)	43	(38.7)	5	(31.3)	31	(30.4)
Dizziness	13	(15.1)	15	(14.0)	7	(15.2)	16	(14.4)	4	(25.0)	21	(20.6)
Vomiting	13	(15.1)	21	(19.6)	20	(43.5)	59	(53.2)	3	(18.8)	40	(39.2)
Anaemia	12	(14.0)	17	(15.9)	12	(26.1)	19	(17.1)	0	(0.0)	32	(31.4)
Decreased Appetite	12	(14.0)	16	(15.0)	1	(2.2)	1	(0.9)	0	(0.0)	3	(2.9)
Oedema Peripheral	11	(12.8)	14	(13.1)	5	(10.9)	10	(9.0)	3	(18.8)	17	(16.7)
Headache	10	(11.6)	11	(10.3)	3	(6.5)	12	(10.8)	2	(12.5)	14	(13.7)
Pruritus	10	(11.6)	10	(9.3)	0	(0.0)	3	(2.7)	2	(12.5)	7	(6.9)
Cough	9	(10.5)	17	(15.9)	7	(15.2)	24	(21.6)	6	(37.5)	27	(26.5)
Pyrexia	9	(10.5)	16	(15.0)	5	(10.9)	25	(22.5)	5	(31.3)	22	(21.6)
Upper Respiratory Tract Infection	9	(10.5)	12	(11.2)	3	(6.5)	9	(8.1)	3	(18.8)	13	(12.7)
Abdominal Pain	7	(8.1)	8	(7.5)	6	(13.0)	24	(21.6)	1	(6.3)	15	(14.7)
Dyspnoea	7	(8.1)	9	(8.4)	13	(28.3)	39	(35.1)	9	(56.3)	34	(33.3)
Hyperglycaemia	7	(8.1)	11	(10.3)	19	(41.3)	54	(48.6)	15	(93.8)	57	(55.9)
Aspartate Aminotransferase Increased	6	(7.0)	6	(5.6)	10	(21.7)	26	(23.4)	6	(37.5)	18	(17.6)
Insomnia	6	(7.0)	11	(10.3)	6	(13.0)	11	(9.9)	0	(0.0)	6	(5.9)
Alanine Aminotransferase Increased	5	(5.8)	5	(4.7)	5	(10.9)	20	(18.0)	7	(43.8)	21	(20.6)
Hypokalaemia	5	(5.8)	7	(6.5)	8	(17.4)	21	(18.9)	2	(12.5)	26	(25.5)
Carbon Dioxide Decreased	4	(4.7)	4	(3.7)	3	(6.5)	8	(7.2)	3	(18.8)	5	(4.9)
Depression	4	(4.7)	5	(4.7)	5	(10.9)	5	(4.5)	1	(6.3)	5	(4.9)
Dyspepsia	4	(4.7)	5	(4.7)	4	(8.7)	8	(7.2)	0	(0.0)	14	(13.7)
Neutropenia	4	(4.7)	6	(5.6)	0	(0.0)	0	(0.0)	0	(0.0)	11	(10.8)
Hypermagnesaemia	3	(3.5)	3	(2.8)	4	(8.7)	10	(9.0)	3	(18.8)	8	(7.8)
Leukopenia	3	(3.5)	4	(3.7)	3	(6.5)	3	(2.7)	0	(0.0)	11	(10.8)
Pollakiuria	3	(3.5)	4	(3.7)	3	(6.5)	16	(14.4)	1	(6.3)	6	(5.9)
White Blood Cell Count Decreased	3	(3.5)	3	(2.8)	2	(4.3)	20	(18.0)	8	(50.0)	22	(21.6)
Back Pain	2	(2.3)	4	(3.7)	5	(10.9)	21	(18.9)	1	(6.3)	9	(8.8)
Hyperkalaemia	2	(2.3)	2	(1.9)	4	(8.7)	17	(15.3)	1	(6.3)	8	(7.8)
Hypophosphataemia	2	(2.3)	2	(1.9)	2	(4.3)	5	(4.5)	5	(31.3)	21	(20.6)

	Population 1		Population 3		Population 4	
	400mg QD continuous (N=86)	Total Patients (N=107)	400mg QD continuous (N=46)	Total Patients (N=111)	400mg QD continuous (N=16)	Total Patients (N=102)
	n %	n	n %	n	n %	n
Muscular Weakness	2 (2.3)	6 (5.6)	1 (2.2)	5 (4.5)	2 (12.5)	8 (7.8)
Rash	2 (2.3)	4 (3.7)	0 (0.0)	1 (0.9)	1 (6.3)	12 (11.8)
Asthenia	1 (1.2)	4 (3.7)	4 (8.7)	10 (9.0)	0 (0.0)	18 (17.6)
Blood Alkaline Phosphatase Increased	1 (1.2)	4 (3.7)	7 (15.2)	23 (20.7)	5 (31.3)	24 (23.5)
Blood Urea Increased	1 (1.2)	2 (1.9)	7 (15.2)	7 (6.3)	0 (0.0)	7 (6.9)
Dehydration	1 (1.2)	9 (8.4)	5 (10.9)	16 (14.4)	5 (31.3)	27 (26.5)
Hypocalcaemia	1 (1.2)	3 (2.8)	3 (6.5)	23 (20.7)	7 (43.8)	31 (30.4)
Hypoglycaemia	1 (1.2)	1 (0.9)	3 (6.5)	5 (4.5)	2 (12.5)	4 (3.9)
Hyponatraemia	1 (1.2)	1 (0.9)	10 (21.7)	26 (23.4)	5 (31.3)	21 (20.6)
Neutrophil Count Decreased	1 (1.2)	1 (0.9)	1 (2.2)	9 (8.1)	3 (18.8)	12 (11.8)
Prothrombin Time Prolonged	1 (1.2)	2 (1.9)	4 (8.7)	21 (18.9)	11 (68.8)	18 (17.6)
Staphylococcal Infection	1 (1.2)	2 (1.9)	1 (2.2)	1 (0.9)	2 (12.5)	2 (2.0)

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
 Population 1: Vorinostat Monotherapy - CTCL
 Population 3: Vorinostat Monotherapy - Solid Tumors
 Population 4: Vorinostat Monotherapy - Hematologic Malignancies

[Ref. 5.3.5.2: P001-define] [Ref. 5.3.5.4: P003V1-define, P004V1-define, P006-define, P011V1-define, P013V1-define, P029V1-define, P030V1-define] [Ref. 5.3.3.2: P008-define] [Ref. 5.3.5.2: P005] [Ref. 5.3.5.4: P002]

- Adverse experiences **more frequent in CTCL patients** (as compared to other safety populations): taste disorders, dry mouth, muscle spasms, and decreased appetite.
- Adverse experiences **less frequent in CTCL patients** (as compared to other safety populations): anorexia, constipation, vomiting, increased blood creatinine, pyrexia, hyperglycemia, increased hepatic enzymes, hypocalcaemia, and leucopenia.

AEs among patients who received Vorinostat at 400 mg once daily dose:

- The incidence of increased blood creatinine reported as an adverse experience was 2.7 and 4.6 fold higher in the solid tumor and hematologic malignancy populations than in the CTCL population.
- The incidence of hyperglycemia reported as an adverse experience was 5.1 fold and 11.6 fold higher in the solid tumor and hematologic malignancy patients, respectively, than in the CTCL population.
- The differences in the AEs noted above appear to be a function of the underlying disease related factors in the respective populations.

Hematological AEs

Thrombocytopenia

Thrombocytopenia occurred in about 20% to 30% of the patients in each population and was the most common hematologic abnormality.

- Thrombocytopenia (all grades, including grades 3 and 4) was at least twice as common in the patients receiving Vorinostat at doses above the MTD compared to the patients receiving doses below the MTD in each of the 3 populations.
- At 400 mg once daily Vorinostat dose, the increase in incidence among non – CTCL as compared to CTCL patients was not noted.

- Above data for thrombocytopenia suggest that thrombocytopenia is a Vorinostat related, dose-dependent toxicity.

Leukopenia

Leukopenia was uncommon in both the CTCL and the solid tumor populations, but occurred in 50% of hematologic malignancies patients receiving 400 mg once daily and in 22% of the entire hematologic malignancy population.

Adverse Experiences of Grades 3, 4, or 5 in the CTCL patient population

More severe adverse experiences (Grade 3, 4, or 5) were uncommon. The most frequent Grade 3, 4, and 5 clinical adverse experiences observed in the CTCL population at the 400 mg once daily dose level:

- | | |
|------------------------|------|
| ○ Thrombocytopenia | 10% |
| ○ Pulmonary embolism | 5.6% |
| ○ Fatigue | 5.6% |
| ○ Nausea | 3.7% |
| ○ Anemia | 3.7% |
| ○ Deep vein thrombosis | 3.7% |
| ○ Pyrexia | 3.7% |
| ○ Sepsis | 2.8% |
-
- Both the *frequency* and the *severity* of adverse experiences were increased when patients were exposed to Vorinostat doses above the clinically recommended 400 mg once daily dose; however, the specific *types* of adverse experiences were generally similar.
 - In the CTCL population treated with 400 mg once daily of Vorinostat, the median time to onset of the first Grade 3, 4, or 5 clinical adverse experience was 41 days (range: 1 to 263 days). The median duration of the first Grade 3 or 4 clinical adverse experience was 15 days (range: 1 to 257+ days). Thus, the majority of the severe clinical adverse experiences occurred before the completion of the first two months of Vorinostat therapy and resolved in about two weeks when the dosing was interrupted.

- Rare, severe adverse experiences of polyneuropathy and subdural hematoma were observed in patients treated with 200 mg twice daily continuously.

***Reviewer Comments:** The applicant commented that the adverse experiences associated with vorinostat usage are either readily apparent to the patient, or are easily monitored by routine analysis of complete blood counts and serum chemistries (electrolytes, glucose, and serum creatinine). It was recommended that patients be monitored by their physician every 2 weeks for the initial 2 months of vorinostat therapy, and then monthly thereafter. The reviewer concurs.*

Deaths

- In the Original Application with 305 patients in the dataset, there were 24 deaths (7.9%). Twenty-one (21) of the 24 deaths (87.5%) were considered by the Investigator to be **not** drug-related, and 14 (58.3%) of the deaths were attributed to disease progression. The remaining 3 deaths (AN 1008 and AN 1048 in Protocol 001 and AN 003 in Protocol 011) were due to single cases of unknown cause, ischemic stroke, and tumor hemorrhage; these were considered by the Investigator to be related to Vorinostat.
- Additionally, 6 deaths were reported in the double-blind, placebo-controlled, randomized Protocol 014.
- During the SUR reporting period, there were 3 additional deaths (in the SUR dataset of 357 patients); a cumulative rate of 7.6% (27/357). All of the new deaths were considered by the Investigator to be **not** related to Vorinostat.

Serious Adverse Experiences

- Serious adverse experiences, while not uncommon, generally were identified by the investigators to be related to the underlying malignancies.
- Serious adverse experiences thought to be related to Vorinostat therapy were more severe variants of the typical adverse experiences, such as fatigue and thrombocytopenia.
- The most common serious, drug-related adverse experiences in 107 **CTCL patients** in two clinical studies, regardless of the dose, included pulmonary embolism (4.7%), dehydration (3.7%), thrombocytopenia (3.7%) and anemia (1.9%). There were single experiences of chest pain, death, deep vein thrombosis, diarrhea, gastrointestinal hemorrhage, hepatic ischemia, hypotension, ischemic stroke, nausea, pyrexia, streptococcal bacteremia, syncope, increased blood creatinine, and vomiting.
- The qualitative pattern of drug-related, serious adverse experiences in the **Solid Tumor – Monotherapy population** was similar to that observed in the CTCL population. In Solid Tumor- Monotherapy patients, there was a higher frequency of drug related serious adverse experiences in patients exposed to doses that exceeded the MTD (34.2%) compared to those treated with 400 mg once daily (9.8%).

- In the **Hematologic Malignancy-Monotherapy population**, there were serious adverse experiences of increased frequency that were distinct from the other populations and that likely reflect the underlying disease and comorbid conditions—particularly cytopenias and infections. Serious adverse experiences of febrile neutropenia and infections were reported in 11.8% and 13.7% of patients, respectively. Serious adverse experiences that were hemorrhagic events that might be expected in thrombocytopenic patients included gastrointestinal hemorrhage (3.9%), subdural hematoma (2.0%), and, cerebral hemorrhage and hemorrhagic shock (1.0%). A higher frequency of serious adverse experiences of dehydration (12.7%) and diarrhea (6.9%) were noted in this patient population. One unusual event reported only in this population was a single case of recurrent Guillain-Barré Syndrome.

Serious Laboratory Adverse Experiences

- *Serious laboratory* adverse experiences were rare across all populations.
- Blood creatinine increases were reported in all populations, but at a slightly higher frequency in patients exposed to the doses that exceeded the MTD.
- In solid tumor patients there were rare increases in transaminases that met the criteria for a serious adverse experience.

Adverse Events of Clinical Interest

Although reported at low frequency, cardiovascular events, cerebrovascular events, and venous thromboembolic events were examined in detail due to the severity of these events. Frequently reported laboratory abnormalities that were evaluated in more detail included hyperglycemia, increased serum creatinine, and thrombocytopenia.

1) Cardiovascular, Cerebrovascular and Venous Thrombosis

- While **cardiac** adverse experiences may be severe when they occur, they are infrequent.
- All of the cardiovascular events occurred in patients with at least one independent risk factor.
- ECG adverse experiences that were drug-related were reported in 20 patients (20/361, 5.5%) and were rarely severe or serious.
- None of the **cerebrovascular** events occurred without prior history of such events or clear risk factors for cerebrovascular disease.
- The incidence of **venous thromboembolic** episodes (VTE), including deep vein thrombosis and pulmonary embolism, in the overall population was 6% (22 of 361).
- The rate of VTE was higher (10.8%, 4/37) in the Vorinostat Combination Therapies patients as compared to the monotherapy patients (18/324, 5.6%). All 4 patients in the Vorinostat Combination Therapies population who developed VTE were from Protocol

012. They were being treated with vorinostat in combination with pemetrexed and cisplatin. Four patients who developed VTE during study drug treatment had prior episodes of VTE and 1 patient was taking oral estrogen.

2) Blood Glucose

Blood glucose elevations were frequently reported in all patient populations. However, no patient discontinued Vorinostat due to glucose elevation. The severity of adverse experiences of hyperglycemia was low.

- Hyperglycemia was reported in 10% of the CTCL patients; however, only a single CTCL patient had a Grade 3 adverse experience of hyperglycemia.
- A much higher incidence of hyperglycemia was seen in the solid tumor (> 40%) and the hematological malignancies (55%) populations.
- The high incidence of hyperglycemia in the solid tumor (> 40%) and the hematological malignancies (55%) populations may reflect the use of concomitant medications, including corticosteroids, and a higher incidence of diabetes mellitus. Furthermore, fasting samples were not mandated in the most of the clinical studies and, some of the high blood glucose levels may reflect a post-prandial state.
- Across the 400 mg once daily dose population, all patients with a Grade 3 or higher adverse experience of hyperglycemia had a history of underlying diabetes mellitus or glucose intolerance.

Reviewer Comments: *The applicant comments that patients with pre-existing glucose intolerance may require monitoring of their diet and adjustment in their medical management. Reviewer concurs.*

3) Blood Creatinine

- Elevated blood creatinine was noted as a lab abnormality in a significant portion of patients across the various Vorinostat studies populations.
- No more than 2% of these lab abnormalities were reported as adverse experiences of Grade 3 or higher. No cases of acute renal failure or need for dialysis were reported. Dose modification was rarely required due to elevation in serum creatinine.

Reviewer Comments: *The applicant comments that creatinine should be monitored on a routine basis while patients are treated with Vorinostat and there is no signal of long term clinical sequelae associated with this laboratory finding. The reviewer concurs.*

4) Thrombocytopenia

- Thrombocytopenia is a dose-dependent adverse event following exposure to vorinostat.
- The observed thrombocytopenia rarely (< 5%) exceeds Grade 2 severity in CTCL patients exposed to 400 mg once daily dosing.
- Thrombocytopenia recovers rapidly and patients can be safely treated at reduced doses of vorinostat after recovery. Hemorrhagic sequelae associated with thrombocytopenia occur at a low frequency, but have included gastrointestinal hemorrhage, tumor hemorrhage, cerebral hemorrhage, and subdural hematoma.

Reviewer Comments: The applicant comments that the patients exposed to vorinostat should have their platelet count monitored at the beginning of each cycle of treatment, and, if interrupted dosing is used, at the time of maximal days of exposure during a cycle.

Laboratory Abnormalities

Laboratory abnormalities were evaluated by the highest CTCAE Grade in a patient and for shifts from the baseline values.

- Changes in serum glucose, blood creatinine, and platelet count have been described above.

CTCL patients receiving Vorinostat at 400 mg once daily

- Decreased hemoglobin (58.6%), decreased lymphocyte count (34.5%), and decreased white blood cell (WBC) count (24.1%), increased cholesterol (66.2%), increased serum triglycerides (66.2%), and increased urine protein (51.4%) were noted (*all grades*).
- The most common *clinically significant* laboratory abnormalities were Grade 3 increased serum glucose in 5 patients (5.7%), Grade 3 decreased serum potassium in 3 patients (3.4%), Grade 4 increased serum uric acid in 3 patients (3.4%), and Grade 3/4 decreased platelet count in 6 patients (6.8%).
- Although INR was increased in some patients, they were receiving warfarin.
- Shift analyses showed that the majority of the patients improved without any alteration in their vorinostat dosing.

Vorinostat Monotherapy – Solid Tumors Population

- One abnormality seen more frequently than in the CTCL population was hyponatremia, in patients who had been treated both at above the MTD and at 400 mg daily doses.

Vorinostat Monotherapy – Hematologic Malignancy Population

- Patients with hematologic malignancies commonly had hematologic lab abnormalities of Grade 3 or higher.

Proteinuria

- Proteinuria was transiently detected in CTCL patients in whom urine protein by dipstick testing was performed. This abnormality does not appear to be associated with either an increase in creatinine or a decrease in serum albumin.

Conclusions

- Findings presented in the SUR are consistent with the safety conclusions made in the Original Application. Overall, to date, the types of adverse experiences reported with Vorinostat use are similar to those presented and discussed in the Integrated Summary of Safety (ISS) in the Original Application. No new or unexpected trends were observed when comparing the updated cumulative safety data in this SUR with the Original Application.

The applicant comments:

The conclusions reached in the Original Application are consistent with and supported by this SUR:

- Vorinostat is generally well tolerated.
- Common clinical adverse experiences include fatigue and a spectrum of gastrointestinal effects: nausea, anorexia, weight loss, and diarrhea.
- Common laboratory abnormalities are thrombocytopenia, anemia, increased creatinine, and increased glucose.
- While adverse experiences are common, they are rarely severe.
- Most of the adverse experiences do not interfere with therapy. Across all patient populations, 10% of patients receiving vorinostat at a dose of 400 mg once daily had to discontinue treatment permanently due to drug-related adverse experiences.
- In both the CTCL and solid tumor populations, majority (>80%) of the patients receiving vorinostat at a dose of 400 mg once daily did not require a dose modification.

- Most *serious adverse experiences* were judged by Investigators to be related to the underlying disease, rather than drug-related.
- The most common serious adverse experiences across populations and dose levels, irrespective of investigator attributed causality, were pulmonary embolism, dehydration, thrombocytopenia, febrile neutropenia and anemia.
- Among CTCL patients treated with 400 mg once daily, the most common drug related
- SAEs were pulmonary embolism (4.7%) and anemia (2.3%). No other serious drug-related AE occurred in more than 1 patient.
- Serious adverse experiences included deep venous thrombosis and pulmonary embolism.
- While the incidence of SAEs is similar to what would be expected in a similar study population with advanced cancers, in the absence of a randomized study, an effect of vorinostat cannot be excluded.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Summary of selected AEs

The following selected AEs (all grades) are considered related to Vorinostat administration in the CTCL population:

- Gastrointestinal Complaints (diarrhea 53%, nausea 49%, anorexia 26%)
- Taste Disorders (dysgeusia 36%, dry mouth 21%)
- Constitutional effects (fatigue 62%, weight loss 23%)
- Thromboembolic events (pulmonary embolism 5%)
- Dehydration (1.2%)
- Muscle spasms (17%, reported severe in 2%)
- Alopecia was noted in greater than 15.0% of the total patients; however, this adverse experience was not reported higher than Grade 2 in severity.
- Hematologic effects (thrombocytopenia 30%, leucopenia 24%, decreased lymphocyte count 35%, and decreased hemoglobin 58%)
- Laboratory abnormalities (hyperglycemia 10%, increased serum creatinine 14%, increased ALT 5%, increased cholesterol 66%, increased serum triglycerides 66%, increased urine protein 51%).
- The most common *clinically significant* laboratory abnormalities were Grade 3 increased serum glucose 6%, Grade 3 decreased serum potassium 3%, and Grade 4 increased serum uric acid 3.4%.

The most frequent Grade 3, 4, and 5 clinical adverse experiences observed in the CTCL population:

- | | |
|----------------------|------|
| ○ Thrombocytopenia | 4.7% |
| ○ Pulmonary embolism | 4.7% |
| ○ Fatigue | 3.5% |
| ○ Nausea | 3.5% |
| ○ Anemia | 2.3% |
| ○ Lymphopenia | 2.3% |

Limitations of the data

- Small number of patients
- Limited exposure to Vorinostat due to frequent discontinuations due to a lack of efficacy
- Lack of a control arm

Conclusions

- Despite the high frequency of adverse experiences, the severity of these events was generally mild (Grade 3 or higher in approximately 5%).
- These adverse events were of limited clinical significance and only infrequently led to discontinuation of study medication or dose adjustment.
- Discontinuations and dose modifications due to adverse experiences occurred in 16% and 12% of the CTCL patients treated at a dose of 400 mg once daily.
- The incidence of creatinine increase was 2.7-fold and 5.4-fold higher in the solid tumor and hematologic malignancy populations than in CTCL patients. Similarly the incidence of hyperglycemia was 9.6-fold and 5.4-fold higher in the solid tumor and hematologic malignancy patients, respectively, than in the CTCL population. Thus, the differences noted maybe a function of the underlying disease rather than the study medication.
- The *frequency* and *severity* of adverse experiences were increased when patients were exposed to doses above the clinically recommended dose and schedule of 400 mg once daily; however, the specific *types* of adverse experiences were generally similar.
- The adverse experiences associated with Vorinostat usage are either readily apparent to the patient, or easily monitored by routine analysis of complete blood counts and serum chemistries (electrolytes, glucose and serum creatinine). It is recommended that patients be monitored by their physician every 2 weeks for the initial 2 months of Vorinostat therapy, and then monthly thereafter.

7.4 General Methodology

7.4.1 Pooling Data across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

- In the safety analysis of Vorinostat the data were analyzed both by pooling across different studies (a total of 12 studies with different patient populations) and by looking at the populations in the pivotal trial (Protocol 001) and the supporting trial (Protocol 005).

7.4.1.2 Combining data

- When the data were pooled across studies, the denominator used was the combined total number of patients.
- As different populations that were pooled for analysis had different underlying diseases and past treatments, with likely different AE experiences, the populations were analyzed individually using the relevant (smaller) denominator.

7.4.2 Explorations for Predictive Factors

- Due to small numbers of patients in different disease based patient populations, and limited durations of exposure to Vorinostat in all of these populations, exploration of the available data for the factors predictive of drug related AEs is unreliable.
- Incidence and severity of the AEs can also be affected by the type and severity of the underlying diseases.

7.4.2.1 Explorations for dose dependency for adverse findings

- Based on the available data, thrombocytopenia, GI and constitutional AEs may dose dependant phenomena.
- In the Solid Tumor- Monotherapy patients, a higher frequency of drug related serious adverse experiences in patients exposed to doses that exceeded the MTD was noted: 34% compared to those treated with 400 mg once daily 10%.

7.4.2.2 Explorations for time dependency for adverse findings

- Inadequate data for conclusively defining time dependency of AEs.

7.4.2.3 Explorations for drug-demographic interactions

- The median age of the patients in the majority of Vorinostat trials was ≥ 60 years, and most of the patients were White, explorations for drug-demographic interactions are unreliable.

7.4.2.4 Explorations for drug-disease interactions

- In the **Solid Tumor- Monotherapy** patients, there was a higher frequency of drug related serious adverse experiences in patients exposed to doses that exceeded the MTD (34.2%) compared to those treated with 400 mg once daily (9.8%).
- In the **Hematologic Malignancy-Monotherapy** population, there were serious adverse experiences of increased frequency that were distinct from the other populations and that likely reflect the underlying disease and comorbid conditions—particularly cytopenias and infections. Serious adverse experiences of febrile neutropenia and infections were reported in 11.8% and 13.7% of patients, respectively. Serious adverse experiences that were hemorrhagic events that might be expected in thrombocytopenic patients included gastrointestinal hemorrhage (3.9%), subdural hematoma (2.0%), and, cerebral hemorrhage and hemorrhagic shock (1.0%). A higher frequency of serious adverse experiences of dehydration (12.7%) and diarrhea (6.9%) was also noted in this patient population. One unusual event reported only in this population was a single case of recurrent Guillain-Barré Syndrome.

- Hyperglycemia was reported in 10% of the CTCL patients (only a single CTCL patient had a Grade 3 adverse experience of hyperglycemia). A much higher incidence of hyperglycemia was seen in the solid tumor (> 40%) and the hematological malignancies (55%) populations. The high incidence of hyperglycemia in the solid tumor (> 40%) and the hematological malignancies (55%) populations may reflect the use of concomitant medications, including corticosteroids, and a higher incidence of diabetes mellitus.

7.4.2.5 Explorations for drug-drug interactions

Valproic acid

A case of sever thrombocytopenia leading to GI hemorrhage was reported with concomitant use of valproic acid which is a histone deacetylase inhibitor like Vorinostat.

Anticoagulants

Vorinostat may prolong the INR in patients on oral anticoagulants (warfarin).

7.4.3 Causality Determination

- See 7.4.2.1 above and other comments in this section.

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8 ADDITIONAL CLINICAL ISSUES

8.1 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 of Vorinostat that was used in the pivotal trial (Protocol 001). 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.
- At this starting dose, 10 patients required one or more dose modifications and 9 patients discontinued Vorinostat due to AEs (7 were considered drug related).
- Most patients discontinued Vorinostat due to lack of efficacy.

Analysis of Clinical Information Relevant to Dosing Recommendations

Safety (Toxicities)

Dose-limiting toxicities (DLTs) of Vorinostat in early clinical studies:

- **Non-hematologic:** anorexia, fatigue, dehydration, diarrhea, vomiting, and nausea
- **Hematologic:** thrombocytopenia

Evaluation of Vorinostat showed that its tolerability was determined by:

1. Total daily dose, and
2. Number of consecutive days of dosing

The Maximum tolerated dose (MTD) for continuous daily dosing without a rest period was established as 400 mg once daily or 200 mg twice daily

The MTD for intermittent dosing was established as 300 mg twice daily for 3 consecutive days every 7 days

Efficacy

In the supporting trial (Protocol 005), which was the basis for the starting dose used in the pivotal trial (Protocol 001), the primary efficacy endpoint was the objective response as measured by the Physician's Global Assessment (PGA) of CTCL. The overall response rate was 24% (8 of 33 patients). The observed response rate in cohort 1 (which received 400 mg orally daily of Vorinostat) was 30.8% (4 of 13 patients). In Cohort 3 the response rate was 33.3% (3 of

9) but toxicity was higher, and in Cohort 2 the response rate was 9.1% (1 of 11). The number of days for which patients received Vorinostat were Cohort 1 > Cohort 3 > Cohort 2. Frequency of discontinuation due to AEs and the incidence of serious adverse experiences (SAEs) were lower in Cohort 1. The efficacy and safety trends observed in different cohorts in Protocol 005 were preserved when the analysis was confined to the sub-group of patients with Stage IIB and higher disease who had received prior bexarotene therapy: Cohort 1 = 44%, Cohort 2 = 0%, and Cohort 3 = 17%).

- Based on the proof of efficacy of the 400 mg once daily dose in Protocol 005, and the safety profile for the same dose established in Protocol 005 and other Phase I studies, 400 mg once daily was chosen as the recommended clinical dose and was studied in the pivotal study, Protocol 001.

In the pivotal trial (Protocol 001), starting dose of 400 mg once daily dose was administered to 74 patients.

- The objective response rate as measured by the Physicians Assessment of Overall Skin Disease using the SWAT was 29.5% (18/61) in patients with Stage IIB and higher disease and 29.7% (22/74) in the overall study population. These response rates correlate well with the results observed in Protocol 005 (response rate for patients with Stage IIB and higher disease in Cohort 1 (Vorinostat at 400 mg once daily dose) was 36% (4/11).
- The majority of the patients (86.5%, 64/ 74) administered 400 mg once daily dose of Vorinostat in Protocol 001 did not require any dose modification.
- The frequency of serious adverse experiences was 21.6% (16/74), comparable to the rate of SAEs reported in Protocol 005 Cohort 1 (23.1%, 3/13).
- Discontinuation due to AEs was 12.2% (9/74), again comparable to the discontinuation rate due to adverse experiences observed in Protocol 005 Cohort 1 (7.7%, 1/13).

Dose adjustment for body weight

- A multivariate logistic regression analysis of Protocol 001 data did not reveal any factors, including normalized dose by body weight, which might be *predictive of response*.
- Further investigation of other baseline characteristics, including normalized dose by body weight (mg/kg), on a multivariate logistic regression analysis did not reveal any factors that might be *predictive of serious adverse experiences*.
- In addition, Protocol 008 also provides support for no correlation of body weight with blood drug concentration.

The lack of correlation of efficacy and Vorinostat blood concentration with weight or body surface area (BSA) justifies the recommendation that Vorinostat be administered at a fixed dose.

8.2 Drug-Drug Interactions

- Formal drug-drug interaction studies with Vorinostat were not conducted.
- Vorinostat is metabolized via hydrolysis followed by B-oxidation and/or glucuronidation to pharmacologically inactive metabolites in rat, dog, and human liver preparations. Vorinostat is not eliminated via cytochrome P450 pathways; therefore, drug-drug interactions at the intended clinical dose and/or pharmacologically relevant concentrations are not anticipated.
- In some patients receiving Vorinostat concomitantly with coumarin-derivative anticoagulants, prolongation of prothrombin time and International Normalized Ratio (INR) were reported, however, no clear drug interaction was demonstrated.
- Vorinostat should not be administered concomitantly with other HDAC inhibitors as class specific adverse experiences may be additive.
 - Inadvertently, 1 patient on Protocol 001 (AN 1044) concurrently took valproic acid and Vorinostat. This patient rapidly developed grade 4 thrombocytopenia with associated gastrointestinal bleeding and anemia.

8.3 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.

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

8.4 Pediatrics

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

8.5 Advisory Committee Meeting

- Vorinostat was not presented to the Oncology Drug Advisory Committee.

8.6 Literature Review

Review of CTCL literature (see Section REFERENCES) shows:

- CTCL is rare = 0.36 per 10⁵ person-years
- Physicians use different clinical methods for assessment of disease burden and response evaluation
- In the trial that led to approval of Ontak by the FDA, SWAT methodology was used
- Systemic treatment of advanced CTCL remains unsatisfactory. Response rates to the available treatments remain in about 30% range and response durations are short (4 to 6 months), and additional treatment are needed.

8.7 Postmarketing Risk Management Plan

Safety issues with Vorinostat are similar to those of other cancer therapies. The applicant proposes routine risk management measures which include adequate labeling and routine pharmacovigilance.

- 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.

8.8 Other Relevant Materials

- See 1.2 RECOMMENDATIONS ON POSTMARKETING ACTION for the recommendations based on the review from the Office of Drug Safety.
- Consult from the Division of Drug Marketing, Advertising, and Communication (DDMAC) was reviewed—

consult is available in the Division Filing System and the concerns will be addressed during Vorinostat labeling meetings.

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9 OVERALL ASSESSMENT

9.1 Conclusions

Efficacy of Vorinostat for treatment of advanced CTCL has been shown in the pivotal trial (Protocol 001). This trial was an open-label, single-arm, multicenter, Phase 2, non-randomized study. 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).

The primary endpoint was the objective tumor response rate based on an 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.

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.

- 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

Response rate

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)

- 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.

Reviewer Comments:

It is important to note that the changes in the Sezary cell count (by using flow-cytometry) were not taken into consideration when determining the objective response of the skin disease. Moreover, correlation between the two was poor. Also, while progression in the lymph node disease negated a response in the skin disease, stable nodal disease did not impact on the skin disease response. Similar to Sezary cell responses, correlation between the nodal and skin responses was poor. Because of these two observations, Vorinostat approval is recommended for the treatment of cutaneous manifestations of CTCL.

Duration of Response

- For the responders: 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 the results (ranges of time endpoints) slightly: 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)

The observed response rates and durations of response demonstrate the efficacy of Vorinostat.

These results are comparable to the results obtained with the approved and available systemic therapies: Targretin (bexarotene) and Ontak (denileukin diftitox):

Targretin

The approval of bexarotene was based on 2 multicenter, open-labeled, historically controlled clinical studies. In 62 patients with early and advanced stage who were refractory to at least one prior systemic therapy, Targretin at a dose of 300 mg/m²/day orally produced an overall response

rate of 32.3% (1 complete tumor response and 19 partial tumor responses). Responses were evaluated by Composite Assessment of Index Lesion Disease Severity (CA). The median time to response was 26 weeks. The rate of relapse in 20 patients who had a tumor response was 30% over a median observation duration of 21 weeks.

- In patients who had failed to respond to bexarotene, the response rate to Vorinostat was 31% (5/16). This rate was similar to the rate (29%, 2/7) observed in the patients who had earlier responded to bexarotene.

Ontak

Another drug that is commonly available in treating CTCL is denileukin diftitox—a recombinant DNA-derived fusion protein designed to direct the cytotoxic action of diphtheria toxin to cells expressing interleukin-2 (IL-2) receptor. Denileukin diftitox received accelerated approval from the FDA for the treatment of patients with persistent or recurrent CTCL whose malignant cells express the CD25 component of the IL-2 receptor. In a randomized, double-blind study designed to evaluate two doses of denileukin diftitox (9 or 18 µg/kg/day) administered intravenously, the tumor response rate assessed using the Severity Weighted Assessment Tool (SWAT) was 23% (95% CI: 10-40%) in 35 patients randomized to the 9 µg/kg/day arm, and 36% (95% CI: 21-54%) in 36 patients randomized to the 18 µg/kg/day arm. The overall tumor response rate for 71 patients was 30% (7 complete tumor responses and 14 partial tumor responses).

Relief of pruritis with Vorinostat

In the pivotal trial (Protocol 001) the 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.

- 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.

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.

- *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 responses.*
 - *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 $\geq 10\%$ body surface area was involved, or by weighted score and measurements of 5 target lesions (when $\leq 10\%$ body surface area was involved)*

9.2 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, ~~_____~~

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9.3 Recommendation on Postmarketing Actions

9.3.1 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.

9.3.2 Required Phase 4 Commitments

- None

9.3.3 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.

9.4 Labeling Review

- Scheduled for a later date

9.5 Comments to Applicant

- None at present

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10 APPENDICES

10.1 Review of Individual Study Reports

Protocol 001: PHASE IIB MULTICENTER CLINICAL TRIAL OF ORAL SUBEROYLANILIDE HYDROXAMIC ACID (SAHA) IN ADVANCED CUTANEOUS T-CELL LYMPHOMA

Generic Name: Vorinostat	Protocol 001
Dosage Form: Capsule	Phase IIb
Indication: CTCL	Study Design: Open-label, single-arm
Sponsor Name:	Merck & Co., Inc.
Clinical Monitor:	Stanley Frankel, M.D.
Study Initiation Date (FPI):	17-Mar-2004
Study Completion Date (LPO):	23-Nov-2005
Investigator Name/Affiliation:	Multicenter in the United States (17) and Canada (1)
GCP Compliance:	Information regarding GCP compliance can be found in Section 5.2
Clinical Study Report Date:	27-Feb-2006

Reviewer Comments:

The table below "Subject/Patient Disposition" lumps together 24 cases of treatment failure due to lack of efficacy, withdrawal of consent, and unacceptable toxicity. This lowers the number of cases labeled Progressive disease and Clinical adverse experience.

**CLINICAL STUDY REPORT
SYNOPSIS**

PROTOCOL TITLE/NO.: Phase IIb Multicenter Clinical Trial of Oral Suberoylanilide #001
Hydroxamic Acid (SAHA) in Advanced Cutaneous T-cell Lymphoma

INVESTIGATORS/STUDY CENTERS: Multicenter (17) in the United States and Canada (1).

PRIMARY THERAPY PERIOD: 17-Mar-2004 to 23-Nov-2005. **CLINICAL PHASE:** IIb
Frozen File occurred 07-Dec-2005. Study is ongoing.

DURATION OF TREATMENT: Treatment continued until disease progression or intolerable toxicity.

OBJECTIVES: Primary: 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 and higher) who have progressive, persistent, or recurrent disease. Secondary: (1) To assess response duration; (2) To evaluate the relief of pruritus; (3) To assess time to progression; (4) To assess time to objective response.

STUDY DESIGN: An open-label, single-arm study in patients with advanced CTCL.

SUBJECT/PATIENT DISPOSITION:

SCREENING FAILURES: Eight (8) patients were screened but were not allocated to receive study drug.

	<u>Vorinostat</u>
ENTERED STUDY	74
Male (age range)	38 (43 to 83)
Female (age range)	36 (39 to 81)
COMPLETED	1
CONTINUING	12
EXTENDED	3
DISCONTINUED: Total	58
Progressive disease	25
Clinical adverse experience	9
Laboratory adverse experience	0
	24

[†] Lack of efficacy, withdrawal of consent, unacceptable toxicity.

DOSAGE/FORMULATION NOS.: Patients were to take 400 mg of vorinostat orally once daily for 7 days/week (with food). Dose modification (300 mg once daily for 7 days/week, 300 mg for 5 consecutive days/week) was allowed by the protocol after recovery from dose-related toxicities.

<u>Product</u>	<u>Formulation No.</u>
Vorinostat 50 mg [‡]	C04-0208-001
Vorinostat 100 mg	DFC001A001, DFC002A001, DCF004A001, DFC005A001
Vorinostat 200 mg	C04-0204-004

[‡] No 50 mg capsules were used in this study.

DIAGNOSIS/INCLUSION CRITERIA: Males and females at least 18 years of age, who had a recent histological diagnosis of CTCL with advanced disease (Stage IB and higher), on or following two systemic therapies, one of which must contain bexarotene (unless contraindicated) and an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-2.

EVALUATION CRITERIA:

EFFICACY MEASUREMENTS: Primary: Efficacy was assessed by an analysis of the response rate of overall skin disease by physician's assessment using a Severity Weighted Assessment Tool (SWAT) in patients with Stage IIB and higher disease. Secondary: A patient questionnaire was used to assess pruritus.

SAFETY MEASUREMENTS: Evaluation of safety included tabulating all adverse experiences, whether or not related to study drug. Routine laboratory assessments were also analyzed.

STATISTICAL PLANNING AND ANALYSIS:

EFFICACY: The primary analysis was based on the proportion of patients (Stage IIB and higher who received at least one dose of study medication) with either a Clinical Complete Response (CCR) or a Partial Response (PR) in overall skin disease as measured by the SWAT. Complete Response was defined as no evidence of disease; 100% improvement. Partial Response was defined as a ≥50% decrease in SWAT assessment compared to baseline which was maintained for at least 4 weeks. Seventy-four patients were enrolled to ensure that there would be at least 50 evaluable patients with CTCL Stage IIB and higher, 61 patients met this criterion. In evaluable patients who have had at least 2 prior systemic therapies, the expected objective response in overall skin disease without treatment is expected to be less than 5%. Vorinostat would be considered active for treatment of CTCL if the observed response rate in overall skin disease met the joint criteria – at least 20% with the lower bound of the corresponding 95% Confidence Interval excluding 5%. With a sample size of 60, this study had a 90% power to meet the joint response criteria if the true response rate was 23% and had the same power to exclude 5% alone if the true response rate was 19%.

SAFETY: All patients who received at least one dose of vorinostat were evaluable for safety. Treatment emergent clinical and laboratory adverse experiences were summarized or listed, as appropriate.

RESULTS:

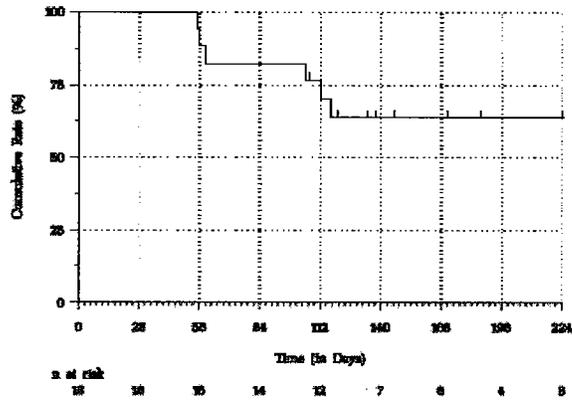
EFFICACY: Eighteen (18/61) patients with Stage IIB and higher disease had a responded. The response rate was 29.5% and the corresponding 95% confidence interval to the response rate of (18.5%, 42.6%), exceeded the pre-specified criteria for a positive trial. These patients had a median time to response of less than 2 months. Similar results were found in the 3 prespecified subgroup populations: all patients, patients with Sezary syndrome, and patients with T3 tumor disease. The median response duration was not reached, but was estimated to be at least 4 months. The median time-to-progression was not reached, but was estimated to be at least 5 months based on all patients Stage IIB and higher.

Number of Patients Treated with Vorinostat with an Objective Response¹
 (All Patients As Treated)

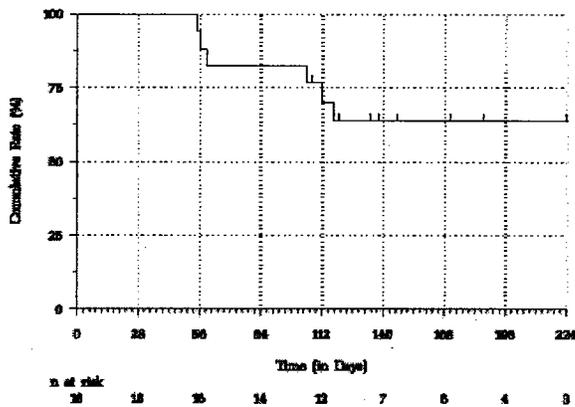
Population	N	Patients with an Objective Response ¹				
		n (%)	(95% CI)	Time to Objective Response ² (days) Median (Range)	Duration of Objective Response (days) Median (Range)	Time to Progressive Disease (days) Median (Range)
All Patients	74	22 (29.7%)	(19.7, 41.5)	55 (28, 171)	.(34+, 322+)	.(78-, 365-)
Stage IIB or Higher CTCL ³	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 T3 tumor disease	22	5 (22.7%)	(7.8, 45.4)	31 (29, 87)	.(55, 280-)	.(148, 317+)

¹ Objective Response: confirmed complete response or partial response.
² Stages IIB, III, IVA, and IVB.
 CI = Confidence Interval.
 + = Response ongoing.

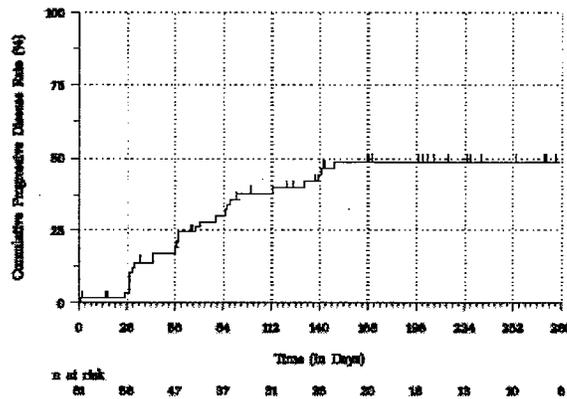
Response Duration
 Observed Kaplan-Meier Curve during Treatment with Vorinostat
 For Patients Who Achieved An Objective Response
 (Patients With Stage IIB And Higher CTCL)



Response Duration
 Observed Kaplan-Meier Curve during Treatment with Vorinostat
 For Patients Who Achieved An Objective Response
 (Patients With Stage IIB And Higher CTCL)



Time to Progressive Disease
 Observed Kaplan-Meier Curve during Treatment with Vorinostat
 (Patients With Stage IIB And Higher CTCL)



Eighteen (18/59, 30.5%) of the patients with Stage IIB and higher disease had clinically important pruritus relief and 8/59 (13.6%) had complete resolution of their pruritus. This relief in pruritus was maintained for at least 4 weeks without an increase in their pruritus medication. The results were similar for patients with pruritus intensity ≥ 3 at baseline and patients with Sezary syndrome.

Number of Patients Treated with Vorinostat with Relief of Pruritus¹ for
 At Least 4 Weeks without An Increase in the Use of Anti-pruritus Medications
 (Among Patients With Stage IIB And Higher CTCL)

Population	N	Patients with complete resolution ¹		Patients with Pruritus Relief ²	
		n (%)	(95% CI)	n (%)	(95% CI)
All Patients	59	8 (13.6%)	(6.0, 25.0)	18 (30.5%)	(19.2, 43.9)
Patients with pruritus intensity ≥ 3 points at baseline	53	6 (11.3%)	(4.3, 23.0)	16 (30.2%)	(18.3, 44.3)
Patients with Sezary Syndrome	30	3 (10.0%)	(2.1, 26.5)	9 (30.0%)	(14.7, 49.4)
Patients with tumor disease	20	2 (10.0%)	(1.2, 31.7)	4 (20.0%)	(5.7, 43.7)

¹ The intensity of pruritus is assessed on the point scale of 0-10, with zero being no pruritus and ten being the worst imaginable pruritus.
² Complete Resolution is sustained pruritus score of 0 for at least 4 continuous weeks.
³ Pruritus Relief is sustained pruritus reduction of 3 or more points or complete resolution for at least 4 continuous weeks.
 Pruritus medication use was not collected for Site 0608: patients 1001, 1002, 1003, 1005, 1037, 1080.
 CI=Confidence Interval.
 Patient allocation numbers 1047 and 1027 had missing pruritus at baseline, and were excluded from the analysis.

The following table provides the relationship between best response to the last systemic therapy the patient received prior to taking vorinostat and their response to vorinostat in this study. Patients were divided into a bexarotene therapy group and a non-bexarotene therapy group. There was no obvious impact observed on the response to last treatment, either bexarotene or other therapies, on the subsequent efficacy of vorinostat.

Relationship Between Best Response To Last Systemic Therapy¹
 And Response² To Vorinostat
 (All Patients As Treated)

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)

¹ Objective Response: confirmed complete response or partial response.
² Excludes systemic procedures as response data to procedures is unavailable.
 CI = confidence Interval.

SAFETY: Clinical adverse experiences were reported in 70/74 (94.6%) patients. Drug-related clinical adverse experiences were reported in 68/74 (91.9%) patients. Nine (9/74, 12.2%) of the patients discontinued study therapy due to a clinical adverse experience. Seven (7/74, 9.5%) patients discontinued study therapy due to a drug-related clinical adverse experience.

Adverse Experience Summary

	400 mg once daily x 7d/wk (N = 74)	
	n	(%)
Clinical Adverse Experiences		
Number (%) of patients:		
With one or more adverse experiences	70	(94.6)
With no adverse experience	4	(5.4)
With drug-related adverse experiences ¹	68	(91.9)
With serious adverse experiences	16	(21.6)
With serious drug-related adverse experiences	8	(10.8)
Who died	3	(4.1)
Discontinued due to adverse experiences	9	(12.2)
Discontinued due to drug-related adverse experiences	7	(9.5)
Discontinued due to serious adverse experiences	6	(8.1)
Discontinued due to serious drug-related adverse experiences	4	(5.4)
Laboratory Adverse Experiences		
Number (%) of patients:		
With at least one lab test postbaseline	74	(100.0)
With one or more adverse experiences	22	(29.7)
With no adverse experience	52	(70.3)
With drug-related adverse experiences ¹	20	(27.0)
With serious adverse experiences	1	(1.4)
With serious drug-related adverse experiences	1	(1.4)

¹ Determined by the investigator to be possibly, probably or definitely drug related.
² The percent = number of patients within the laboratory adverse experience category / number of patients with one or more laboratory tests postbaseline.
 No patients discontinued due to a laboratory adverse experience, and there were no laboratory adverse experiences which resulted in death.

Summary of Specific Clinical or Laboratory Adverse Experiences by Preferred Term
 (Incidence ≥ 10% in One or More Dose Levels)
 All Patients Adverse Experiences

	Total Patients (N=74)							
	All Experiences				Related Experiences Only			
	All Grades		Grade 3-5		All Grades		Grade 3-5	
	n	%	n	%	n	%	n	%
Diarrhoea	38	(51.4)	0	(0.0)	36	(48.6)	0	(0.0)
Fatigue	38	(51.4)	5	(6.8)	34	(45.9)	4	(5.4)
Nausea	32	(43.2)	3	(4.1)	32	(43.2)	3	(4.1)
Anorexia	20	(27.0)	2	(2.7)	19	(25.7)	2	(2.7)
Dysgeusia	20	(27.0)	0	(0.0)	18	(24.3)	0	(0.0)
Thrombocytopenia	15	(20.3)	3	(4.1)	15	(20.3)	3	(4.1)
Weight Decreased	15	(20.3)	1	(1.4)	14	(18.9)	1	(1.4)
Alopecia	14	(18.9)	0	(0.0)	13	(17.6)	0	(0.0)
Chills	13	(17.6)	1	(1.4)	9	(12.2)	1	(1.4)
Blood Creatinine Increased	12	(16.2)	1	(1.4)	10	(13.5)	1	(1.4)
Constipation	12	(16.2)	0	(0.0)	8	(10.8)	0	(0.0)
Muscle Spasms	12	(16.2)	2	(2.7)	12	(16.2)	2	(2.7)
Anaemia	11	(14.9)	1	(1.4)	10	(13.5)	1	(1.4)
Dizziness	11	(14.9)	1	(1.4)	5	(6.8)	1	(1.4)
Vomiting	11	(14.9)	1	(1.4)	9	(12.2)	0	(0.0)
Pruritus	10	(13.5)	1	(1.4)	1	(1.4)	0	(0.0)
Headache	9	(12.2)	0	(0.0)	4	(5.4)	0	(0.0)
Oedema Peripheral	9	(12.2)	0	(0.0)	2	(2.7)	0	(0.0)
Upper Respiratory Tract Infection	9	(12.2)	0	(0.0)	2	(2.7)	0	(0.0)
Dry Mouth	8	(10.8)	0	(0.0)	8	(10.8)	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 3.1

CONCLUSIONS: In this study of patients with advanced CTCL receiving vorinostat, it can be concluded that: (1) Vorinostat provides clinically meaningful responses in a substantial proportion of patients with advanced CTCL (Stage IIB and higher), who have progressive, persistent, or recurrent disease on or following 2 systemic therapies. Prior therapy must have included bexarotene unless the patient is intolerant of or not a candidate for bexarotene therapy. (2) Vorinostat provides clinically meaningful responses in a substantial number of patients within the 3 prespecified subgroups: Sezary syndrome patients, T3 tumor patients, as well as in the overall population including lower clinical stage patients. (3) The median duration of objective response and the median time to progression are clinically meaningful. The median duration of objective response has not been reached, but exceeds 4 months. The median time to progression has not been reached but is estimated to exceed 5 months. (4) The median time to response is less than 2 months. (5) Vorinostat provides clinically meaningful reduction in pruritus in a substantial number of symptomatic patients with CTCL refractory to or intolerant of at least 2 prior therapies including bexarotene. (6) There was no discernable impact of response to last treatment or response to prior bexarotene treatment on subsequent efficacy of vorinostat. (7) Vorinostat has an acceptable safety profile and is generally well tolerated in this patient population.

AUTHORS:

List of abbreviations

4. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse experience
AN	Allocation number
APaT	All Patients as Treated
aPTT	Activated partial thromboplastin time
β-hCG	Beta-human chorionic gonadotropin
BSA	Body surface area
CAP	A regimen of cyclophosphamide, doxorubicin (adriamycin), and cisplatin
CBC	Complete blood count
CCR	Clinical complete response
CI	Confidence interval
CIB	Confidential Investigator's Brochure
CNS	Central nervous system
CRF	Case report form
CRO	Contract research organization
CSR	Clinical study report
CTCAE	Common terminology criteria for adverse events (formerly Common Toxicity Criteria)
CT	Computerized Tomography
CTCL	Cutaneous T-cell Lymphoma
DAP	Data analysis plan
DLBCL	Diffuse Large B-Cell Lymphoma
DBP	Diastolic blood pressure
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ECP	Extracorporeal photopheresis
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxy-glucose positron emission tomography
GCP	Good Clinical Practices
GI	Gastrointestinal
HDAC	Histone deacetylase
HDL	High density lipoprotein
IL-2	Interleukin-2
IFN α	Interferon alpha
IRB	Institutional Review Board
ISCL	International Society of Cutaneous Lymphoma
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
MedDRA	Medical dictionary for regulatory activities
mg	Milligram
mm	Millimeter
mSWAT	Modified Severity Weighted Assessment Tool
MF	Mycosis fungoides
NCI	National Cancer Institute
PD	Progressive disease, pharmacodynamics
PET	Positron emission tomography
PBMC	Peripheral blood mononuclear cells
PR	Partial response
PTT	Partial thromboplastin time

Abbreviation	Definition
PUVA	Psoralen plus ultraviolet light
RXR	Retinoid X receptor
SAHA	Suberoylanilide hydroxamic acid
SBP	Systolic blood pressure
SD	Stable disease, standard deviation
SIRT1	Sirtuin-1, Silent information regulator
SS	Sezary syndrome
STAT	Signal transducer and transcription activator
SWAT	Severity weighted assessment tool
TBSA	Total body surface area
TG	Triglyceride
UVAR	Ultraviolet photopheresis system
WBC	White blood (cell) count

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Ethics

Independent Ethics Committee

The protocol and its amendments were reviewed by an Institutional Review Board (IRB). A list of all review committees and their chairmen presented in 16.1.3 of the original study report was reviewed.

Ethical Conduct of the Study

This study was 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.

Patient Information and Informed Consent Form

- 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 risk, was read by and explained to all 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 his/her 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. Examples of the final informed consent agreements for all protocol amendments provided in 16.1.3 of the original study report were reviewed. The first amendment was in place prior to the first site screening a patient; therefore a specific informed consent was never established for the original protocol.

Investigators and Study Administrative Structure

Eighteen (18) centers participated in this study. Seventeen (17) of these study sites were in the United States and one was in Canada. A list of the names of the primary investigators and their locations is in the section 16.1.4 of the original study report.

The curricula vitae of the primary investigators are also in this section.

Prior to Aton Pharma Inc. becoming a wholly owned subsidiary of Merck & Co., Inc., (SPONSOR) Data Management for the study was conducted by:

While non-protocol-specified tests could have been performed by local laboratories at the discretion of the investigator, protocol-specified blood and urine specimens were analyzed by:

Monitoring visits were conducted by the following contract research organization (CRO):

Patient photographs were collected and stored by:

Peripheral blood mononuclear cells (PBMCs) and skin biopsies (patch, plaque, and/or tumor) were collected and analyzed at:

Rosetta Inpharmatics
A wholly owned subsidiary of Merck & Co., Inc.
401 Terry Avenue N
Seattle, WA 98109

Introduction

Vorinostat, also known as suberoylanilide hydroxamic acid (SAHA) or MK-0683, is a potent inhibitor of the activity of histone deacetylase (HDAC), an enzyme involved in removing acetyl groups from histones and other proteins. HDAC inhibitors are a novel class of agents that can induce tumor cell growth arrest, differentiation, or apoptosis *in vitro* and inhibit tumor growth in animals.

In cancer, links between altered HDAC activity and tumorigenesis have been identified. Signal transducer and transcription activator (STAT) proteins are transcription factors activated in response to most cytokines and growth factors. The functions of STAT family proteins, especially STAT3 and STAT5, have been directly associated with oncogenesis. In cutaneous T-cell lymphoma (CTCL), constitutive activation of members of the STAT family has been found in patients with mycosis fungoides and Sezary syndrome, which are the most common forms of CTCL. Recent data have demonstrated that HDAC activity is required for the transcriptional activity mediated by the STAT proteins. Inhibiting HDAC activity can prevent expression of STAT target genes and may explain the observation that HDAC inhibitors of diverse structures have shown anti-tumor activity in CTCL *in vitro* and *in vivo*.

Three classes of HDACs have been identified. A number of HDAC inhibitors have entered clinical trials. Among these agents, Vorinostat is a potent inhibitor of HDAC that can be administered orally

with excellent bioavailability. Vorinostat inhibits the activity of both Class I (HDAC1 and 3) and Class II (HDAC4 and 9) HDACs.

CTCL is an uncommon malignant lymphoma with primary manifestation in the skin. It represents approximately 75-80% of all primary cutaneous lymphomas. The overall incidence rate is 4-5 per 1,000,000. The mean age of onset is 50 years with few cases seen before the age of 30 years. There is a gradual increase of incidence with age. The incidence of CTCL was observed to be twice as frequent among Blacks as Whites and it has been reported as 1.6 to 2.2 times more common in males as females. Approximately 1,000 new cases are diagnosed every year in the United States and 1,200 new cases in Europe. There are approximately 16,000 to 20,000 cases across the United States, approximately 3,000 cases across Canada, and approximately 28,000 cases in Europe. Due to the difficulty of diagnosing the disease in its early stages and the lack of an accurate reporting system, these numbers are estimates. The mortality rate increases with age. The annual average age adjusted mortality rate in the United States ranges between 2.8 to 8.4 per 10,000,000.

CTCL is a heterogeneous group of T-cell neoplasms that display a variety of clinical and histopathological presentations. The majority of CTCL cases are classified as either mycosis fungoides or Sezary syndrome. Mycosis fungoides is the most common form; it typically progresses clinically through patch, plaque and tumor stages. Sezary syndrome is the erythrodermic leukemic variant of CTCL, defined by the presence of generalized erythroderma, lymphadenopathy, and circulating tumor cells.

Clinically, mycosis fungoides begins with an erythematous macular eruption commonly appearing in non-sun-exposed skin ("bathing trunk distribution") that can last for months to years without a definitive diagnosis of mycosis fungoides. Other initial manifestations include patches, plaques, tumors or generalized erythema. Patches and plaques may develop into tumor stage disease or erythroderma as the disease progresses. Ulceration, with secondary infection of the tumors, is a common cause of morbidity.

Sezary syndrome is widely regarded to be a distinctive erythrodermic and "leukemic" variant of CTCL. Sezary cells most commonly possess either a CD4 (+) CD7 (-) or CD4 (+) CD26 (-) immunophenotype. The presence of Sezary cells generally increases as patients progress to more advanced stages of CTCL. The hematologic criteria recommended by the International Society for Cutaneous Lymphoma (ISCL) to define Sezary syndrome consists of one or more of the following:

- (1) Absolute Sezary cell count of 1000 cells/mm³ or more
- (2) CD4/CD8 ratio of 10 or higher caused by an increase in circulating T-cells and/or an aberrant loss or expression of pan-T-cell markers by flow cytometry
- (3) Increased lymphocyte counts with evidence of a T-cell clone in the blood by the Southern blot or polymerase chain reaction technique
- (4) A chromosomally abnormal T-cell clone.

Clinical features of Sezary syndrome typically include diffuse erythroderma, edema of the skin, hyperkeratosis of palms and soles, alopecia, generalized lymphadenopathy, and circulating pleiomorphic lymphoid cells.

The prognosis of patients with CTCL is based on the clinical stage at presentation. Cutaneous disease typically progresses from an eczematous patch/plaque stage covering less than 10% of the body

surface (T1) to plaque stage covering greater than or equal to 10% of the body surface (T2), and finally to tumors (T3) that frequently undergo necrotic ulceration. Sezary syndrome is an advanced form of CTCL with generalized erythroderma (T4) and peripheral blood involvement. This progression in the severity of disease may evolve over 10-20 years. More advanced stages of both mycosis fungoides and Sezary syndrome may involve extra-cutaneous sites such as liver, breast, bone marrow, or central nervous system. The presence of lymphadenopathy and involvement of peripheral blood and viscera increase in likelihood with worsening cutaneous involvement and define poor prognostic groups.

CTCL patients with superficial skin involvement (Stages I and IIA) have a median survival of more than 12 years. About 10% of people diagnosed with CTCL will experience a progression with lymph node, visceral involvement, or serious complications. However, patients with more advanced stage disease characterized by 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. Patients with visceral involvement have a median survival of 2.5 years or less. 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. Curative modalities, however, have thus far proven elusive, with the possible exception of patients with minimal disease confined to the skin.

The symptoms of CTCL may increase with disease stage. In the early stages, the skin may itch and develop dry, dark patches. As more and more of the skin become involved, it may become ulcerated or infected. Sezary syndrome patients may become red from head to toe and experience hot, sore, extremely itchy skin. Other symptoms include loss of hair, thickening of palms and soles, and drooping eyelids.

Currently, treatment is determined by type and stage of disease. The goal of treatment for most patients is decreasing tumor burden, improving appearance, relieving pruritis, and preventing life-threatening complications. Treatments can be categorized into topical therapy, phototherapy, ionizing therapy and systemic therapy.

The skin-directed treatments are commonly used in patients with early-stage mycosis fungoides, which include topical corticosteroids, topical mechlorethamine (nitrogen mustard), topical carmustine, or topical bexarotene. Treatments such as psoralens plus ultraviolet A light (PUVA), extracorporeal photopheresis (ECP), or electron beam radiation have demonstrated clinical benefits to patients with either early or late stage disease. These treatments tend to be associated with a high relapse rate when used alone. Therefore, current practice favors combinations of skin-directed therapies with systemic treatment such as the retinoid-X receptor (RXR)-selective retinoid bexarotene. More advanced disease is treated with systemic therapies, such as purine analogs, cytotoxic drugs, monoclonal antibodies, or interferon- α (IFN- α).

Bexarotene is a RXR-selective retinoid agonist, which provides an option for both early and advanced stage CTCL. In a multicenter study where oral bexarotene was given to patients with refractory early stage CTCL, the total response rate, as assessed by a "Primary Endpoint Assessment" for patients treated at a dose of 300 mg/m², was 45%. However, the method for response involved either a Physician's Global Assessment (PGA) score or a composite assessment grading of 5 lesions. **Progressive disease was not measured from the best response but only from**

the baseline. The response rates with new regimens have been higher than the conventional treatments.

Treatment of CTCL remains an unmet medical need. Although available approaches may be applied sequentially, either alone or in combination, there is no curative therapy that is widely applicable to CTCL patients. Ultimately CTCL patients become intolerant of, or refractory to, the currently available treatments.

The evidence supporting the exploration of Vorinostat as a treatment for CTCL came from 2 clinical studies. The anti-tumor activity of Vorinostat was demonstrated in patients with lymphoma in a Phase I study. Seven (7) patients with heavily pre-treated diffuse large B-cell lymphoma (DLBCL) were entered. One complete response and one partial response (PR) were observed. In addition, one patient had a significant fluorodeoxy-glucose positron emission tomography (FDG-PET) scan response. The complete response lasted 14 months, the partial response 5 months, and the FDG-PET scan response 6 months. In this study, one patient with CTCL had an impressive transient response. Results from studies of another HDAC inhibitor, depsipeptide, also hinted at anti-tumor activity in CTCL. Therefore, the investigation of Vorinostat in CTCL is warranted.

The conduct and design of the study described in this clinical study report (CSR) was discussed with the United States FDA. Concurrence was reached with respect to the inclusion of the following components in the study design / statistical analysis:

- Patients 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 is intolerant of or not a candidate for bexarotene therapy.
- A pre-specified subgroup analysis would be performed in those patients with T3 disease, in which the response rate in overall skin disease will 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 were included in the study to serve as supportive information for the primary endpoint.
- Radiation, PUVA, photopheresis and/or interferon were not allowed during the study and patients who required these therapies would be withdrawn from the study.
- In cases where the disease was primarily evaluable by computed tomography (CT) scan, follow-up CT scans were encouraged whenever practical.

Study Objectives

Primary Objective

- To determine the response rate of oral Vorinostat 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 2 systemic therapies, one of which must contain bexarotene unless the patient is intolerant of or not a candidate for bexarotene therapy.

Secondary Objectives

- To assess response duration
- To evaluate the relief of pruritis, a tumor-related symptom in patients with CTCL; to assess time to progression; to assess time to objective response
- To assess the safety and tolerability of oral Vorinostat in this patient population. (Response rate and all secondary objectives will also be assessed in all patients treated, *i.e.*, Stage IB or higher disease).

Investigational Plan

Overall Study Design and Plan: Description

This was an open-label, single-arm, multicenter study which evaluated the effect of oral Vorinostat 400 mg once daily for 7 days/week in 74 patients (70 planned) with advanced disease CTCL (Stage IB or higher). The protocol and all protocol amendments can be found in the section 16.1.1 of the original study report and were reviewed.

All patients began the study by granting informed consent and signing an informed consent form. Patients were then assigned a baseline number and underwent screening procedures. Eligible patients had baseline measurements performed and were started on study drug (Visit 1) within 2 weeks of signing informed consent. During the first 2 months of treatment with study drug, 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.

Patients could have returned for unscheduled visits at any time per the discretion of the investigator. Safety was monitored throughout the treatment period and adverse experiences were collected for 30 days following the last dose of study therapy from discontinued patients.

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 study drug or prior to the initiation of new treatment. The post-treatment follow-up could be conducted by telephone if the patient was unable to return to the clinic. Patients who did not have disease progression, and who continued to meet the eligibility criteria, were offered continued treatment with Vorinostat on a continuation protocol. The continuation protocol did not apply to those patients who discontinued study drug.

- The first patient administered study drug 17-Mar-2004
- The last date for data collection for a patient 23-Nov-2005
- The in-house cut-off date for the receipt of additional patient data 25-Nov-2005
- Frozen File 07-Dec-2005

The following table shows the schedule of clinical observations and laboratory measurements.

Table 177. Schedule of Clinical Observations and Laboratory Measurements (Applicant's Table)

Procedure	Visit	Treatment Period					Post-Treatment Follow-up Visit ¹	
		Baseline	Visit 1 Day 1	Visit 2 Week 2	Visit 3 Week 4	Visit 4 Week 6		Visit 5 Week 8 ²
Study drug administration and count			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	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 ³					X ³		
CBC with differential, platelets, comprehensive panel ⁴	X	X	X	X	X	X	X	
PT, aPTT	X						X	
Thyroid function	X					X ⁵	X	
β-hCG ⁶	X							
Urinalysis	X			X		X	X	
ECG	X			X		X ⁷	X	
Adverse experience assessment		X	X	X	X	X	X	
Efficacy evaluation: SWAT, BSA involvement photos, body diagram ⁸	X			X		X	X	
Pruritus intensity assessment	X	X	X	X	X	X	X	
Peripheral blood flow cytometry for Sezary syndrome patients	X ⁹					X ⁹		
Correlative studies	X ¹⁰		X ¹¹					

¹ Visits conducted every 4 weeks thereafter until the patient discontinues from the study.
² Within 4 weeks after the last dose of study medication or prior to the initiation of new treatment.
³ 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 partial or complete response after a second assessment confirms the response.
⁴ Albumin, alkaline phosphatase, total bilirubin, bicarbonate, blood urea nitrogen, calcium, calcium chloride, creatinine, glucose, lactic dehydrogenase, phosphorus, potassium, total protein, serum glutamic oxaloacetic transaminase serum glutamic pyruvic transaminase, sodium, uric acid, cholesterol, triglyceride, low-density lipoprotein, and high-density lipoprotein.
⁵ Every 3 weeks during treatment.
⁶ Serum pregnancy test (women of child-bearing potential).
⁷ 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 prior to the daily vorinostat dose. The baseline and 2 hour post-dose ECG tracings will be sent directly to Merck & Co., Inc.
⁸ Photos must include full body (front and back).
⁹ Repeat every 3 weeks for Sezary cell patients who have evidence of at least a partial response.
¹⁰ 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-dose at Visit 2, and at the time of disease progression. Skin biopsies must be obtained from the sites that have not been exposed to any topical agents within 12 hours prior to the biopsies. Up to 2 skin biopsies should be obtained: (1) a patch or plaque lesion, and (2) a skin tumor nodule (if present). For Visit 2 only, the vorinostat dose should be given in the clinic, whenever possible, to ensure that samples are collected at 2 hours following dosing. If this is not possible, patients should be instructed to miss that day's dose of vorinostat to 2 hours prior to tissue sample acquisition. In addition, post-treatment samples were requested in patients who developed progressive disease after a partial or complete remission.
 CT = Computed tomography; CBC = Complete blood count; PT = Prothrombin time
 aPTT = Activated partial thromboplastin time; β-hCG = Beta-human chorionic gonadotropin; ECG = Electrocardiogram
 SWAT = severity weighted assessment tool; BSA = Body surface area; Sezary syndrome = Sezary syndrome
 PET = Positron-emission tomography

Data Source: [16.1.1]

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Discussion of Study Design, Including the Choice of Control Groups

Study Design

The primary objective of this Phase II study was to determine the clinical benefit of Vorinostat in patients with advanced stage CTCL (Stage IIB and higher) who have progressive, persistent, or recurrent disease 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. Although the benefit of a new therapy may be best evaluated in the most severely affected population of patients, patients with earlier stage disease who have failed multiple prior therapies also may benefit from new treatment options. Therefore, Stage IB and IIA patients were eligible for enrollment in this study to broaden the safety assessment and informally evaluate whether there was benefit in earlier stage disease.

CTCL is a group of lymphoproliferative disorders characterized by localization of the malignant T-lymphocytes to the skin at presentation. Mycosis fungoides and Sezary syndrome make up the majority of cases of CTCL. The etiology of mycosis fungoides and Sezary syndrome remains unknown. The molecular mechanism underlying the migration of malignant T-lymphocytes into the epidermis (epidermotropism) has not been elucidated.

Because cure is not achievable with current therapies, the goals of treatment are symptom relief and durable remission while limiting long term sequelae. There is no evidence that early aggressive systemic therapy improves overall survival. Treatment strategies can be skin-directed or systemic. Skin-directed therapy includes topical chemotherapy and radiation therapy. Systemic therapy includes cytotoxic chemotherapy, photopheresis, retinoids, interferon, and other biologic therapies. No prospective randomized controlled study has been performed to compare the efficacy of various therapies. The decision of which therapy to choose usually depends on physician and patient preference.

Limited therapeutic options for CTCL have received specific regulatory approval. Bexarotene, (Targretin®) a retinoid that selectively activates the retinoid X receptors, has been approved in many countries, including the United States and European Union, for the treatment of cutaneous manifestations of CTCL in patients who are refractory to at least one prior systemic therapy. Denileukin diftitox (Ontak®) is a recombinant DNA-derived fusion protein designed to direct the cytotoxic action of diphtheria toxin to cells that express the interleukin-2 (IL-2) receptor. Denileukin diftitox has been approved in the United States for the treatment of patients with persistent or recurrent CTCL whose malignant cells express the CD25 component of the IL-2 receptor but is not available in most other countries throughout the world. Methoxsalen (Uvadex®) is indicated for use with the UVAR Photopheresis System in the palliative treatment of the skin manifestations of CTCL that are unresponsive to other forms of treatment. Although these various therapies exist for CTCL, they are often considered inadequate due to short response durations or significant toxicities. Approval of these agents has been based on non-randomized studies with response endpoints rather than survival benefit. New therapies are needed for these patients.

The report summarizes all patient data received up to and including 25-Nov-2005. These data capture information received from patient visits through 23-Nov-2005.

Dosing Regimen

Vorinostat 400 mg once daily for 7 days/week had previously demonstrated efficacy in another ongoing study examining CTCL and peripheral T-cell lymphoma, protocol 005. At the time of the original drafting of the protocol, 40 patients with solid tumors or hematologic malignancies had received this dose and had displayed an acceptable safety profile.

The investigator was given the option of withholding Vorinostat for Grade 3 or 4 non drug related toxicity if the physician felt it was unsafe to continue its administration. Vorinostat was to be held in the presence of Grade 3 or Grade 4 drug-related toxicities until the toxicity resolved to Grade 1 or less. The exception to this was Grade 3 anemia or thrombocytopenia, which did not require the cessation of Vorinostat. Vorinostat may have been withheld for up to 2 weeks. The table below illustrates the dose modification criteria specified after recovery from a drug-related toxicity which resulted in a study drug interruption. Any patient who (1) required more than 2 dose modifications or (2) had treatment delays by greater than 2 weeks was not to receive any further treatment unless the physician felt that treatment with Vorinostat provided the patient with clinical benefit.

Table 178. Dose Modification (Applicant's Table)

	Initial Dosing Schedule	1 st Dose Reduction	2 nd Dose Reduction
Protocol CL-01-0303 Amendment 01	400 mg once daily for 7 days/week	400 mg once daily for 5 consecutive days/week	300 mg once daily for 5 consecutive days/week
Amendment 02 Amendment 03	400 mg once daily for 7 days/week	300 mg once daily for 7 days/week	300 mg once daily for 5 consecutive days/week

Data Source: [16.1.1]

The original protocol and the first amendment to the protocol allowed for an initial dose reduction from 400 mg once daily for 7 days/week to 400 mg on 5 consecutive days per week. This dose specific modification was removed in the following amendments. There was only a single patient (AN1001) who was reduced to this dose (400 mg for 5 consecutive days per week).

Correlative Studies

Up to 2 skin biopsies and corresponding PBMC samples were collected at Baseline (Visit 1) and Visit 2 (Week 2) for those patients who agreed to this optional procedure. The skin biopsies should have included (1) a patch or plaque and (2) a skin tumor (if present).

The collected samples will be used in the future to search for (1) gene expression profiles, performed using DNA microarrays that predict response to Vorinostat and (2) expression changes that occur after exposure to Vorinostat. In addition, post-treatment samples were requested in patients who developed progressive disease after a partial or complete remission. These samples will allow for investigation of gene expression changes that occur after acquired resistance to Vorinostat. The samples will also be used for confirmatory studies based on the gene expression results. These results may provide important information regarding mechanisms of response and mechanisms of resistance to Vorinostat. Ultimately, these results could guide the selection of patients for treatment with Vorinostat and guide strategies for preventing or overcoming resistance to Vorinostat. Details of sample collection and handling were provided in the study operations manual.

Selection of Study Population

Inclusion Criteria

Patients met the following criteria to participate in the study:

1. Patients must have advanced disease documented 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 is intolerant of or not a candidate for bexarotene therapy.

Persistent disease is 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. Patients are considered intolerant of oral bexarotene therapy if they were discontinued from oral bexarotene therapy because of toxicities. Patients are considered not to be candidates for oral bexarotene therapy if they have 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 oral bexarotene package insert.

- Systemic therapies are photopheresis and antineoplastic agents including investigational drugs or biological therapy administered parenterally or orally
 - Patients are considered to have had 2 systemic therapies if they received any one of the following combination treatments (either consecutively or concurrently):
 - An antineoplastic agent in combination with photopheresis
 - Commonly used chemotherapy regimen (*e.g.*, CHOP, CVP, CAP) in combination with bexarotene.
 - Commonly used chemotherapy regimen (*e.g.*; CHOP, CVP, CAP) in combination with a biological agent (*e.g.*, interferon, Ontak)
 - A biological agent in combination with bexarotene
 - A cytotoxic agent (*e.g.*, methotrexate, gemcitabine) in combination with bexarotene
 - A cytotoxic agent in combination with a biological agent
2. Histological diagnosis of CTCL documented by biopsy performed within one year prior to enrollment. Note: the histological diagnosis of CTCL must be confirmed at the study site prior to enrollment.
3. Age \geq 18 years.
4. ECOG performance status 0-2.
5. Life expectancy greater than 3 months.
6. Adequate bone marrow function:
- Absolute neutrophil count \geq 1,500/ μ L
 - Platelets \geq 100,000/ μ L
7. Adequate liver function:
- Total bilirubin within institutional normal limits
 - AST (SGOT) and ALT (SGPT) \leq 2.5x institutional upper limit of normal or \leq 5x institutional upper limit of normal if the liver has tumor involvement.
8. Adequate renal function:
- Creatinine \leq 2 mg/dL or creatinine clearance $>$ 60 mL/min

9. Patients must be at least 3 weeks from prior chemotherapy (including topical chemotherapy and photopheresis), psoralen plus ultraviolet light (PUVA), radiation therapy, major surgery, or investigational anticancer therapy and have recovered from toxicities of prior therapy. Patients with rapidly progressing disease will be considered on an individual basis for enrollment in less than 3 weeks from prior treatments if they have recovered from all prior treatment-related toxicities.
10. Patients must be able to swallow capsules.
11. All patients must agree to practice effective contraception during the entire study period unless documentation of infertility exists.
12. Ability to understand and willingness to sign the informed consent form.

Exclusion Criteria

Patients with any of the following conditions were excluded from the study. The following criteria were put in place to protect the safety of the patient and to provide a patient population suitable for this study:

1. Prior treatment with any HDAC inhibitor (e.g., Depsipeptide, MS-275, LAQ-824) or currently under treatment with any potential HDAC inhibitor (e.g., valproic acid).
2. Patients on systemic steroids, with the exception of Sezary syndrome patients.
 - Sezary syndrome patients who have been on systemic steroids for the last 3 months prior to study entry and who were on a stable daily dose of steroids equivalent to ≤ 10 mg prednisone during the 4 weeks immediately prior to study entry are eligible to participate.
3. Patients on topical steroids except for those who have been using topical steroids for at least 3 months prior to study entry and the dosage does not exceed 0.1% triamcinolone acetonide cream (Aristocort A® 0.1% cream) or similar strength steroid cream during the 4 weeks immediately prior to study entry
4. Concurrent use of retinoids, orally or topically
 - Concurrent use of any vitamin A, other than a single multivitamin tablet daily
5. Concurrent use of chemotherapy, radiotherapy, biological therapy or investigational anticancer therapy
6. Acute infection requiring intravenous antibiotics or antifungal agents
7. Known HIV infection
8. Active hepatitis B and/or hepatitis C infection
9. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements
10. Cancer other than CTCL which was diagnosed or had recurrence in the last 5 years
11. Pregnant or lactating women
12. Known allergies to any component of the study drug
13. Any circumstances at the time of enrollment that would preclude completion of the study or the required follow-up

Discontinuation of Patient from Therapy or Study Observation

Patients had the right to withdraw from the study at any time for any reason. The investigator had the right to withdraw patients from the study at his/her discretion. As an excessive rate of withdrawals could render the study not interpretable, the investigator was to avoid unnecessary withdrawal of patients.

When a patient discontinued treatment early, every effort was made to conduct a follow-up visit within 4 weeks after the last dose of study drug or prior to the initiation of new treatment. This follow-up evaluation may be conducted over the telephone if the patient was unable to return to the clinic. The reason(s) for withdrawal must have been recorded.

There was no replacement of patients who terminated the study early if they had received at least one dose of Vorinostat. Patients who terminated the study early without receiving Vorinostat were to be replaced.

Criteria for terminating participation in the study are listed below:

- Progressive disease
- Unacceptable toxicity
- Patient withdrawal of consent
- Uncontrolled intercurrent illness: a condition, injury, or disease unrelated to cancer, that renders continuing Vorinostat treatment unsafe or regular study visits impossible, including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
- General or specific changes in the patient's condition that render the patient ineligible for further treatment
- Non-compliance with study medication or protocol-required evaluations and study visits
- Lack of efficacy
- Sponsor decision

Treatments

Treatments Administered

Patients who qualified for entry were allocated to Vorinostat 400 mg once daily for 7 days/week.

- Patients took Vorinostat every day with food, if possible.
- Management and dose modifications for adverse events were outlined above.
- Patient compliance with study medication was monitored by capsule count at each visit.
- Treatment was administered on an outpatient basis.
- Dose escalation was not allowed.

Study visits occurred at Baseline, Day 1, Week 2, Week 4, Week 6, Week 8, and every 4 weeks thereafter until the patient discontinued from the study.

Vorinostat was supplied in 50 mg, 100 mg, and 200 mg capsules. The 50 and 200 mg capsules were provided in bottles containing 100 capsules each. The 100 mg capsule was provided in bottles containing 120 capsules. Vorinostat capsules were repackaged by the pharmacist (or designee) and dispensed in new bottles which met the United States Pharmacopeia definition for well-closed containers. Clinical supplies were dispensed in accordance with the protocol. Vorinostat was dispensed to patients at each visit with only enough capsules to allow their required dosing needs until the next scheduled visit plus a window of an additional 3 days. A 17 day supply (14 days of continuous dosing, plus a 3 day window) of Vorinostat was dispensed to patients at the Day 1, Week

2, Week 4, and Week 6 Visits. A 31 day supply (28 days of continuous therapy, plus a 3 day window) of Vorinostat was dispensed at all subsequent visits until the patient completed the study. Study drug administration was outlined in the Study Drug Management Plan section of the Operations Manual.

The original intent was to use only the 100 mg capsules for patient dosing, however due to production delays with the 100 mg capsule, Tufts-New England Medical Center (Site 004) and Stanford University School of Medicine (Site 008) initially started with the 200 and 50 mg capsules prior to receiving the 100 mg capsules. The formulation for the 50 mg capsule differs from that for the other dose levels and the sites were instructed to only dispense the 50 mg capsules in situations where the patient was dose reduced to 300 mg and the site did not have 100 mg capsules on hand. This situation did not occur in the study. No patients received the 50 mg capsules.

Identity of Clinical Supplies

The summary of details for the identity of clinical supplies is provided in the table below. Control numbers for the 50 and 200 mg capsules were not available. These 50 and 100 mg capsules were manufactured by _____, prior to the acquisition of Aton Pharma, Inc. by Merck & Co., Inc.

Table 179. Identity of Clinical Supplies (Applicant's Table)

Drug	Potency	Formulation No.	Dosage Form	Control No.
Vorinostat	50 mg	C04-0208-001	Capsule	--
Vorinostat	100 mg	DFC001A001, DFC002A001, DFC004A001, DFC005A001	Capsule	WP-L948, WP-L850, WP-L921, WP-918, WP-M102
Vorinostat	200 mg	C04-0204004	Capsule	--

Data Source: [Not Applicable]

Clinical supplies were received, distributed, and handled in accordance with the protocol and GCPs. At the end of the study, all clinical supplies including partial and empty containers were verified by a Merck & Co., Inc. representative then destroyed at the site according to institutional guidelines and applicable laws and regulations.

Method of Assigning Patients to Treatment Groups

Allocation numbers (AN) were assigned in ascending sequence when an individual patient qualified. Qualification was confirmed through a voice-activated system established by Aton Pharma, Inc. and conducted through a CRO responsible for monitoring the investigative centers. **There was no stratification in this study.**

Selection of Doses in the Study and Timing of Dose for Each Patient

All patients were assigned a starting dose of Vorinostat 400 mg once daily for 7 day/week. Patients were instructed to take their daily dose with food whenever possible. Patients continued on this dose unless the patient experienced an adverse experience resulting in dose reduction or met a pre-specified dose modification requirement.

Study Blinding

This was an open-label, non-randomized study and did not require the use of blinding procedures.

Prior and Concomitant Therapies

Patients must have received at least 2 systemic therapies, one of which must have contained bexarotene (unless contraindicated). For the purposes of this study, systemic therapies were defined as photopheresis, commonly used chemotherapy regimens, and antineoplastic agents including investigational drugs or biologic therapy administered parenterally or orally. Chemotherapy (including topical agents and photopheresis), PUVA, radiation therapy, and investigational anticancer therapy must have been completed for at least 3 weeks prior to treatment with study therapy. The patient must also have recovered from any toxicities related to the previously mentioned therapy. Exceptions to this 3 week window were considered for patients with rapidly progressing disease if they had recovered from all prior treatment-related toxicities.

Patients who had received prior treatment with any HDAC inhibitor or were under treatment with a potential HDAC inhibitor (e.g. valproic acid) were excluded. Patients who required intravenous antibiotics or antifungal agents, as well as patients taking retinoids (with the exception of any vitamin A contained in a single daily multivitamin tablet) were excluded. Use of systemic or topical steroids was also exclusionary with the following exceptions:

- Sezary syndrome patients who had been on systemic steroids for at least 3 months, with a stable daily dose equivalent to ≤ 10 mg of prednisone for at least 4 weeks immediately prior to receiving study therapy
- Patients who had been on topical steroids for at least 3 months, with a dose which did not exceed 0.1% triamcinolone acetonide cream (or similar strength steroid cream) for at least 4 weeks immediately prior to receiving study therapy

Treatment Compliance

Patient compliance with study medication was monitored by capsule count which occurred at each visit and was recorded on the Study Drug Accountability CRF. This CRF captured the date and number of capsules dispensed along with the date and number of capsules returned. Compliance was defined as the percent of drug amount (mg) actually taken during the course of the study while the patient was on active treatment.

While the Study Drug Accountability CRF provided the amount of study therapy actually taken, the Study Medication CRF provided the dose level the patient should have been taking.

Efficacy, Safety, and Tolerability Parameters

Measurements Assessed and Timing of Assessment

The efficacy and safety variables measured in this study were described above and the table showed the Schedule of Clinical Observations and Laboratory Measurements.

Efficacy Measurements Assessed

The efficacy parameters briefly summarized below are described in detail in both the protocol and the operations manual.

SWAT Form

Using the standard SWAT method, lesion types (patches, plaques and tumors or ulcers) are mapped onto body diagrams. The modified SWAT, incorporated prospectively after discussion with the FDA, utilized a template of 12 main body areas which were assessed with maximum BSA assignments as follows: head (7%), neck (2%), anterior trunk (13%), posterior trunk (13%), buttocks (5%), genitalia (1%), upper arms (8%), forearms (6%), hands (5%), thighs (19%), lower legs (14%), and feet (7%). The area of involvement by each lesion type and body is then calculated by using a transparency of each patient's palm. A palm with 4 closed fingers without the thumb is equal to 1% total body surface area. The physician will indicate the extent of skin disease by drawing on a body diagram. The body diagram is meant to be a worksheet for the physician and cannot be used to derive the total body surface area involved by disease. For purposes of this report, this "modified" method of the SWAT assessment will still be referred to as SWAT rather than "modified SWAT".

The SWAT case report form was used by the physician to assess overall skin disease. This assessment was administered at baseline, every 4 weeks on treatment, and at the post-treatment visit. The SWAT case report form allowed the investigator to determine the percentage of Total Body Surface Area (TBSA) involvement by skin disease and then weigh these percentages based upon the lesion type. A **patch** was defined as abnormal skin not elevated from normal skin, a **plaque** was defined as abnormal skin elevated from normal skin by < 5 mm, a plaque elevated \geq 5 mm was considered a **tumor**. The TBSA for each lesion type was then weighted by a multiplier (patch- x 1, plaque- x 2, and tumor- x 4).

Serial, close-up photographs of distinct individual lesions, as well as global half-body photographs, were also taken as documentation of change in skin disease. These photographs were supportive only and were not used to derive SWAT scores. Whenever possible, the same physician was to perform the overall assessment of skin disease for a given patient over the course of the study. Detailed instructions contained in the study operations manual were also provided in an effort to optimize intra-observer objectivity.

Pruritis Assessment Questionnaire

Patients completed a self-administered two-part questionnaire at all scheduled visits. The questionnaire contained a 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 anti-itching medication which they used in the past week compared to the previous week (did not use, used less, no change in use, used more).

Safety Measurements Assessed

At each visit, patients were questioned as to whether they had experienced an adverse experience (AE) since their last visit. Adverse experiences were collected throughout the study.

Adverse experience means any unfavorable and unintended change in the structure (signs), functions (symptoms), or chemistry (laboratory data) of the body temporally associated with any of the Aton Pharma, Inc., product (Merck & Co., Inc. product after acquisition) whether or not considered related to the use of the product.

The onset and end dates, severity, and relationship to study drug were recorded for each adverse experience. The severity of the adverse experience was assessed and **graded** according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events v3.0 (CTCAE) published December 12, 2003.

If disease progression was noted during a protocol-specified re-evaluation and the progression was manifested solely by results of tumor markers and/or radiologic imaging, that occurrence of progressive disease was NOT to be recorded as an adverse experience.

A serious adverse experience (SAE) is any adverse experience occurring at any dose that:

- Results in death, or
- Is life threatening (places the subject/patient, in the view of the investigator, at immediate risk of death from the experience as it occurred. [Note: This does not include an adverse experience that had it occurred in a more severe form, might have caused death.], or
- Results in a persistent or significant disability/incapacity (substantial disruption of one's ability to conduct normal life functions), or
- Results in or prolongs an existing inpatient hospitalization (hospitalized is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation.) (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse experience), or
- Is a congenital anomaly/birth defect (in offspring of subject taking the product regardless of time to diagnosis), or
- Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the subject/patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

In addition, Merck & Co., Inc. requires the collection of the following:

Cancer that is not the condition under study, or overdose (whether accidental or intentional)

Appropriateness of Measurements

No generally accepted standard has been established in clinical studies for the efficacy assessment of patients with CTCL. In this protocol, the primary endpoint was assessed by collecting SWAT scores of all lesions. This measure provided for a more quantitative objective consecutive set of assessments that could be supported by body diagrams and photographs in comparison to the PGA which had a simplified subjective 0-6 scale. The response rate of overall skin improvement was measured by SWAT. Skin assessment score derivation from SWAT is described above.

Primary Response Parameters

Evaluation of Efficacy Measurements

Response Rate

The clinical endpoint was based on the assessment of overall skin disease in patients with CTCL Stage IIB and higher as measured by SWAT.

An **Objective Clinical Response** was defined as no evidence of clinical disease or a marked improvement that is a 50% decrease in the SWAT score compared to the baseline with a second assessment after at least 4 weeks.

A **Clinical Complete Response (CCR)** required 100% improvement with no evidence of disease and a **Partial Response (PR)** required at least a 50% decrease in SWAT scores compared to baseline.

Confirmation of response required a second assessment after at least 4 weeks. Patients who achieved a CCR or PR by SWAT had a full CT assessment of their nodal disease after the response was confirmed by a second assessment.

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

Progressive Disease (PD) required at least a 25% increase in SWAT scores compared to 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 baseline, also while the patient was currently taking study drug.* Patients assessed with PD were to receive confirmation by a second assessment 1-4 weeks later whenever possible. This would allow patients who experienced a temporary flare of disease due to skin infection or other intercurrent illness to continue in the study.

Table 180. Assessment of Overall Skin Disease (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 SWAT scores compared to baseline and improvement is maintained for 4 weeks	PR
Slight improvement	Less than 50% decrease in SWAT scores compared to baseline	SD
Worse	≥25% increase in SWAT scores compared to baseline while the patient is actively taking the study drug or ≥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

Data Source: [16.1.1]

Duration of Overall Response

The duration of overall response was measured from the time when criteria were first met for CCR or PR (whichever is first recorded) until the first date when an increase in skin assessment by SWAT score was greater than 50% of the difference between baseline score and nadir score and if that magnitude of increase in the score was confirmed by a second assessment at 1-4 weeks thereafter, if possible.

Pruritis Relief

The intensity of pruritis was evaluated by the patient at baseline and during each visit using a 10-point scale which assessed skin itch over the past week (0=no itching, 10=itching as bad as it can be). 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 is ≥ 3 at baseline.

Time to Progression

Time to progression was measured from the start of the treatment until the criteria for progression were first met.

Time to Response

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

Evaluation of Safety Measurements

Study Participant Population

The safety analysis was based upon an All Patients as Treated (APaT) approach which included all patients who received one or more doses of the study drug.

- Patient 1048 was sent home with study medication, with the expectation that the patient would take the first dose at home with dinner. This patient was found dead the next day and the first responders discarded all study medication. While there is no way of verifying if this patient did or did not take a dose of Vorinostat, AN1048 is included in the APaT population.

Extent of Exposure to Drug

Summary statistics of number of days in the study, number of days of unscheduled drug interruption, number of days patient received drug, and average assigned daily dose are included in the following sections.

Adverse Experiences

The incidence of adverse experiences overall, within each body system, and for individual adverse experiences were summarized in the following sections.

Clinical Safety

Eastern Cooperative Oncology Group (ECOG) performance status, vital signs, weight, and lipid parameters over time are summarized in the following sections. Electrocardiogram (ECG) abnormalities regarded as clinically significant are also summarized.

Laboratory Safety

Abnormalities for standard laboratory measures (made at every visit) are summarized in the following sections. Laboratory adverse experiences were reported by the investigator when clinically significant lab abnormalities were detected that were not otherwise reported as clinical adverse experiences. For example, a clinically significant decrease in platelet count was to be reported as the clinical experience of thrombocytopenia rather than decreased platelet count.

Data Quality Assurance

From the study initiation 17th-Mar-2004 to the acquisition of Aton Pharma, Inc, by Merck & Co, Inc on the 30th-Mar-2004 Aton Pharma Inc, conducted quality assurance measures for this study. Subsequent to the acquisition, Merck & Co., Inc., assumed responsibility for the study. Clinical studies conducted worldwide by Merck & Co., Inc., are subject to Quality Control and Quality Assurance measures as dictated by company and departmental Standard Operating Procedures.

Quality Control activities are intrinsic to all clinical study-related activities and are conducted by those individuals responsible for the actual conduct of the study. Such activities included, but were not limited to, on-site monitoring; adverse experience reporting; review of clinical study patient data and resultant databases; and quality reviews of clinical/regulatory documents.

The Quality Assurance activities were conducted by an organization independent from those who conduct the Quality Control. Through an established and comprehensive program, the Quality Assurance department conducted periodic audits of the Quality Control activities employed to ensure compliance to applicable GCP requirements, and company policies and procedures. Such audits included, but were not limited to, assessments of the effectiveness of field monitoring, data management, adverse experience reporting, and clinical/regulatory document reviews.

This trial had an investigator meeting conducted by Aton Pharma, Inc. at the outset of study initiation to review all protocol procedures and investigator responsibilities under GCPs. Once under the guidance of Merck & Co., Inc, a second investigator meeting was conducted to again review all protocol procedures and investigator responsibilities under GCPs. At these meetings, the conduct of the study was explained and instructions were provided to ensure accuracy and consistency in data collection. Investigators unable to attend the centrally located investigator meetings participated in individual teleconferences/webcasts to review all protocol procedures and responsibilities under GCPs.

The investigator meetings also included training for the investigators in the assessment of patients to facilitate consistency in the reporting of assessments related to the SWAT. Additional SWAT training was completed by each investigator or their designee through the review of patient

photographs and the submission of their corresponding SWAT assessments to Merck & Co., Inc. Training and inter-investigator standardization tools for the SWAT were reviewed.

All investigators received Data Handling and Entry Guidelines. A Data Management Plan which documented data management procedures, as well as database validation plans and results, was prepared and utilized by Merck & Co., Inc. The study used several organizations detailed in Section 6 to standardize the monitoring, collection, analysis, and reporting of protocol-specified samples and data.

Statistical Methods Planned in the Protocol and Determination of Sample Size

Statistical and Analytical Plans to Address Study Objectives

The primary efficacy endpoint for this study, the proportion of patients (Stage IIB and higher) with either a CCR or PR response of overall skin disease, was calculated along with its corresponding 95% exact Confidence Interval (CI). Summary statistics were provided for secondary efficacy endpoints: duration of response, time to progression, relief of pruritis, and time to objective response.

Efficacy analyses were performed in the 3 pre-specified subgroups: 1) Sezary syndrome patients, 2) patients with T3 tumor disease, and 3) patients with Stage IIB or higher disease.

A secondary objective of this study was to determine safety and tolerability of oral Vorinostat administered in this patient population. This objective was addressed by summarizing and/or listing clinical and laboratory adverse experiences.

Determination of Sample Size and Power Analysis to Address Study Hypotheses

The study was planned to enroll at least 50 evaluable patients with CTCL Stage IIB and higher. Patients were considered evaluable if they had received at least one dose of Vorinostat. A total of approximately 50-70 patients with CTCL Stage IB and higher were planned to ensure that there were at least 50 evaluable patients with Stage IIB and higher disease. The actual sample size was slightly higher to ensure adequate number of patients with post-treatment assessments while being compliant with protocol.

In patients with CTCL Stage IIB and higher who have had at least 2 systemic therapies, a conservative estimate of the maximum theoretical spontaneous response rate is 5%. Oral Vorinostat is considered active for the treatment of CTCL if the observed response rate in overall skin disease meets the joint criteria: at least 20% with the lower bound of the corresponding 95% confidence interval excluding 5%. With a sample size of 50, this study had a 90% power to meet the joint criteria if the true response rate was 27% and had the same power to exclude 5% alone if the true response rate was 20%. With a sample size of 60, this study had a 90% power to meet the joint criteria if the true response rate was 23% and had the same power to exclude 5% alone if the true response rate was 19%.

Statistical/Analytical Methods and Issues

Adjustments for Covariates

Adjustments for covariates are not applicable to this study.

Handling of Dropouts or Missing Data

The analysis of primary endpoint response rate was based upon an APaT approach that included all patients who received one or more doses of the study medication. Patients without any post-treatment measurements were conservatively treated as non-responders by this approach.

Interim Analyses and Data Monitoring

An interim analysis was conducted after 30 patients with CTCL Stage IIB and higher had 3 months of follow-up. The null hypothesis of $\leq 5\%$ response rate was formally tested at $\alpha = 1.3\%$ (two-sided), which was prespecified in the Data Analysis Plan (DAP). Per guideline in the Data Analysis Plan, the results of the interim analysis were not shared with the investigators because the decision was to continue the study based on the analysis.

Multicenter Studies

This was a multicenter study. Because the number of patients enrolled at each center was small, there was no formal statistical test of center effect. However, the site number of every responder is provided in Section 11 of the study for the ease of identifying potential outliers.

Multiple Comparisons/Multiplicity

There is no multiplicity adjustment for this study.

Changes in the Conduct of the Study

The initial protocol was approved 15-Oct-2003. The study was amended 3 times. The original protocol and the first amendment were implemented by Aton Pharma, Inc. On 30-Mar-2004 Aton Pharma, Inc. became a wholly owned subsidiary of Merck & Co., Inc. The second and third amendments were issued by Merck & Co., Inc. These final 2 protocol amendments have protocol numbers assigned by both Aton Pharma Inc., and Merck & Co., Inc, respectively. Details of editorial, administrative, and protocol changes are in the summary of each amendment. There were no substantial changes to the conduct of the study or the planned analyses. Correlative studies were introduced in protocol amendment 02. the following table summarizes the administrative protocol changes.

Table 181. Summary of Protocol Amendments (Applicant's Table)

Aton Pharma, Inc. Protocol/ Amendment	Merck & Co., Inc. Protocol/ Amendment	Sponsor Approval Date	Summary of Additions	Rationale for Changes
CL-01-0303	Not applicable	15-Oct-2003	Not applicable – original protocol	Not applicable
CL-01-0303 (1)	Not applicable	26-Feb-2004	Revise dosage strength	To permit 50 and 200 mg capsules.
CL-01-0303 (2)	001-02	23-Apr-2004	<ol style="list-style-type: none"> 1. Specification for primary and secondary endpoints. 2. Give examples of drugs that are metabolized by P450 isoenzymes and to specify that coagulation parameters must be monitored regularly in patients on coumadin derivatives. 3. Include SWAT assessment and use of body diagram per regulatory guidance. 4. Revise the definition of PD and response duration. 5. Provide instruction on the use of SWAT and Patient Questionnaire on pruritus and the use of anti-pruritic medication. 	<ol style="list-style-type: none"> 1. Assessment of patient population. 2. Explanation of drug-drug interaction. 3. Describe methodology for SWAT assessment. 4. To provide for response. 5. To clarify SWAT and questionnaire procedure.
CL-01-0303 (3)	001-03	23-Aug-2004	<ol style="list-style-type: none"> 1. Include language which pertains to the continuation protocol. 2. Incorporate updated safety and risk profile information from the CIB. 3. Provide supportive care guidance. 4. Provide clarification for Inclusion/Exclusion criteria. 	<ol style="list-style-type: none"> 1. To provide guidance for transition to continuation protocol. 2. Include overview of safety updates. 3. Describe supportive care options. 4. Clarify eligibility requirements.

SWAT = Severity weighted assessment tool.
 PD = Pharmacodynamic.
 CIB = Confidential investigator's brochure.

Data Source: [16.1.1]

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Changes in Planned Analyses

There were no changes to the statistical methods. All the primary efficacy analyses prespecified in the protocol or the Data Analysis Plan were conducted and reported. The exploratory Cox-regression analysis of time-to-response was replaced with a logistic regression analysis of response rate because response rate was considered a more important dependent variable. Additional exploratory analyses (e.g., analysis of best SWAT response) were included, as appropriate.

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Study Patient and Data Sets Analyzed

Accounting for Patients in the Study

Eighteen sites (17 in the United States and 1 in Canada) received study drug. All sites enrolled at least one patient. There were 74 patients who received at least one dose of Vorinostat. The following tables show the number of patients enrolled by investigator, tumor staging, and diagnosis, respectively. The diagnosis of Sezary syndrome was determined by the investigator, based upon recommendations provided in the protocol. Patients who did not have the primary diagnosis of Sezary syndrome were diagnosed with mycosis fungoides. Of all the patients enrolled in the study, 61/74 (82.4%) had advanced stages of CTCL (defined as clinical staging \geq IIB) and 30/74 (40.5%) of patients enrolled were diagnosed with Sezary syndrome.

Eight (8) patients were screened for inclusion into the study but not assigned to study therapy. their details along with their baseline characteristics can be found in 16.2.4.

Table 182. Number of Patients Entered by Investigator (Overall Population) (Applicant's Table)

Study Number	Investigator Name	400 mg once daily x 7d/wk (N = 74)	Total (N = 74)
0010002	Duvic, Madeleine	6	6
0010004		5	5
0010005		4	4
0010006		3	3
0010007		2	2
0010008		7	7
0010009	Kuzel, Timothy	6	6
0010010		3	3
0010011	Pacheco, Theresa	5	5
0010012		3	3
0010013		4	4
0010014		3	3
0010015		5	5
0010017		3	3
0010018		3	3
0010020		2	2
0010021		3	3
0010022		2	2

Data Source: [16.1.4; 16.4.1]

Table 183. Number of Patients Entered by Investigator (Patients with Clinical Staging \geq IIB) (Applicant's Table)

Study Number	Investigator Name	400 mg once daily x 7d/wk (N = 61)	Total (N = 61)
0010002	Duvic, Madeleine	6	6
0010004		3	3
0010005		3	3
0010006		3	3
0010007		2	2
0010008		4	4
0010009	Kuzel, Timothy	6	6
0010010		5	5
0010011	Pacheco, Theresa	3	3
0010012		3	3
0010013		4	4
0010014		3	3
0010015		4	4
0010017		2	2
0010018		2	2
0010020		2	2
0010021		3	3
0010022		1	1

Data Source: [16.1.4; 16.4.1]

Table 184. Number of Patients Entered by Investigator (Patients with Sezary Syndrome) (Applicant's Table)

Study Number	Investigator Name	400 mg once daily x 7d/wk (N = 30)	Total (N = 30)
0010002	Duvic, Madeleine	3	3
0010004		2	2
0010005		3	3
0010007		2	2
0010008		4	4
0010009	Kuzel, Timothy	6	6
0010010		1	1
0010011	Pacheco, Theresa	1	1
0010012		1	1
0010014		1	1
0010017		1	1
0010018		2	2
0010020		1	1
0010021		1	1
0010022		1	1

Data Source: [16.1.4; 16.4.1]

Patient disposition

The following three tables summarize patient disposition in the overall population, in the patients with a clinical staging \geq IIB, and in the patients diagnosed with Sezary syndrome, respectively:

Among all patients enrolled, the most common reasons for discontinuation:

- Progressive disease 25/74 (33.8%)
- Withdrawal of consent 18/74 (24.3%)

Reviewer Comments: Reasons for withdrawal of consent can be several—disease progression and toxicity are likely to be common; either way at least 43/74 patients (58%) failed treatment.

At the time of Frozen File, patients who had not previously discontinued from this study were either transitioned, or in the process of transitioning, to a continuation study (Protocol 007). This continuation study allowed any patients showing clinical benefit (subjective to investigator interpretation) to continue receiving treatment with Vorinostat. Patients who were enrolled in this continuation were counted in the “pat extended” category of the Overall Disposition of Patients. Additional sites were awaiting IRB approval for this continuation study. Patients at these sites who intended to take part in the continuation are counted in the “pat. contin. trial” group. AN1016 completed a year of study therapy. The site at which AN1016 was a patient, decided not to participate in the continuation. AN1016 was thus considered completed.

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Table 185. Overall Disposition of Patients (Overall Population) (Applicant's Table)

	400 mg once daily x7d/wk N=74 n=74
pat. completed	1
pat. contra. trial	12
pat. discont. clinical AE	58
disc. progressive disease	8
lack efficacy	15
pat. discont. for other	5
pat. withdrew consent	1
pat. extended	18
pat. extended	3
Although patients are counted only once within a Time Frame, patients, may be counted in more than one Time Frame. Patients are counted within a Time Frame based on the earliest discontinuation reason for that patient.	

Data Source: [16.4.1; 16.4.2]

Table 186. Overall Disposition of Patients (Patients with Clinical Stage ≥ IIB) (Applicant's Table)

	400 mg once daily x7d/wk N=61 n=61
pat. completed	1
pat. contra. trial	11
pat. discont. clinical AE	46
disc. progressive disease	8
lack efficacy	19
pat. discont. for other	3
pat. withdrew consent	1
pat. extended	15
pat. extended	3
Although patients are counted only once within a Time Frame, patients, may be counted in more than one Time Frame. Patients are counted within a Time Frame based on the earliest discontinuation reason for that patient.	

Data Source: [16.4.1; 16.4.2]

Table 187. Overall Disposition of Patients (Patients with Sezary Syndrome) (Applicant's Table)

	400 mg once daily x7d/wk N=30 n=30
pat. completed	1
pat. contra. trial	4
pat. discont. clinical AE	24
disc. progressive disease	5
lack efficacy	9
pat. withdrew consent	2
pat. extended	8
pat. extended	1
Although patients are counted only once within a Time Frame, patients, may be counted in more than one Time Frame. Patients are counted within a Time Frame based on the earliest discontinuation reason for that patient.	

Data Source: [16.4.1; 16.4.2]

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Protocol Deviations

The per-protocol analysis population excluded patients with clinically important deviations from the protocol-specified criteria who did not receive a waiver from the SPONSOR prior to study entry. The per-protocol population consists of patients with efficacy measurements at baseline and at least once during treatment without major protocol violations.

Nine (9) patients (AN1005, AN1006, AN1022, AN1044, AN1048, AN1052, AN1066, AN1072, and AN1073) were identified as protocol violators and were not included in the per protocol analysis. A supportive efficacy analysis was performed on this per-protocol population. Patients excluded from the per-protocol analysis were identified in the revised Protocol Violator Memo for Frozen File dated 17-Jan-2006. This revised memo added AN1022 to the list of violators and documented the violation criteria of AN1066. The original memo is superseded by the revision. Both memos can be found in 16.2.2. This was not a repetition of the inclusion and exclusion criteria from the protocol but rather a clinical assessment of protocol-specified criteria that might either affect or confound the measures of efficacy.

Multiple Violations (n = 1)

AN1006 did not obtain histological confirmation of CTCL within one year of enrollment without obtaining a waiver. This patient was also initially diagnosed with Sezary syndrome and treated with systemic steroids. This diagnosis was later changed to mycosis fungoides; however, the systemic steroids were not discontinued. This patient also did not discontinue high-potency topical steroids outside of the 28 day window mandated by the protocol and did not receive a waiver.

Inclusion Criteria Violations (n = 1)

AN1022 was viewed as previously not being treated with 2 systemic therapies. The patient received PUVA and bexarotene prior to entering the study; PUVA was not considered a systemic treatment.

Exclusion Criteria Violations (n = 3)

AN1005, AN1052, and AN1072 continued their use of high-potency topical steroids throughout the study and did not receive a waiver.

Other Violations (n = 4)

AN1073 began PUVA prior to follow-up visits. AN1044 and AN1066 used prohibited HDAC inhibitors (valproic acid) during the course of the study. While not a protocol violator, AN1048 expired prior to having a follow-up efficacy assessment and was therefore not evaluable for efficacy.

Patient Whose Treatment Was Prematurely Un-blinded

Since this was an open-label study, drug information for all patients was unblinded to the patient, investigator, and the SPONSOR.

Reviewer Comments: *This undermines the reliability of patient reported outcomes (PRO)*

Efficacy Populations Analyzed

Seventy-four (74) unique patients are counted as having received at least one dose of study drug. These 74 patients constitute the APaT population and were used in the primary efficacy and safety analysis. Nine (9) patients were considered protocol violators and were excluded from the supportive per-protocol efficacy analysis. The following table provides a summary of all patients included and excluded from the per-protocol analysis.

Table 188. Number of Patients in each Patient Population (All Patients As Treated) (Applicant's Table)

All Enrolled Patients	(N=74)
All Patients as Treated (APaT)	74 (100.0%)
Included in per-protocol population	65 (87.8%)
Excluded in per-protocol population	9 (12.2%)
- Concomitant Use of Valproic Acid	2 (2.7%)
- Concomitant use of high potency topical steroid	4 (5.4%)
- No qualified on-treatment efficacy assessments	2 (2.7%)
- One systemic therapy	1 (1.4%)

Data Source: [16.4.1; 16.4.3]

The following table provides a summary of the patients with clinical stage \geq IIB who were included and excluded from the per-protocol analysis. This group included the majority of patients in every category. There was only a single patient \leq Stage IIA excluded from the per protocol analysis due to concomitant use of a high potency topical steroid.

Table 189. Number of Patients in each Patient Population (Stage IIB or Higher CTCL) (Applicant's Table)

All Enrolled Patients	(N=61)
All Patients as Treated (APaT)	61 (100.0%)
Included in per-protocol population	54 (88.5%)
Excluded in per-protocol population	7 (11.5%)
- Concomitant Use of valproic acid	2 (3.3%)
- Concomitant use of high potency topical steroid	3 (4.9%)
- No qualified on-treatment efficacy assessments	2 (3.3%)

Data Source: [16.4.1; 16.4.3]

The following table provides the same summary for patients with Sezary syndrome. A patient was included within the Sezary syndrome group based upon the diagnosis provided by each individual investigator on the CRF.

Table 190. Number of Patients in each Patient Population in the Study (Patients With Sezary Syndrome) (Applicant's Table)

All Enrolled Patients	(N=30)
All Patients as Treated (APaT)	30 (100.0%)
Included in per-protocol population	27 (90.0%)
Excluded in per-protocol population	3 (10.0%)
- Concomitant Use of valproic acid	1 (3.3%)
- Concomitant use of high potency topical steroid	2 (6.7%)

Data Source: [16.4.1; 16.4.3]

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Demographic and Disease Characteristics

The following table provides the baseline characteristics for the overall patient population.

- Gender was almost evenly split among the patients receiving Vorinostat.
- The CTCL staging was derived from skin, node, viscera, and blood scores.
- Majority of the patients had IIB or higher disease 61/74 (82%). The majority of patients in the study had baseline tumor staging of IIB or III while very few were graded as IIA or IVB. Baseline characteristics for the patients with a clinical stage \geq IIB and for patients with Sezary syndrome can be found in 16.2.4 and were found to be similar.

Table on the next page ...

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Table 191. Baseline Patient Characteristics (All Patients As Treated) (Applicant's Table)

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	
Presence of clinically abnormal lymph nodes, n (%)	34 (45.9%)
Presence of histologically involved lymph nodes, n (%)	19 (25.7%)
Presence of skin tumor, n (%)	22 (29.7%)
Presence of Sezary syndrome, n (%)	30 (40.5%)
Number of prior systemic treatments, median (range)	3.0 (1.0, 12.0)
BSA involvement (%), median (range)	
Patch	15.6 (0.0, 100.0)
Plaque	5.9 (0.0, 98.0)
Tumor	0.0 (0.0, 91.5)

Table continued on the next page ...

Characteristics	Vorinostat (N=74)
SWAT Score	
Mean (SD)	82.5 (70.2)
Median (Range)	73.7 (1.5, 366.0)
Pruritus scores	
Mean (SD)	6.0 (2.5)
Median (Range)	6.0 (0.0, 10.0)
<p>Initial diagnostic dates for several patients were not correctly reported. The median (range) time from first treatment of CTCL was 2.9 (0.7, 27.3) years. The median (range) time from the most recent treatment was 2.0 (0.2, 27.3) years. SD = Standard Deviation. Patients with missing baseline information are excluded from the corresponding analysis. AN1022 had PUVA in addition to bexarotene and as a result is the only patient with one prior systemic therapy.</p>	

Data Source: [16.4.1; 16.4.3]

Age Distribution of Patients Enrolled in the Study

The following table provides a summary of patients treated with Vorinostat in a specific age group categorized by male and female. The majority of patients were between the ages of 56 and 75 years old. No patients under the age of 39 participated in this study.

Table 192. Number of Patients Entered by Age Category and Gender (Overall Population) (Applicant's Table)

Age	400 mg once daily x 7d/wk		Total (N = 74)
	Male (N = 38)	Female (N = 36)	
25 And Under	0	0	0
26 to 35	0	0	0
36 to 45	1	6	7
46 to 55	7	12	19
56 to 65	13	6	19
66 to 75	11	10	21
Over 75	4	2	6
Mean	64.2	58.0	61.2
SD	9.87	12.05	11.34
Median	64.0	55.5	60.0
Range	43 - 83	39 - 81	39 - 83

Data Source: [16.4.1]

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Pre-study Treatments

The following table shows the more common prior treatments for CTCL administered to patients prior to enrollment in the study. The 3 most common prior CTCL systemic treatments were bexarotene in 71/74 (95.9%) patients, interferon in 47/74 (63.5%) patients, and photopheresis in 27/74 (26.5%) patients.

Table 193. Number (%) of Patients with Specific Prior CTCL Systemic Treatments (Incidence >0% in One or More Dose Levels; Most Common Selected Specific Prior CTCL Systemic Treatments) (Applicant's Table)

	400 mg once daily x 7d/wk (N=74)		Total Patients (N=74)	
	n	%	n	%
Bexarotene	71	(95.9%)	71	(95.9%)
Interferon	47	(63.5%)	47	(63.5%)
Photopheresis	27	(36.5%)	27	(36.5%)
Folic Acid Analogues (Methotrexate)	26	(35.1%)	26	(35.1%)
Denileukin difitox	23	(31.1%)	23	(31.1%)
Glucocorticoids [†]	18	(24.3%)	18	(24.3%)
Doxorubicin	13	(17.6%)	13	(17.6%)
Gemcitabine	12	(16.2%)	12	(16.2%)
Cyclophosphamide	9	(12.2%)	9	(12.2%)
Chlorambucil	7	(9.5%)	7	(9.5%)

[†]: includes prednisone and dexamethasone.
 A patient is counted only once within a specific prior treatment grouping if they received the drug as monotherapy, in combination, or both.

Data Source: [16.4.1]

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Pre-Study Response Rates

The following table summarizes the best response from the last systemic therapy taken prior to receiving Vorinostat. This assessment was based on clinical records available at the investigator's site or, if not available, from patient history. Prior therapy response assessment may have been assessed by methods other than SWAT. The overall response rate to the last systemic therapy was approximately 30%. Median treatment duration of the last prior systemic therapy was approximately 7 months. The treatment duration was shorter for patients who received a subsequent systemic therapy after progressing from their prior bexarotene therapy. Despite response to prior treatment, all patients had a recurrence of disease prior to participating in this study.

Table 194. Analysis of Patients with an Objective Response to the Last Systemic Therapy prior to Vorinostat (All Patients as Treated) (Applicant's Table)

	N	Patients With an Objective Response to Last Systemic Therapy	
		n (%)	Treatment Duration (Days) Median (Range)
All Patients	74	22 (29.7%)	214 (32, 3546)
- Bexarotene Users	23	7 (30.4%)	215 (32, 277)
- Other Systemic Therapy Users	51	15 (29.4%)	154 (32, 3546)

† Objective Response: complete response or partial response.
 ‡ Excludes systemic procedures as response data to procedures is unavailable.

Data Source: [16.4.1; 16.4.3]

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Secondary diagnoses at study entry

Table 14-1 located in Section 14.2 (page 185) provides the incidence of secondary diagnosis by body system for patients enrolled in the study.

- Other than CTCL, a prerequisite of the study, the most common secondary diagnoses at baseline were hypertension, hypothyroidism, and depression. All of these diagnoses had an incidence >30%.

Prior therapies

Table 14-2 located in Section 14.2 (page 204) provides the incidence of prior therapies by drug categories for the patients enrolled in the study. In determining most frequently used classes of prior therapies, antineoplastic and immunomodulating agents, as well as dermatological corticosteroid preparations, were discounted due to their common use as standard of care in this patient population. As expected for a population with a median age above 60, study patients commonly had multiple pre-existing medical diagnoses and prior medical therapies. The most frequently used classes of prior therapies were psychoanalptics, analgesics, psycholeptics, and serum lipid reducing agents.

- Nearly one-quarter of the patients had a history of hyperlipidemia or hypertriglyceridemia and 27/74 (36.5%) patients were taking lipid lowering agents.
- Prior history of deep vein thrombosis (DVT) was reported in 2/74 (2.7%) patients. Four (4/74) patients (5.4%) were taking warfarin.
- Prior history of ECG abnormalities were reported in 12/74 (16.2%) patients.
- Antipruritic medications were commonly used and topical corticosteroids were used by 38/74 (51.4%) patients, antihistamines by 20/74 (27.0%) patients, doxepin by 12/74 (16.2%) patients, emollients by 8/74 (10.8%) patients, and other dermatologic therapies by 7/74 (9.5%) patients.

Prior cancer therapies

Table 14-3 located in Section 14.2 (page 218) details prior cancer therapies.

- Fifty-nine (59/74, 79.7%) patients had reported previous use of skin directed therapy.
- Light therapy such as PUVA or UV therapy had reported use in 41/74 (55.4%) and 11/74 (14.9%) patients, respectively.
- Topical alkylating agents, nitrogen mustard 32/74 (43.2%) and carmustine (10.8%) were also frequently used.
- Bexarotene gel was used by 16/74 (21.6%) patients and at least 20/74 (27.0%) patients used high potency topical steroids.
- Eight (8/74, 10.8%) patients underwent electron beam therapy. Other radiotherapies were used by 38/74 (51.4%) patients, with 18/74 (24.3%) patients reported using this treatment on 2 or more locations.

Concomitant therapies

Table 14-4 located in Section 14.2 (page 223) provides the incidence of concomitant therapies by drug category for patients enrolled in the study.

Measurements of Treatment Compliance

A capsule count was performed at each office visit to assess compliance with study drug. Compliance was assessed by the percentage of total drug amount (mg) actually taken (as reflected by capsule counts and dose level) while the patient was on active treatment. If the compliance was over 100%, likely due to errors in pill counts, it was truncated to 100%. The data for AN1070 was entered into the production database, but not the Frozen File database, and is reflected in the table below. (The sponsor states that the compliance rate tended to be underestimated especially for patients still continuing in the study because the most current data on returned study drug may not have been available at the time of Frozen File. An example of this is AN1014, who did respond to study drug and was continuing the study but is the sole patient with <50% compliance. This compliance calculation is the most conservative estimation given the unavailability of complete drug accountability data.)

The following table is summary of drug compliance in the overall patient population.

- o The overall drug compliance was in excess of 94%. Over 87% of the patients had a compliance rate of at least 80%.

Table 195. Summary of Drug Compliance while on Active Treatment with Vorinostat (All Patients As Treated) (Applicant's Table)

Drug Compliance	Vorinostat (N=74)
Percentage of drug taken (%)	
Mean (SD)	94.2 (11.3)
Median (Range)	98.6 (46.5, 100.0)
Number (%) of patients with	
≥ 80% compliance	65 (87.8%)
50% - 80% compliance	8 (10.8%)
< 50% compliance	1 (1.4%)
SD = Standard Deviation.	

Data Source: [16.4.1; 16.4.2]

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Efficacy Evaluation and Results

- The efficacy analyses were based upon an **APaT population** that includes all patients who received one or more doses of the study medication. This approach considered patients without any post-treatment measurements as non-responders.
- A supportive efficacy analysis was based on a **per-protocol** approach that included a subset of the APaT population who had efficacy measurements at baseline and at least once during treatment without major protocol violations (e.g., concomitant use of high potency topical steroids).

Improvement in Overall Skin Disease

The **primary efficacy objective** was to determine the **response rate** to oral Vorinostat in the treatment of skin disease in patients with advanced CTCL (Stage IIB and higher) as measured by the Physician's Assessment of Overall Skin Disease using the SWAT.

- A patient was considered to have an **objective response** (or response) in overall skin disease if the patient had a CCR or PR (whichever was first recorded) by SWAT skin assessment scores. **Confirmation of response** required a second assessment by SWAT after at least 4 weeks of the last response assessment. This confirmation qualified the objectivity of the response. **Patient photographs** and **body diagrams** which were supportive of the independent SWAT skin assessment are in 16.2.6.
- **Time to response** was measured from the start of the treatment to the time when criteria were first met for a response.
- The **duration of overall response** was measured from the time 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 and if that magnitude of increase in the skin score was confirmed by a second assessment at 1-4 weeks later (unless confirmation assessment was not available).
- **Time to progression** was measured from the start of the treatment until the criteria for progression were first met. Progression of disease was to be confirmed by a second assessment 1-4 weeks later (unless confirmation assessment is not available).
- Number of weeks relative to the first treatment visit was used in derivations of the above efficacy endpoints. The first 4 bi-weekly visits allowed a tolerance of ± 3 days and future visits allowed a tolerance of ± 7 days.

The following table shows the primary results of this study based on the APaT approach.

- Eighteen (18/61) patients with Stage IIB and higher disease had a responded. The response rate was 29.5% and the corresponding 95% confidence interval to the response rate of (18.5%, 42.6%), exceeded the pre-specified criteria for a positive trial.
- These patients had a median time to response of less than 2 months. Neither the median response duration nor the median time to progression was reached.
- Similar results were found in the 3 prespecified subgroup populations: all patients, patients with Sezary syndrome, and patients with T3 tumor disease.

Table 196. Objective Response Rates to Vorinostat (All Patients As Treated) (Applicant's Table)

Population	N	Patients with an Objective Response ¹				
		n (%)	(95% CI)	Time to Objective Response ¹ (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 and higher CTCL ²	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 T3 tumor disease	22	5 (22.7%)	(7.8, 45.4)	31 (29, 87)	.(55, 280+)	.(148, 317+)

¹ Objective Response: confirmed complete response or partial response.
² Stages IIB, III, IVA, and IVB.
 CI = Confidence Interval.
 += Response ongoing.

Data Source: [16.4.1; 16.4.3]

Table 197. Objective Response Rate to Vorinostat (Per-Protocol Approach) (Applicant's Table)

Population	N	Patients with an Objective Response ¹				
		n (%)	(95% CI)	Time to Objective Response ¹ (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 and higher CTCL ²	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)	.(36, 244+)	.(85, 365+)
Patients with T3 tumor disease	20	5 (25.0%)	(3.7, 49.1)	31 (29, 87)	.(35, 280+)	.(148, 317+)

¹ Objective Response: confirmed complete response or partial response.
² Stages IIB, III, IVA, and IVB.
 CI = Confidence Interval.
 += Response ongoing.

Data Source: [16.4.1; 16.4.3]

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Responders

The following table lists all the patients who responded to Vorinostat during the study.

- All responses but one were partial (PRs)
- Patient AN1025 achieved CCR after 281 days of treatment. Patient AN1027 obtained a 55 days long response but remained on Vorinostat as criteria for progressive disease were not met. Subsequently, this patient obtained a second PR with duration of 84+ days.
- None of the investigator sites yielded more than 2 responders. Therefore, there was no apparent site effect.
- Fourteen (14) of 22 patients (63.6%) continued to show response at the time of their last assessment.
- Two (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. Only 6/22, (27.3%) patients who achieved an objective response met the criteria for progressive disease. The time to progressive disease for patients censored at time of data lock showed ongoing time to progressive disease ranging from 136+ to 365+ days.

Table 198. List of Patients Treated with Vorinostat: Time to Objective Response and Duration of Objective Response (All Patients As Treated) (Applicant's Table)

Site	Allocation Number	Stage	Sezary (Yes/No)	T3 Tumor (Yes/No)	Time to objective response ¹ (days)	Duration of objective response (days) ²	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	1036	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	IB	No	Yes	87	55	317+	pat. contin. trial
0011	1024	III	Yes	No	29	56	83	discontinued
0012	1025	IB	No	Yes	29	280+	309+	pat. contin. trial
	1029	IVA	No	Yes	31	117	148	discontinued
0015	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	IB	No	Yes	87	137+	224+	pat. contin. trial
	1068	IB	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	1033	IVA	Yes	No	114	119+	233+	pat. contin. trial
0022	1042	IB	No	No	30	48+	78+	discontinued

¹ Objective Response: confirmed complete response or partial response.

² 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.

Data Source: [16.4.1; 16.4.3]

Table 14-5 in Section 14.2 (page 239) provides a listing of individual primary and secondary efficacy measurements in all patients and also the links to the individual patient photographs and body diagrams that were used as supportive information for the SWAT skin assessment.

Time to Event Analyses

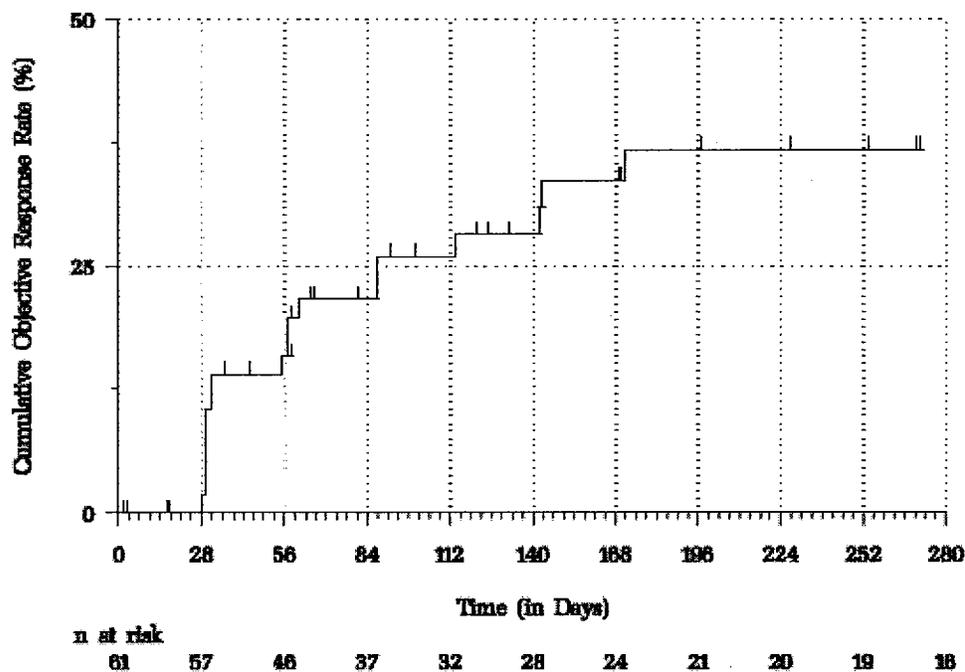
Kaplan-Meier plots of time to objective response, response duration and time to progression, and plot of mean changes in SWAT skin measurement scores based on patients with Stage IIB and higher disease.

- The median response duration was not reached, but was estimated to be at least 4 months
- The median time-to-progression was not reached, but was estimated to be at least 5 months based on all patients Stage IIB and higher

Kaplan-Meier Plots are available for the overall patient population on protocol 001 on pages 80, 82, and 84, and were reviewed.

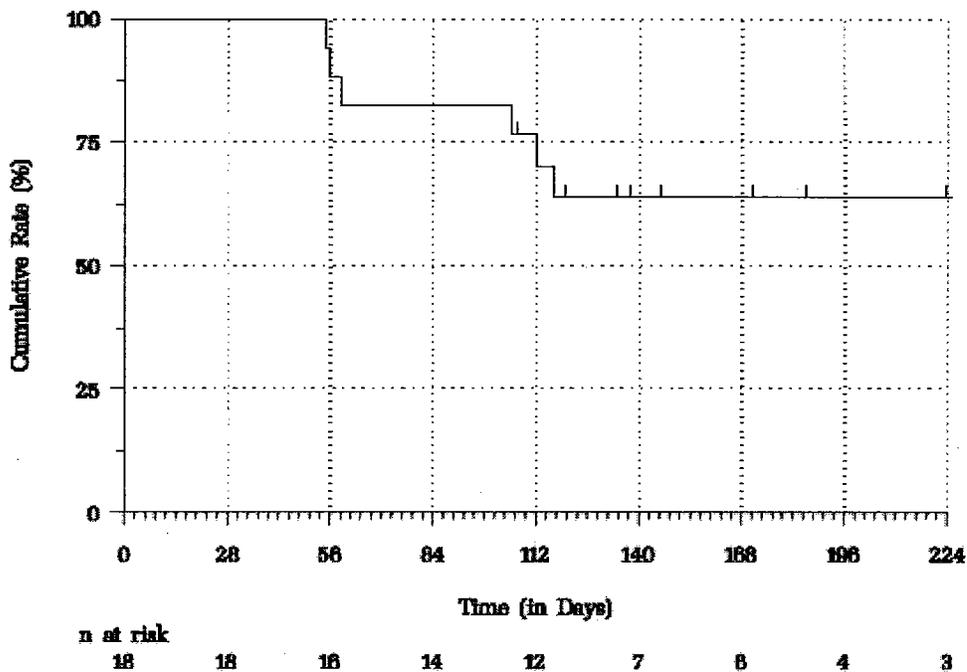
- Findings are generally consistent between overall population and patients with Stage IIB and higher disease except that the median time-to-progression was reached after 5 months of follow-up.

Figure 3. Time to Objective Response on Vorinostat (Stage IIB and Higher CTCL) (Applicant's Figure)



Data Source: [16.4.1; 16.4.3]

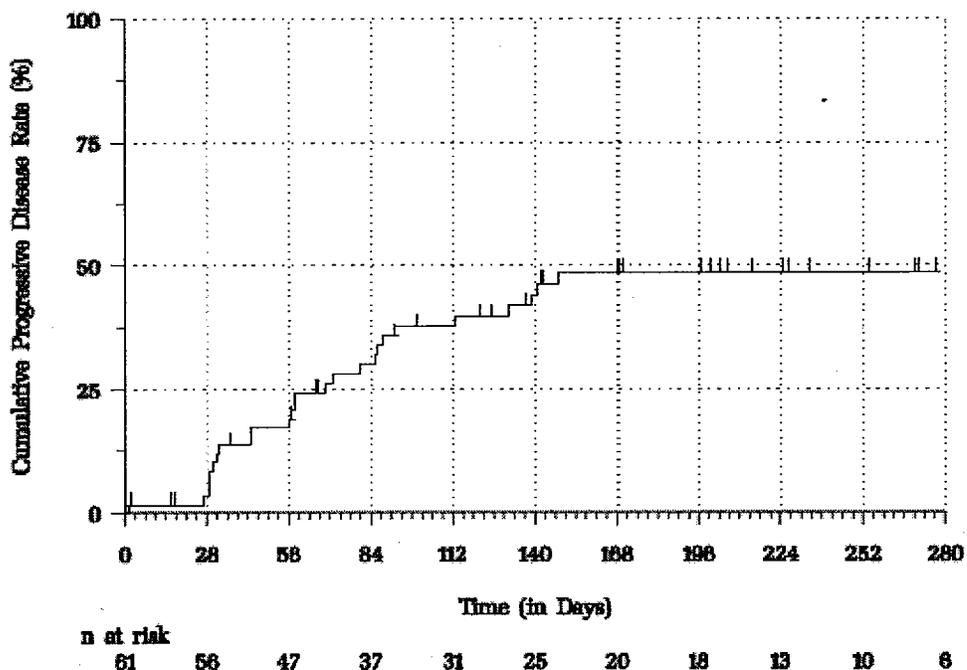
Figure 4. Response Duration (Kaplan-Meier plot during Treatment with Vorinostat for Patients who achieved an Objective Response (Stage IIB or Higher CTCL) (Applicant's Figure))



Data Source: [16.4.1; 16.4.3]

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Figure 5. Time to Progressive Disease (Kaplan-Meier Curve during Treatment with Vorinostat for patients With Stage IIB or Higher CTCL) (Applicant's Figure)



Data Source: [16.4.1; 16.4.3]

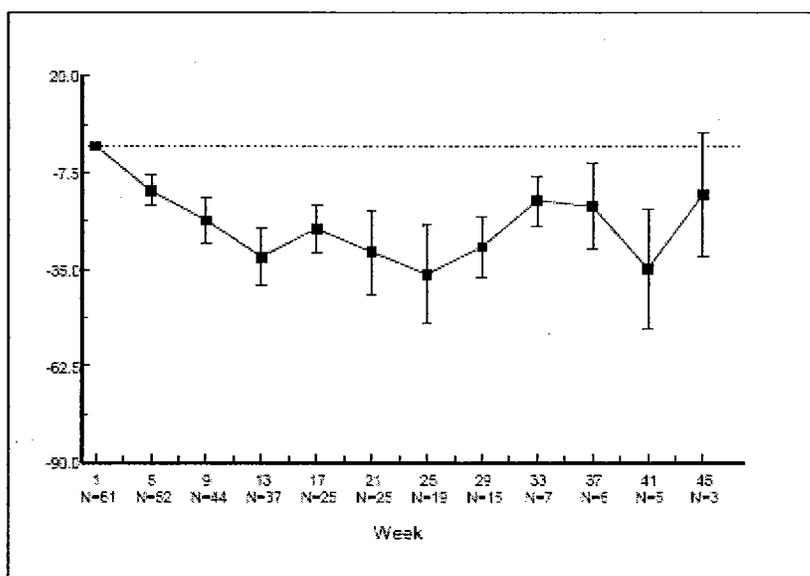
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Changes in the SWAT Score over time

The following figure shows the mean changes in SWAT scores during the study and shows a clear decreasing trend.

Reviewer Comments: This data is not reliable over time as the number of patients decreases and the standard error increases.

Figure 6. Mean Changes (%) (Standard Error) from Baseline in SWAT Score during the Study with Vorinostat (Patients with Stage IIB and Higher CTCL) (Applicant's Figure)



Data Source: [16.4.1; 16.4.3]

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Analyses of Reductions in SWAT Scores Including those that did not meet the Criteria for an Objective Response

The following table provides the numbers of patients with a $\geq 50\%$ reduction in SWAT skin assessment score from baseline anytime during the study. Twenty-three (23/61, 37.7%) patients with Stage IIB and higher disease had a $\geq 50\%$ reduction in SWAT skin assessment scores at any time during the study.

Table 199. Number of Patients Treated with Vorinostat with a $\geq 50\%$ Reduction in SWAT Score (All Patients As Treated) (Applicant's Table)

Population	N	Patients with a $\geq 50\%$ reduction in SWAT Score	
		n (%)	(95% CI)
All Patients	74	29 (39.2%)	(28.0, 51.2)
Stage IIB and higher CTCL [†]	61	23 (37.7%)	(25.6, 51.0)
Patients with Sezary syndrome	30	13 (43.3%)	(25.5, 62.6)
Patients with T3 tumor disease	22	7 (31.8%)	(13.9, 54.9)

[†] Stages IIB, III, IVA, and IVB.
 CI = Confidence Interval.

Data Source: [16.4.1; 16.4.3]

Additional analyses were performed to examine varying degrees of reduction in SWAT skin assessment scores. The following table shows the number of patients who experienced at least a 25% reduction without reaching a 50% reduction in the SWAT score.

Table 200. Number of Patients Treated with Vorinostat with a 25 to 50% Reduction in SWAT Score (All Patients As Treated) (Applicant's Table)

Population	N	Patients with a 25 to 50% reduction in SWAT Score	
		n (%)	(95% CI)
All Patients	74	17 (23.0%)	(14.0, 34.2)
Stage IIB or Higher CTCL [†]	61	12 (19.7%)	(10.6, 31.8)
Patients with Sezary syndrome	30	6 (20.0%)	(7.7, 38.6)
Patients with T3 tumor disease	22	4 (18.2%)	(5.2, 40.3)

[†] Stages IIB, III, IVA, and IVB.
 CI = Confidence Interval.

Data Source: [16.4.1; 16.4.3]

The following table shows the number of patients who experienced any reduction in SWAT score.

Table 201. Number of Patients Treated with Vorinostat with a $>0\%$ Reduction in SWAT Score (All Patients As Treated) (Applicant's Table)

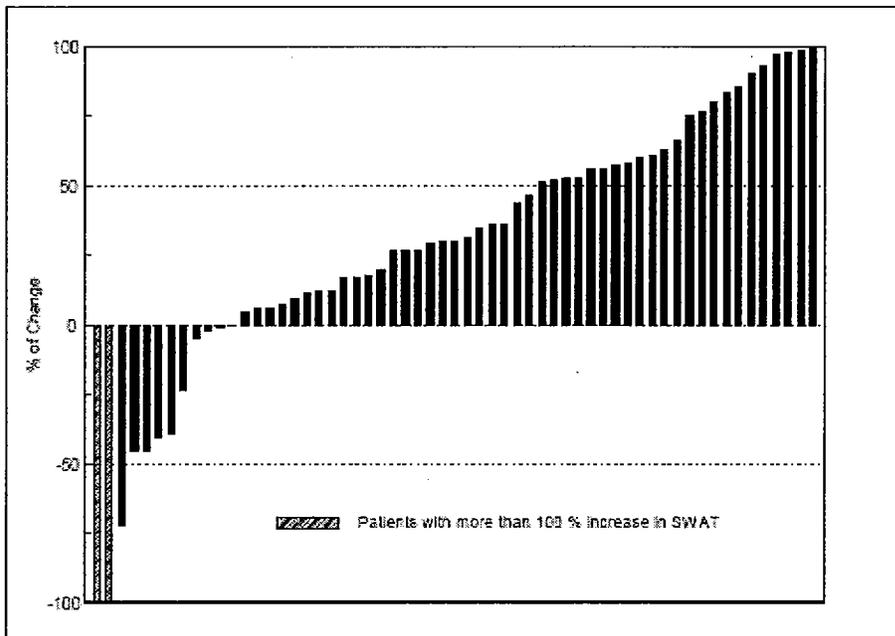
Population	N	Patients with a greater than 0% reduction in SWAT Score	
		n (%)	(95% CI)
All Patients	74	60 (81.1%)	(70.3, 89.3)
Stage IIB or Higher CTCL [†]	61	47 (77.0%)	(64.5, 86.8)
Patients with Sezary syndrome	30	24 (80.0%)	(61.4, 92.3)
Patients with tumor disease	22	16 (72.7%)	(49.8, 89.3)

[†] Stages IIB, III, IVA, and IVB.
 CI = Confidence Interval.

Data Source: [16.4.1; 16.4.3]

The following figure shows a bar-chart of best response in terms of maximum SWAT score reduction from the baseline based on patients with Stage IIB and higher disease. Bars above the line represent reductions in SWAT scores. Improvement in skin disease at some point during Vorinostat treatment, as measured in terms of best response, was attained in 60/74 (81.1%) of patients treated with Vorinostat.

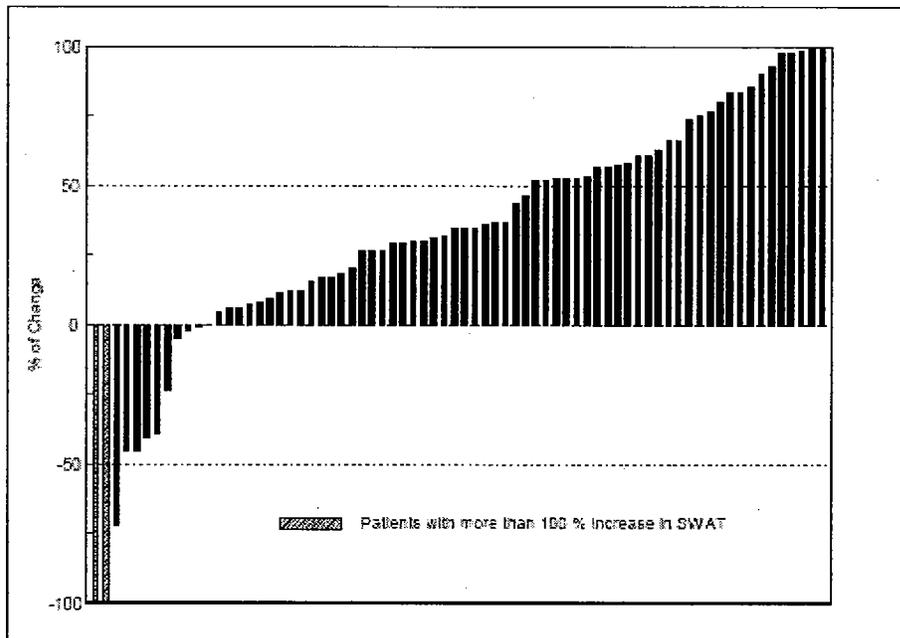
Figure 7. SWAT Score Decreases during the Study with Vorinostat (Patients with CTCL Stage IIB and Higher CTCL) (Applicant's Figure)



Data Source: [16.4.1; 16.4.3]

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**Figure 8. SWAT Score Decreases during the Study with Vorinostat (All Patients As Treated)
(Applicant's Figure)**



Data Source: [16.4.1; 16.4.3]

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Analysis for any relationships between the responses observed on Vorinostat and the last systemic therapy or other patient and disease characteristics

Best response to the last systemic therapy

The following table shows the response rates to Vorinostat for the responders and non-responders from the last systemic therapy. Patients are divided into a bexarotene therapy group and a non-bexarotene therapy group.

- o No obvious impact of the response to last treatment (either bexarotene or to other therapies) is observed on the subsequent efficacy of Vorinostat.

Table 202. Relationship between Best Response to Last Systemic Therapy and Response to Vorinostat (All Patients As Treated) (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%)	(11.9, 61.6)
Non-responder	36	10 (27.8%)	(14.2, 45.2)

¹ Objective Response: confirmed complete response or partial response.
[†] Excludes systemic procedures as response data to procedures is unavailable.
 CI = confidence interval.

Data Source: [16.4.1; 16.4.3]

Best response to bexarotene therapy

The following table provides the data to explore any relationship between best response to bexarotene therapy the patient received at any time prior to taking Vorinostat and their response to Vorinostat in this study.

- o No obvious impact of past response to bexarotene was observed on the subsequent efficacy of Vorinostat. Response to any previous systemic therapy does not appear to be predictive of response to Vorinostat.

Table 203. Relationship between Response to Bexarotene Systemic Therapy and Response to Vorinostat (All Patients As Treated) (Applicant's Table)

Population	N	Responder to Vorinostat	
		n (%)	(95% CI)
Patients on bexarotene as systemic therapy	71	21 (29.6%)	(19.3, 41.6)
Responder to most recent use	20	7 (35.0%)	(15.4, 59.2)
Non-responder to most recent use	39	10 (25.6%)	(13.0, 42.1)
Unknown response to most recent use	12	4 (33.3%)	(9.9, 65.1)

¹ Objective Response: confirmed complete response or partial response.
 CI = confidence interval.

Data Source: [16.4.1; 16.4.3]

Impact of other patient and disease factors on response to Vorinostat

- Investigation of other pre-specified baseline characteristics including gender, age, ECOG, serum lactate dehydrogenase (LDH), disease stage and disease type, and response to prior therapy based on a multivariate logistic regression analysis did not reveal any factors that might be predictive of response. These data are shown in the table below.
- Three (3) non-pre-specified variables (baseline SWAT score, race, and normalized dose by body weight) were explored:
 - There was a statistically significant difference at the 5% level (P = 0.048) in response rates by race favoring white.
 - None of the other effects were statistically significant at the 5% level.
- The lack of weight effect suggests that the use of normalized dose by body weight for efficacy improvement is not warranted.

Table 204. Analyses of Predictive Factors to Objective Response: Exploratory Analyses – Logistic Regression (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

Data Source: [16.4.1; 16.4.2; 16.4.3]

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Improvement in Pruritis Scores

A 3-point improvement in pruritis intensity was pre-specified as the minimally important difference based on the standard deviation (SD) of pruritis intensity at baseline among patients who had pruritis at study entry (N= 72 patients, SD = 2.5). This represents one SD, which is 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 [16.1.12.44].

- Patients reported the intensity of their pruritis on a visual analog point scale of 0 to 10, with 0 being no pruritis and 10 being the worst imaginable pruritis.
- A 3-point drop on the 0 to 10 point scale without an increase in the use of anti-pruritic medications was considered clinically significant in those who had pruritis intensity ≥ 3 prior to receiving Vorinostat.
- Patients who had complete resolution of pruritis without an increase in the use of anti-pruritic medications were also analyzed.
- Both the ≥ 3 point drop in the pruritis scale and the complete resolution of pruritis were to be maintained for at least 4 weeks to qualify for pruritis relief. (The first 4 biweekly visits allowed a tolerance of ± 3 days and future visits allowed a tolerance of ± 7 days.)

The following table shows that 18/59 (30.5%) of the patients with Stage IIB and higher disease had clinically important pruritis relief and 8/59 (13.6%) had complete resolution of their pruritis. This relief in pruritis was maintained for at least 4 weeks without an increase in their pruritis medication. The results were similar for patients with pruritis intensity ≥ 3 at baseline and patients with Sezary syndrome.

Table 205. Number of Patients Treated with Vorinostat with Relief of Pruritus for at least 4 Weeks without An Increase in the Use of Anti-pruritus Medications (Patients with Stage IIB or Higher CTCL) (Applicant's Table)

Population	N	Patients with complete resolution ¹		Patients with Pruritus Relief ²	
		n (%)	(95% CI)	n (%)	(95% CI)
All Patients	59	8 (13.6%)	(6.0, 25.0)	18 (30.5%)	(19.2, 43.9)
Patients with pruritus intensity ≥ 3 points at baseline	53	6 (11.3%)	(4.3, 23.0)	16 (30.2%)	(18.3, 44.3)
Patients with Sezary Syndrome	30	3 (10.0%)	(2.1, 26.5)	9 (30.0%)	(14.7, 49.4)
Patients with T3 tumor disease	20	2 (10.0%)	(1.2, 31.7)	4 (20.0%)	(5.7, 43.7)

¹ The intensity of pruritus is assessed on the point scale of 0-10, with zero being no pruritus and ten being the worst imaginable pruritus.
² Complete Resolution is sustained pruritus score of 0 for at least 4 continuous weeks.
 Pruritus Relief is sustained pruritus reduction of 3 or more points or complete resolution for at least 4 continuous weeks.
 Pruritus medication use was not collected for Site 0008: patients 1001, 1002, 1003, 1005, 1037, 1080.
 CI=Confidence Interval.
 Patient allocation numbers 1047 and 1027 had missing pruritus at baseline, and were excluded from the analysis.

Data Source: [16.4.1; 16.4.3]

The following table provides the corresponding analyses for all patients. The overall results were consistent. Twenty-three (23/72, 31.9%) patients had pruritus relief and 8/72 (11.1%) had complete resolution of their pruritus. Notice that, because all patients with Sezary syndrome or T3 tumor disease were in Stage IIB and higher, the analysis of these patients is the same between the two tables.

Table 206. Number of Patients Treated with Vorinostat with Relief of Pruritus for at Least 4 Weeks without an Increase in the Use of Anti-pruritus Medications (All Patients as Treated) (Applicant's Table)

Population	N	Patients with complete resolution ¹		Patients with Pruritus Relief ²	
		n (%)	(95% CI)	n (%)	(95% CI)
All Patients	72	8 (11.1%)	(4.9, 20.7)	23 (31.9%)	(21.4, 44.0)
Patients with pruritus intensity ≥3 points at baseline	65	6 (9.2%)	(3.5, 19.0)	21 (32.3%)	(21.2, 45.1)
Patients with Sezary Syndrome	30	3 (10.0%)	(2.1, 26.5)	9 (30.0%)	(14.7, 49.4)
Patients with T3 tumor disease	20	2 (10.0%)	(1.2, 31.7)	4 (20.0%)	(5.7, 43.7)

¹ The intensity of pruritus is assessed on the point scale of 0-10, with zero being no pruritus and ten being the worst imaginable pruritus.
² Complete Resolution is sustained pruritus score of 0 for at least 4 continuous weeks.
³ Pruritus Relief is sustained pruritus reduction of 3 or more points or complete resolution for at least 4 continuous weeks.
 Pruritus medication use was not collected for Site 0008: patients 1001, 1002, 1003, 1004, 1005, 1037, 1080.
 CI=Confidence Interval.
 Patient allocation numbers 1047 and 1027 had missing pruritus at baseline, and were excluded from the analysis.

Data Source: [16.4.1; 16.4.3]

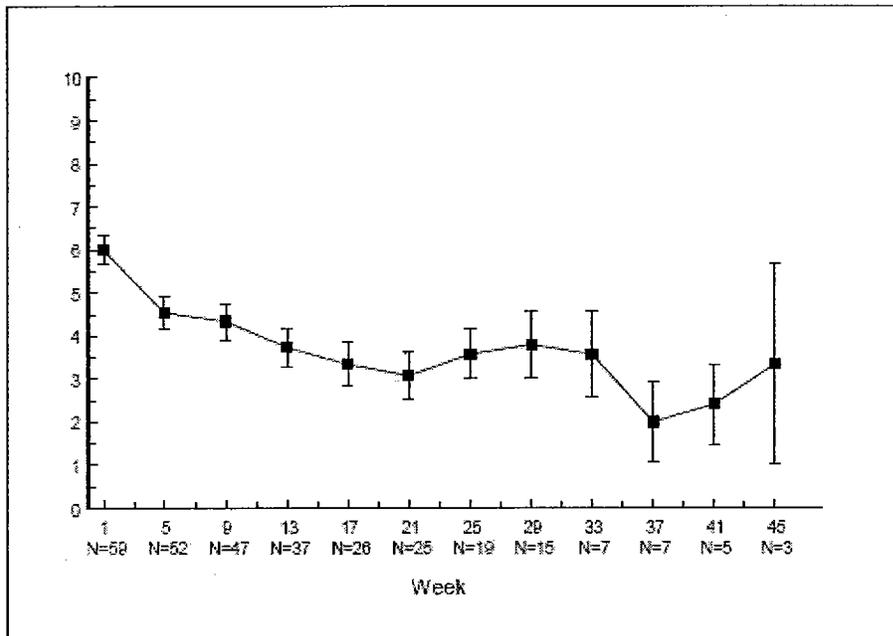
Mean pruritus intensity score over time

The following two figures provide the plots of mean pruritus intensity scores over time for patients with Stage IIB and higher disease and for all patients, respectively. The mean pruritus scores had a clear decreasing trend.

Reviewer Comments: Due to a low number of the patients at the start and further lowering of the number of patients with time (and widening standard error) these results are not reliable.

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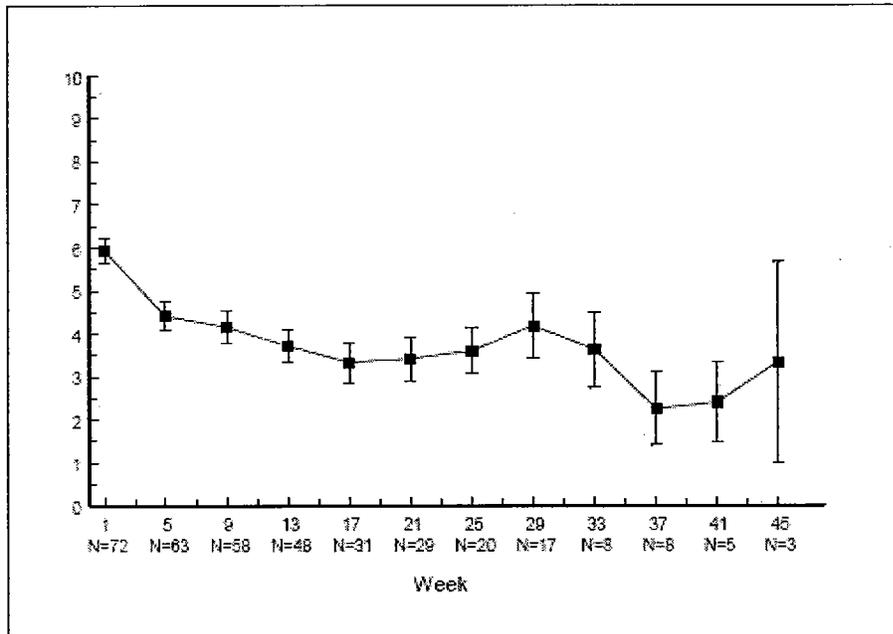
Figure 9. Mean Score (Standard Error) of Pruritus Intensity during Treatment with Vorinostat (Patients with Stage IIB and Higher CTCL) (Applicant's Figure)



Data Source: [16.4.1; 16.4.3]

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Figure 10. Mean Score (Standard Error) of Pruritus Intensity during Treatment with Vorinostat (All Patients As Treated) (Applicant's Figure)



Data Source: [16.4.1; 16.4.3]

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Response to Vorinostat and pruritis

The following tables show the number of patients with pruritus relief by whether they responded to Vorinostat for patients with Stage IIB and higher disease and all patients, respectively. Among the patients with Stage IIB and higher disease, 9/17 (52.9%) of the patients with an objective response experienced pruritus relief; however 9/42 (21.4%) patients who did not have an objective response also experienced pruritus relief. Similar results were seen in the APaT population as well.

Table 207. Pruritis relief by response to Vorinostat (Patients with Stage IIB and Higher CTCL) (Applicant's Table)

Population	N	Patients with Pruritus Relief [†]	
		n (%)	(95% CI)
All Patients	59	18 (30.5%)	(19.2, 43.9)
- Patients with an objective response [‡]	17	9 (52.9%)	(27.8, 77.0)
- Patients without an objective response [‡]	42	9 (21.4%)	(10.3, 36.8)

[†] Pruritus Relief is sustained pruritus reduction of 3 or more points or complete resolution for at least 4 continuous weeks.
[‡] Objective Response: complete response or partial response.
 CI = Confidence Interval.
 Patient allocation numbers 1047 and 1027 had missing pruritus at baseline, and were excluded from the analysis.

Data Source: [16.4.1; 16.4.3]

Table 208. Pruritis relief by response to Vorinostat (All Patients As Treated) (Applicant's Table)

Population	N	Patients with Pruritus Relief [†]	
		n (%)	(95% CI)
All Patients	72	23 (31.9%)	(21.4, 44.0)
- Patients with an objective response [‡]	21	10 (47.6%)	(25.7, 70.2)
- Patients without an objective response [‡]	51	13 (25.5%)	(14.3, 39.6)

[†] Pruritus Relief is sustained pruritus reduction of 3 or more points or complete resolution for at least 4 continuous weeks.
[‡] Objective Response: complete response or partial response.
 CI = Confidence Interval.
 Patient allocation numbers 1047 and 1027 had missing pruritus at baseline, and were excluded from the analysis.

Data Source: [16.4.1; 16.4.3]

The following tables show the number of patients with baseline pruritus scores ≥ 3 who experienced pruritus relief by whether they responded to Vorinostat (patients with Stage IIB and higher disease and all patients, respectively). The time to pruritus relief and the duration of pruritus relief are also provided for these populations. End of pruritus relief is defined to be a return to baseline or higher.

Among patients with Stage IIB and higher disease, who has a baseline pruritus score ≥ 3 , seven (7) of 13 (53.8%) patients with an objective response experienced pruritus relief. The median time to pruritus relief was 29 days and the median duration of pruritus relief was 160 days.

Pruritus relief was also noted to occur rapidly among some patients who did not meet the criteria for objective response. Nine (9) of 40 patients (22.5%) with a baseline pruritus score ≥ 3 did not have an objective response but experienced pruritus relief. The median time to pruritus relief in this population was 15 days and the median duration of pruritus relief was 71 days. Similar results were also seen in the APaT population as well.

Table 209. Pruritus relief by objective response to Vorinostat (Patients With Stage IIB And Higher CTCL) (Applicant's Table)

Population	N	Patients with Pruritus Relief [†]			
		n (%)	(95% CI)	Time to Pruritus Relief [‡] (days) Median (Range)	Duration of Pruritus Relief (days) Median (Range)
All Patients with ≥ 3 baseline pruritus	53	16 (30.2%)	(18.3, 44.3)	16 (14, 87)	113 (3+ , 295+)
Patients with an objective response [‡]	13	7 (53.8%)	(25.1, 80.8)	29 (14, 43)	160 (74, 295+)
Patients without an objective response [‡]	40	9 (22.5%)	(10.8, 38.5)	15 (14, 87)	71 (34+, 155)

[†] Pruritus Relief is sustained pruritus reduction of 3 or more points or complete resolution for at least 4 continuous weeks.
[‡] Objective Response: confirmed complete response or partial response.
 CI = Confidence Interval.
 + = Response ongoing.

Data Source: [16.4.1; 16.4.3]

Table 210. Pruritus relief by objective response to Vorinostat (All Patients at Treated) (Applicant's Table)

Population	N	Patients with Pruritus Relief [†]			
		n (%)	(95% CI)	Time to Pruritus Relief [‡] (days) Median (Range)	Duration of Pruritus Relief (days) Median (Range)
All Patients with ≥ 3 baseline pruritus	65	21 (32.3%)	(21.2, 45.1)	16 (14, 87)	84 (34+, 295+)
Patients with an objective response [‡]	17	8 (47.1%)	(23.0, 72.2)	30 (14, 43)	148 (74, 295+)
Patients without an objective response [‡]	48	13 (27.1%)	(15.3, 41.8)	15 (14, 87)	71 (34+, 155)

[†] Pruritus Relief is sustained pruritus reduction of 3 or more points or complete resolution for at least 4 continuous weeks.
[‡] Objective Response: confirmed complete response or partial response.
 CI = Confidence Interval.
 + = Response ongoing.

Data Source: [16.4.1; 16.4.3]

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Improvement in Disease-Specific Biomarkers

Sezary cell reduction and SWAT response

The following table shows the number of patients with Sezary syndrome who had a $\geq 25\%$ reduction in Sezary cell count during the study, as part of the prespecified subgroup analysis. CD4+/CD26- cells were quantified by flow cytometry as an automated method to perform Sezary cell count. Overall, 14/27 (51.9%) of the patients with Sezary syndrome had a $\geq 25\%$ reduction in Sezary cells.

For the 6 patients with an objective response who did not show a 25% reduction in Sezary cells only one had a baseline Sezary cell count exceeding 4,000/mL. Low baseline Sezary cell counts may be subject to variability that would preclude detection of a clinically meaningful decrease. Conversely, patients with objective response tended to have higher Sezary cell counts at baseline. There was a single patient who showed both an objective response and a $\geq 25\%$ reduction in Sezary cell with a baseline Sezary cell count less than 4,000/mL.

Table 211. Number of Patients with a $\geq 25\%$ Sezary Cell Reduction during Treatment with Vorinostat (All Patients As Treated) (Applicant's Table)

	N	Patients with Sezary Cell Reduction [†]	
		n (%)	(95% CI)
Patients with Sezary syndrome	27	14 (51.9%)	(31.9, 71.3)
- Patients with an objective response [‡]	10	4 (40.0%)	(12.2, 73.8)
- Patients without an objective response [‡]	17	10 (58.8%)	(32.9, 81.6)

[†] Sezary cell reduction is defined as a 25% reduction of Sezary cell counts (CD4+CD26-) from baseline.
[‡] Objective response: complete response or partial response.
 Patient allocation numbers 1001, 1002 and 1005 have missing Sezary cell counts (CD4+CD26-) at baseline, and were excluded from the analysis.
 Objective responder's baseline Sezary cell counts: 404/mL; 45,710/mL; 13,577/mL; 11,053/mL.
 Non-responders baseline Sezary cell count: 190/mL; 3,058/mL; 105/mL; 3,591/mL; 659/mL; 10,907/mL

Data Source: [16.4.1; 16.4.3]

Reviewer Comments: 14 patients had a $\geq 25\%$ reduction in the Sezary cell counts, four (4) were responders and 10 were non-responders by SWAT. There does not seem to be any association between the objective response and Sezary cell responses.

T3 tumor disease and response

The following table shows the number of patients with T3 tumor disease who had a $\geq 50\%$ reduction in body surface area covered by tumor during the study. Overall, 9/16 (56.3%) of the patients with tumor disease had a $\geq 50\%$ reduction.

Table 212. Number of Patients with $\geq 50\%$ Reduction in Tumor Body Surface Area during Treatment with Vorinostat (All Patients As Treated) (Applicant's Table)

Population	N	Patients with a $\geq 50\%$ reduction in tumor body surface area	
		n (%)	(95% CI)
Patients with T3 tumor disease	16	9 (56.3%)	(29.9, 80.2)
- Patients with an objective response ¹	4	4 (100.0%)	(39.8, 100.0)
- Patients without an objective response ¹	12	5 (41.7%)	(15.2, 72.3)

¹ Objective response: complete response or partial response.
 CI = Confidence Interval.
 Allocation numbers 1047, 1097, 1050, 1028, 1029 and 1061 have missing total tumor at baseline, and are excluded from the analysis.

Data Source: [16.4.1; 16.4.3]

Patients with palpable lymph nodes

The following table shows the number of patients with palpable clinically abnormal lymph nodes who had a $\geq 50\%$ reduction in the sum of products of the greatest diameters of their index lymph nodes by physical exam during the study. Overall, 10/24 (41.7%) of the patients had a $\geq 50\%$ reduction of products of the greatest diameters of their index lymph nodes.

Table 213. Number of Patients with a $\geq 50\%$ Reduction in Sum of Products of the Greatest Diameters of Index Lymph Nodes by Physical Exam during the Study with Vorinostat (All Patients As Treated) (Applicant's Table)

Population	N	Patients with a $\geq 50\%$ Reduction	
		n (%)	(95% CI)
Patients with palpable clinically abnormal lymph nodes	24	10 (41.7%)	(22.1, 63.4)
- Patients with an objective response	6	4 (66.7%)	(22.3, 95.7)
- Patients without an objective response	18	6 (33.3%)	(13.3, 59.0)

¹ Objective response: complete response or partial response.
 CI=Confidence Interval.
 Allocation numbers 1047, 1076, 1077, 1009, 1030, 1070, 1016, 1039, 1012, and 1061 have missing baseline data and are excluded from the analysis.

Data Source: [16.4.1; 16.4.3]

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Safety Evaluation

Seventy-four (74) patients with CTCL enrolled in the study, received at least 1 dose of Vorinostat, and were considered evaluable for safety.

Extent of Exposure

Drug Exposure

A total of 74 patients were exposed to active study drug. The following table summarizes the actual patient exposure to Vorinostat for the overall population.

- All patients were started at a dose of 400 mg of Vorinostat administered once daily for 7 days/week, while 10 patients were dose reduced at some point.
- The **mean duration of exposure** to study drug at **any dose** was 130.7 days, with a range of 2 to 365 days.
- Patients who remained on a dose of **400 mg** of Vorinostat administered once daily for 7 days/week throughout the study had a **mean duration of exposure** to study drug of 120.5 days, with a range of 2 to 365 days.
- Thirty-eight (38/74, 51.4%) patients remained on study therapy for more that 16 weeks and 20/74 (27.0%) patients remained on study therapy for more than 24 weeks.
- Patients had continued to participate in this study, as well as, the extension study after the time of Frozen File. It is likely that there will be patients followed past 365 days.

Table 214. Number of Patients on Vorinostat by Dose and Actual Duration of Treatment (Overall Population) (Applicant's Table)

MK-0683	≤2 wks	>2 wks to ≤4 wks	>4 wks to ≤6 wks	>6 wks to ≤12 wks	>12 wks to ≤16 wks
ANY DOSE	2	4	3	19	8
300 mg	1	4	0	0	1
400 mg	2	7	5	18	8
MK-0683	>16 wks to ≤20 wks	>20 wks to ≤24 wks	>24 wks	Total	Range of Days on Drug
ANY DOSE	10	8	20	74	2 to 365
300 mg	1	1	1	9	13 to 291
400 mg	10	6	18	74	2 to 365
MK-0683					Mean Number of Days on Drug
ANY DOSE					130.7
300 mg					84.4
400 mg					120.5

Although some patients may have taken two or more different dosages, they have been counted only one time each, on the 'ANY DOSE' row.
 Data Source: [16.4.1; 16.4.2]

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Extent of Drug Exposure

The following table summarizes the extent of drug exposure to Vorinostat for patients in this study.

- The number of **days on treatment** was defined as the duration from the first dosing day to the last dosing day, including both scheduled and unscheduled off-drug days.
- The number of **days patients actively received drug** was defined as the absolute number of non-zero dose days according to the prime therapy records, excluding both scheduled and unscheduled off-drug days.
- The average **assigned daily dose** while on active treatment was defined as the maximum daily dose patients should have received according to the prime therapy records. This takes into account patients who remained at 400 mg once daily for 7 days/week, as well as those patients who underwent a dose modification (300 mg once daily for 7 days/week, 300 mg once daily for 5 consecutive days per week). This estimation of average assigned daily dose is considered a conservative approach and may overestimate the actual daily dose of drug received by patients.
- Overall, the **median number of days on treatment** was 118.5 days (range of 2 to 365 days). Patients continued to participate in this study and in the extension study after the time of data cut-off. Therefore there will be patients remaining on treatment beyond 365 days.
- During the first 4-week cycle, nearly all patients remained on their starting dose without discontinuation or dose modification.
- The time on treatment was likely influenced by efficacy as well as tolerability.

Table 215. Summary of Extent to Drug Exposure (All Patients As Treated) (Applicant's Table)

Drug Exposure (N=74)	Mean (SD)	Median (Range)
Number of days on protocol treatment	134.7 (90.8)	118.5 (2.0, 365.0)
Number of days of unscheduled drug interruption	4.1 (12.1)	0.0 (0.0, 83.0)
Number of days patients receive drug	130.7 (90.8)	115.5 (2.0, 365.0)
Average assigned daily dose while on active treatment		
First 4-weeks	399.5 (4.5)	400.0 (361.5, 400.0)
Second 4-weeks	394.7 (21.4)	400.0 (300.0, 400.0)
Third 4-weeks	393.3 (25.8)	400.0 (300.0, 400.0)

Data Source: [16.2.8; 16.4.2]

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Dose Modifications due to Adverse Experiences

The following table summarizes the dose modifications due to adverse experiences, regardless of the assigned causality.

- During the course of the study 10/74 (13.5%) of the patients required dose modifications due to adverse experiences.
- The median time to dose modification was 41 days (range 17 to 66 days).

Table 216. Summary of Dose Modifications Due to Adverse Experiences After Treatment with Vorinostat (All Patients As Treated) (Applicant's Table)

Dose Modifications	Overall (N=74)
Number (%) of patients with	
one dose modification	8 (10.8%)
two or more dose modifications	2 (2.7%)
no dose modifications	64 (86.5%)
Time to first AE resulting in a dose modification (days)	
Median (Range)	41 (17, 66)

Data Source: [16.4.1; 16.4.2; 16.4.3]

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Adverse Experiences

Brief Summary of Adverse Experiences

- Adverse experiences were graded according to the NCI CTCAE, v3.0 whenever possible.
- If a patient had multiple episodes of the same adverse experiences, only the highest CTCAE grade was counted in the summary reports.
- Adverse experiences which could not be assigned a grade per CTCAE were graded as:
 - Grade 1 (asymptomatic)
 - Grade 2 (symptomatic but not interfering significantly with function)
 - Grade 3 (causing significant interference with function)
 - Grade 4 (life-threatening)
- All adverse experiences were to be followed to resolution (if possible at the time of Frozen File). Serious adverse experiences, including death, which occurred during the study or within 30 days following discontinuation of the study drug, were reported. In addition, all serious adverse experiences with a suspected causal relationship to study therapy that occurred at any time following completion of the study were also reported.
- Clinical adverse experience dictionary terms are presented as preferred terms by system organ class according to the Medical Dictionary for Regulatory Affairs (MedDRA), Version 8.1.
- Laboratory adverse experiences are presented as specific terms and by convention have duration of one day.
- Investigators were instructed to code laboratory abnormalities to the corresponding clinical adverse experience in preference to the laboratory term. For example, patients with a clinically significant decrease in platelet count were to be reported as the clinical adverse experience of “thrombocytopenia” rather than the laboratory adverse experience of “decreased platelets”.

Clinical Adverse Experiences

The following table summarizes the clinical adverse experiences for the overall population.

- **Clinical adverse experiences** were reported in 70/74 (94.6%) patients.
- **Drug-related clinical adverse experiences** were reported in 68/74 (91.9%) patients.
 - Nine (9/74, 12.2%) of the patients discontinued study therapy due to a clinical adverse experience
 - Seven (7/74, 9.5%) patients discontinued study therapy due to a drug-related clinical adverse experience
- **Serious clinical adverse experiences** were reported in 16/74 (21.6%) patients.
- Eight (8/74, 10.8%) patients were reported as having **drug-related serious clinical adverse experiences**.
 - Six (6/74, 8.1%) patients discontinued study therapy due to a serious clinical adverse experience.
 - Four (4/74, 5.4%) patients discontinued study therapy due to a drug-related serious clinical adverse experience.
- Three (3/74, 4.1%) **deaths** were reported in the overall population
- One patient (AN1048) was found dead at home the day after study medication was dispensed; one patient (AN1008) had an ischemic stroke on day 227 of study treatment and

died 30 days later, and one patient (AN1033) was noted to have progressive disease on day 43 of study treatment and died 9 days later.

Table 217. Clinical Adverse Experience Summary (Overall Population) (Applicant's Table)

	400 mg once daily x 7d/wk (N = 74)	
	n	(%)
Number (%) of patients:		
With one or more adverse experiences	70	(94.6)
With no adverse experience	4	(5.4)
With drug-related adverse experiences†	68	(91.9)
With serious adverse experiences	16	(21.6)
With serious drug-related adverse experiences	8	(10.8)
Who died	3	(4.1)
Discontinued due to adverse experiences	9	(12.2)
Discontinued due to drug-related adverse experiences	7	(9.5)
Discontinued due to serious adverse experiences	6	(8.1)
Discontinued due to serious drug-related adverse experiences	4	(5.4)

† Determined by the investigator to be possibly, probably or definitely drug related.

Data Source: [16.4.2]

The following table provides details of patients by dose levels who developed clinical adverse experiences resulting in discontinuation:

- Nine (9) patients discontinued due to a clinical adverse experiences at 3 different dose levels (400 mg daily, 300 mg daily, and 300 mg for 5 consecutive days per week).
- Seven (7) patients did not undergo dose modification prior to discontinuation.
- Seven (7) patients were discontinued due to clinical adverse experiences that were considered by the investigator to be drug-related. These drug related events resulting in discontinuation were deep vein thrombosis, chest pain, death, angioneurotic edema, pulmonary embolism, ischaemic stroke, and the combination of asthenia and lethargy.

Table 218. Patients who discontinued study drug due to Clinical Adverse Experiences by Dose Level (Overall Population) (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
400 mg once daily x 7d/wk														
683601	1004	F	black	52	Treatment	140	Dermatologic Erythema	10 days	140	3	Y	def not poss	discontinued PRx	recovered
	1013	F	black	42	Treatment	56	Deep Vein Thrombosis	15 days	56	4	Y	def not poss	discontinued PRx	recovered
	1046	M	white	53	Treatment	39	Chest Pain	36 days	43	2	N	poss	discontinued PRx	recovered
	1048	F	black	46	Treatment	1	Death	1 day	2	5	Y	poss	discontinued PRx	fatal
	1057	M	white	67	Treatment	27	Angioneurotic Edema	2 days	27	2	N	prob	discontinued PRx	recovered
	1059	M	white	64	Treatment	183	Pulmonary Embolism		185	4	Y	post	discontinued PRx	not recovered
	1063	F	white	80	Treatment	124	Spinal Cord Injury	1 day	124	3	Y	def not	discontinued PRx	recovered
300 mg once daily x 7d/wk														
683601	1008	F	white	71	Treatment	227	Ischaemic Stroke	30 days	227	4	Y	post	discontinued PRx	fatal
300 mg once daily x 5d/wk														
683601	1044	M	white	53	Treatment	187	Asthenia Lethargy		189	3	N	post	discontinued PRx	not recovered
									189	3	N	post	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 3.1

Data Source: [16.4.1, 16.4.2]

Laboratory Adverse Experiences

The following table summarizes the laboratory adverse experiences for the overall population.

- All patients had post-baseline laboratory tests.
- Laboratory adverse experiences were reported in 22/74 patients (29.7%).
- Drug-related laboratory adverse experiences were reported in 20/74 patients (27.0%).
- A single patient (1.4%) experienced a serious laboratory adverse experience, which was considered drug-related.
- Laboratory adverse experiences did not account for any discontinuations or deaths in this study.

Table 219. Laboratory Adverse Experience Summary (Overall Population) (Applicant's Table)

	400 mg once daily x 7d/wk (N = 74)	
	n	(%) [†]
Number (%) of patients:		
With at least one lab test postbaseline	74	
With one or more adverse experiences	22	(29.7)
With no adverse experience	52	(70.3)
With drug-related adverse experiences [‡]	20	(27.0)
With serious adverse experiences	1	(1.4)
With serious drug-related adverse experiences	1	(1.4)
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)

[†] 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 postbaseline.

Data Source: [16.4.1; 16.4.2]

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Display and Analysis of Overall Adverse Experiences

The following table provides a summary of all clinical and laboratory adverse experiences with an incidence $\geq 10\%$ in the overall APaT population. This table also describes the relative severity and the relationship to study drug of the adverse experiences. Although adverse experiences were frequent, they were rarely severe.

Table 220. Summary of Specific Clinical or Laboratory Adverse Experiences by Preferred Term (Incidence $\geq 10\%$ at One or More Dose Levels; All Patients As Treated) (Applicant's Table)

	Total Patients (N=74)							
	All Experiences				Related Experiences Only			
	All Grades		Grade 3-5		All Grades		Grade 3-5	
	n	%	n	%	n	%	n	%
Diarrhoea	38	(51.4)	0	(0.0)	36	(48.6)	0	(0.0)
Fatigue	38	(51.4)	5	(6.8)	34	(45.9)	4	(5.4)
Nausea	32	(43.2)	3	(4.1)	32	(43.2)	3	(4.1)
Anorexia	20	(27.0)	2	(2.7)	19	(25.7)	2	(2.7)
Dysgeusia	20	(27.0)	0	(0.0)	18	(24.3)	0	(0.0)
Thrombocytopenia	15	(20.3)	3	(4.1)	15	(20.3)	3	(4.1)
Weight Decreased	15	(20.3)	1	(1.4)	14	(18.9)	1	(1.4)
Alopecia	14	(18.9)	0	(0.0)	13	(17.6)	0	(0.0)
Chills	12	(16.2)	1	(1.4)	9	(12.2)	1	(1.4)
Blood Creatinine Increased	12	(16.2)	1	(1.4)	10	(13.5)	1	(1.4)
Constipation	12	(16.2)	0	(0.0)	8	(10.8)	0	(0.0)
Muscle Spasms	12	(16.2)	2	(2.7)	12	(16.2)	2	(2.7)
Anemia	11	(14.9)	1	(1.4)	10	(13.5)	1	(1.4)
Dizziness	11	(14.9)	1	(1.4)	5	(6.8)	1	(1.4)
Vomiting	11	(14.9)	1	(1.4)	9	(12.2)	0	(0.0)
Pruritus	10	(13.5)	1	(1.4)	1	(1.4)	0	(0.0)
Headache	9	(12.2)	0	(0.0)	4	(5.4)	0	(0.0)
Oedema Peripheral	9	(12.2)	0	(0.0)	2	(2.7)	0	(0.0)
Upper Respiratory Tract Infection	9	(12.2)	0	(0.0)	2	(2.7)	0	(0.0)
Dry Mouth	8	(10.8)	0	(0.0)	8	(10.8)	0	(0.0)

A patient is counted only once within a specific preferred term, even if more than one adverse experience with specific preferred terms occurred.
 Adverse experience terms are from MedDRA Version 8.1

Data Source: [16.4.2]

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Clinical Adverse Experiences (by system organ class)

The following table summarizes specific clinical adverse experiences by system organ class (incidence ≥ 10%) for the overall population. Of the 16 system organ classes that exceeded this frequency, the 4 most common groups of adverse experiences were:

- Gastrointestinal disorders 74.3%
- General disorders and administration site conditions 71.6%
- Nervous system disorders 56.8%
- Skin and subcutaneous tissue disorders 52.7%

Table 221. Number (%) of Patients with Specific Clinical Adverse Experiences by System Organ Class (Incidence ≥ 10% in One or More Treatment Groups; Most Common Toxicities of All Grades) (Applicant's Table)

	400 mg once daily x 7d/wk (N=74)	
	n	%
Gastrointestinal Disorders	55	(74.3)
General Disorders And Administration Site Conditions	53	(71.6)
Nervous System Disorders	42	(56.8)
Skin And Subcutaneous Tissue Disorders	39	(52.7)
Metabolism And Nutrition Disorders	36	(48.6)
Infections And Infestations	28	(37.8)
Respiratory, Thoracic And Mediastinal Disorders	27	(36.5)
Blood And Lymphatic System Disorders	24	(32.4)
Investigations	24	(32.4)
Musculoskeletal And Connective Tissue Disorders	24	(32.4)
Psychiatric Disorders	16	(21.6)
Renal And Urinary Disorders	12	(16.2)
Cardiac Disorders	11	(14.9)
Injury, Poisoning And Procedural Complications	10	(13.5)
Vascular Disorders	9	(12.2)
Eye Disorders	8	(10.8)

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 treatment group for the individual patient.
 Adverse experience terms are from MedDRA Version 8.1

Data Source: [16.4.2]

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Clinical Adverse Experiences (All CTCAE Grades by Preferred Term)

The following table summarizes specific clinical adverse experiences of all CTCAE Grades by preferred term (incidence ≥ 10%) for the overall population.

Table 222. Number (%) Of Patients with Specific Clinical Adverse Experiences by Preferred Term (Incidence ≥ 10% in One or More Treatment Groups; Most Common Toxicities of All Grades) (Applicant's Table)

	400 mg once daily x 7d/wk (N=74)	
	n	%
Diarrhoea	38	(51.4)
Fatigue	38	(51.4)
Nausea	32	(43.2)
Anorexia	20	(27.0)
Dysgeusia	20	(27.0)
Thrombocytopenia	15	(20.3)
Weight Decreased	15	(20.3)
Alopecia	14	(18.9)
Chills	13	(17.6)
Constipation	12	(16.2)
Muscle Spasms	12	(16.2)
Anaemia	11	(14.9)
Dizziness	11	(14.9)
Vomiting	11	(14.9)
Pruritus	10	(13.5)
Headache	9	(12.2)
Oedema Peripheral	9	(12.2)
Upper Respiratory Tract Infection	9	(12.2)
Cough	8	(10.8)
Decreased Appetite	8	(10.8)
Dry Mouth	8	(10.8)
Proteinuria	8	(10.8)

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

Data Source: [16.4.2]

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Clinical Adverse Experiences (CTCAE Grades 3, 4, and 5 by Preferred Term)

The following table summarizes specific CTCAE Grade 3, 4, or 5 clinical adverse experiences by preferred term (incidence ≥ 5%) for the overall population. Only 2 clinical adverse experiences fell into this group:

- Fatigue 6.8%
- Pulmonary embolism 5.4%

Table 223. Number (%) of Patients with Specific Clinical Adverse Experiences by Preferred Term (Incidence ≥ 5% in One or More Treatment Groups; Most Common Grade 3-5 Toxicities) (Applicant's Table)

	400 mg once daily x 7d/wk (N=74)	
	n	%
Fatigue	5	(6.8)
Pulmonary Embolism	4	(5.4)

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

Data Source: [15.4.2]

Time to Onset and Duration of Drug Related Adverse Events of CTCAE Grades 3, 4, and 5

- The median time to onset and duration for drug-related CTCAE Grade 3, 4, or 5 clinical adverse experiences was 43 days (range, 1 to 185 days) and 10 days (range, 1 to 172 days), respectively.
- AN1008 suffered an ischaemic stroke which was considered by the investigator to be possibly drug-related and assigned a severity of CTCAE Grade 4. This event became fatal, but the severity was not modified to Grade 5 by the investigator. Therefore, this event does not appear in the following table as a Grade 5 adverse experience although it did result in death.

Table 224. Onset and Duration of First Drug Related Adverse Events of CTCAE Grades 3, 4, and 5 (Applicant's Table)

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	Overall (N=74)	
	Drug Related	Overall
Patients with Grade 3 or 4 Clinical Adverse Experience, n (%)	21 (28.4%)	27 (36.5%)
Patients with Grade 5 Clinical Adverse Experience, n (%)	1 (1.4%)	2 (2.7%)
Time to Onset of First Grade 3, 4 or 5 Clinical Adverse Experience (days)		
Mean	67.8	56.2
SD	56.61	50.04
Median	43.0	41.0
Range	1 - 185	1 - 185
Duration of the First Grade 3 or 4 Clinical Adverse Experience (days) †		
Median	10.0	10.0
Range	1 - 172	1 - 114+
SD = Standard Deviation		
+ : ongoing		
† Patients with ongoing adverse experiences are censored at date of last therapy + 30 days.		
AN1008 suffered a fatal ischaemic stroke which was considered by the investigator to be possibly drug-related. This adverse experience was given a CTCAE Grade of 4 and is counted in that grouping.		

Data Source: [16.4.2]

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Laboratory Adverse Experiences

The following table summarizes specific laboratory adverse experiences of all grades by preferred term with incidence $\geq 10\%$ in the overall population.

- Increased blood creatinine is the most common laboratory adverse experience

Table 225. Number (%) of Patients with Specific Laboratory Adverse Experiences by Preferred Term (Incidence $\geq 10\%$ in One or More Treatment Groups; all grades) (Applicant's Table)

	400 mg once daily x 7d/wk (N=74)	
	n/m	%
Blood Creatinine Increased	12/74	(16.2)

n/m = number of patients with laboratory adverse experiences / number of patients for whom the laboratory test was recorded postbaseline.
 A patient is counted only once within a specific preferred term, even if more than one adverse experience with specific preferred term occurred.

Data Source: [16.4.2]

The following table summarizes specific CTCAE Grade 3, 4, or 5 laboratory adverse experiences by preferred term for the overall population. There was a single patient (1.4%) who fell into this group. AN1008 had a Grade 3 laboratory adverse experience of blood creatinine increased.

Table 226. Number (%) of Patients with Specific Laboratory Adverse Experiences by Preferred Term (Incidence $>0\%$ in One or More Treatment Groups; Grade 3, 4, and 5 experiences) (Applicant's Table)

	400 mg once daily x 7d/wk (N=74)	
	n/m	%
Blood Creatinine Increased	1/74	(1.4)

n/m = number of patients with laboratory adverse experiences / number of patients for whom the laboratory test was recorded postbaseline.
 A patient is counted only once within a specific preferred term, even if more than one adverse experience with specific preferred term occurred.

Data Source: [16.4.2]

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Display and Analysis of Drug-Related Adverse Experiences

Drug-Related Clinical Adverse Experiences

The following table summarizes specific drug-related clinical adverse experiences by system organ class (incidence ≥ 10%) for the overall population. The 4 most common classes of drug-related adverse experiences reported:

- Gastrointestinal disorders 70.3%
- General disorders and administration site conditions 59.5%
- Nervous system disorders 43.2%
- Metabolism and nutrition disorders 39.2%

Table 227. Number (%) Of Patients With Specific Drug-related Clinical Adverse Experiences by System Organ Class (Incidence ≥ 10%) (Applicant's Table)

	400 mg once daily x 7d/wk (N=74)	
	n	%
Gastrointestinal Disorders	52	(70.3)
General Disorders And Administration Site Conditions	44	(59.5)
Nervous System Disorders	32	(43.2)
Metabolism And Nutrition Disorders	29	(39.2)
Skin And Subcutaneous Tissue Disorders	25	(33.8)
Blood And Lymphatic System Disorders	21	(28.4)
Investigations	18	(24.3)
Musculoskeletal And Connective Tissue Disorders	15	(20.3)
Respiratory, Thoracic And Mediastinal Disorders	15	(20.3)
Renal And Urinary Disorders	9	(12.2)
Cardiac Disorders	8	(10.8)

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 treatment group for the individual patient.
 Adverse experience terms are from MedDRA Version 8.1

Data Source: [16.4.2]

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The following table summarizes specific drug-related clinical adverse experiences by preferred term (incidence $\geq 10\%$) for the overall population. The 5 most common drug-related adverse experiences reported were diarrhoea (48.6%), fatigue (45.9%), nausea (43.2%), anorexia (25.7%) and dysgeusia (24.3%). These were also the most common adverse experiences overall, regardless of relation. The incidence of drug-related and overall adverse experiences was generally similar across the study.

Table 228. Number (%) of Patients with Specific Drug-related Clinical Adverse Experiences by Preferred Term (Incidence $\geq 10\%$) (Applicant's Table)

	400 mg once daily x 7d/wk (N=74)	
	n	%
Diarrhoea	36	(48.6)
Fatigue	34	(45.9)
Nausea	32	(43.2)
Anorexia	19	(25.7)
Dysgeusia	18	(24.3)
Thrombocytopenia	15	(20.3)
Weight Decreased	14	(18.9)
Alopecia	13	(17.6)
Muscle Spasms	12	(16.2)
Anaemia	10	(13.5)
Vomiting	10	(13.5)
Chills	9	(12.2)
Constipation	8	(10.8)
Dry Mouth	8	(10.8)

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

Data Source: [16.4.2]

The following summarizes specific CTCAE Grade 3, 4, or 5 drug-related clinical adverse experiences by preferred term (incidence $\geq 5\%$) for the overall population. Only 2 drug-related clinical adverse experiences fell into this group, fatigue (5.4%) and pulmonary embolism (5.4%).

Table 229. Number (%) of Patients with Specific Drug-related Grade 3 – 5 Clinical Adverse Experiences by Preferred Term (Incidence $\geq 5\%$) (Applicant's Table)

	400 mg once daily x 7d/wk (N=74)	
	n	%
Fatigue	4	(5.4)
Pulmonary Embolism	4	(5.4)

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

Data Source: [16.4.2]

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Drug-Related Laboratory Adverse Experiences

The following table summarizes specific laboratory adverse experiences by preferred term (incidence $\geq 10\%$) for the overall population. The most common drug-related laboratory adverse experience reported was increased blood creatinine.

Table 230. Number (%) of Patients with Specific Drug-Related Laboratory Adverse Experiences by Preferred Term (Incidence $\geq 10\%$) (Applicant's Table)

	400 mg once daily x 7d/wk (N=74)	
	n/m	%
Blood Creatinine Increased	10/74	(13.5)

n/m = number of patients with laboratory adverse experiences / number of patients for whom the laboratory test was recorded postbaseline.
 A patient is counted only once within a specific preferred term, even if more than one adverse experience with specific preferred term occurred.

Data Source: [16.4.2]

The following table summarizes specific CTCAE Grade 3, 4, or 5 laboratory adverse experiences by preferred term for the overall population. A single patient (1.4%) fell into this group. AN1008 had a Grade 3 drug-related laboratory adverse experience of blood creatinine increased.

Table 231. Number (%) of Patients with Specific Drug-Related Laboratory Adverse Experiences by Preferred Term (Incidence $>0\%$) (Applicant's Table)

	400 mg once daily x 7d/wk (N=74)	
	n/m	%
Blood Creatinine Increased	1/74	(1.4)

n/m = number of patients with laboratory adverse experiences / number of patients for whom the laboratory test was recorded postbaseline.
 A patient is counted only once within a specific preferred term, even if more than one adverse experience with specific preferred term occurred.

Data Source: [16.4.2]

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Display and Analysis of Serious Adverse Experiences

Serious Clinical Adverse Experiences

The following table summarizes specific serious clinical adverse experiences by preferred terms for the overall population. The only serious adverse experiences reported by more than one patient throughout the study were pulmonary embolism (5.4%), squamous cell carcinoma (4.1%), and T-cell lymphoma (2.7%). Based on coding conventions, patients with worsening of their CTCL were reported in the database as T-cell lymphoma. Multiple serious clinical adverse experiences that occur in the same patient are reported individually. For example, patient AN 1044 had the contemporaneous adverse experiences of anemia, gastrointestinal hemorrhage, streptococcal bacteremia, and thrombocytopenia.

Table 232. Number (%) of Patients with Specific Serious Clinical Adverse Experiences by Preferred Term (Incidence >0%) (Applicant's Table)

	400 mg once daily x 7d/wk (N=74)	
	n	%
Pulmonary Embolism	4	(5.4)
Squamous Cell Carcinoma	3	(4.1)
T-Cell Lymphoma	2	(2.7)
Anaemia	1	(1.4)
Death	1	(1.4)
Deep Vein Thrombosis	1	(1.4)
Dehydration	1	(1.4)
Dermatitis Exfoliative	1	(1.4)
Enterococcal Infection	1	(1.4)
Gastrointestinal Haemorrhage	1	(1.4)
Ischaemic Stroke	1	(1.4)
Lung Neoplasm	1	(1.4)
Myocardial Infarction	1	(1.4)
Pelvi-Uteric Obstruction	1	(1.4)
Sepsis	1	(1.4)
Spinal Cord Injury	1	(1.4)
Streptococcal Bacteremia	1	(1.4)
Syncope	1	(1.4)
Thrombocytopenia	1	(1.4)
Ureteric Obstruction	1	(1.4)

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

Data Source: [16.4.2]

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The following table summarizes specific *drug-related* serious clinical adverse experiences by preferred term for the overall population. The only drug-related serious adverse experience reported by *more than one* patient was pulmonary embolism (5.4%).

Table 233. Number (%) of Patients with Specific Serious Drug-Related Clinical Adverse Experiences by Preferred Term (Incidence >0%) (Applicant's Table)

	400 mg once daily x 7d/wk (N=74)	
	n	%
Pulmonary Embolism	4	(5.4)
Anaemia	1	(1.4)
Death	1	(1.4)
Deep Vein Thrombosis	1	(1.4)
Dehydration	1	(1.4)
Gastrointestinal Haemorrhage	1	(1.4)
Ischaemic Stroke	1	(1.4)
Streptococcal Bacteraemia	1	(1.4)
Syncope	1	(1.4)
Thrombocytopenia	1	(1.4)

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

Data Source: [16.4.2]

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The following table provides a listing and details of all patients with serious clinical adverse experiences.

Table 234. Listing of Patients with Serious Clinical Adverse Experiences by Dose Level Overall Population (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	
400 mg once daily x 7d/wk															
683801	1004	F	black	50	Treatment	31	Myocardial Infarction	1 day	140	4	Y	def not	interrupted PRx	recovered	
						140	Dermatosis Exfoliativa	10 days	140	3	Y	def not	discontinued PRx	recovered	
	1012	F	white	74	Treatment	10	Sepsis	15 days	56	3	Y	prob not	no action with test drug	recovered	
	1015	F	black	42	Treatment	56	Deep Ven. Thrombosis	15 days	56	4	Y	poss	discontinued PRx	recovered	
						63	Pulmonary Embolism	5 days	56	4	Y	poss	no action with test drug	recovered	
	1027	M	white	70	Treatment	161	Squamous Cell Carcinoma	20 days	317	2	Y	def not	no action with test drug	recovered	
	1030	M	white	70	Treatment	141	Squamous Cell Carcinoma	33 days	323	2	Y	prob not	no action with test drug	recovered	
	1040	F	white	53	Treatment	64	T-Cell Lymphoma		63	3	Y	def not	no action with test drug	not recovered	
	1044	M	white	85	Treatment	27	Anaemia	7 days	189	4	Y	poss	interrupted PRx	recovered	
								Gastrointestinal Hemorrhage	7 days	189	3	Y	poss	interrupted PRx	recovered
								Streptococcal Bacteremia	14 days	189	3	Y	poss	interrupted PRx	recovered
								Thrombocytopenia	16 days	189	4	Y	prob	interrupted PRx	recovered
							45	Squamous Cell Carcinoma	19 days	189	2	Y	def not	no action with test drug	recovered
	683801	1048	F	black	46	Treatment	2	Death	1 day	2	5	Y	poss	discontinued PRx	fatal
		1057	M	white	67	Treatment	27	Syncope	1 day	27	3	Y	prob	no action with test drug	recovered
1058		F	white	57	Treatment	141	Pulmonary Embolism		224	4	Y	poss	no action with test drug	not recovered	
1059		M	white	64	Treatment	165	Pulmonary Embolism		185	4	Y	poss	discontinued PRx	not recovered	
1063		F	white	80	Treatment	124	Spinal Cord Injury	1 day	124	5	Y	def not	discontinued PRx	recovered	
1064		M	white	53	Treatment	61	Uterine Obstruction	18 days	114	2	Y	def not	interrupted PRx	recovered	
						64	Enterocolic Infection	21 days	114	3	Y	prob not	no action with test drug	recovered	
							Pelvi-Uterine Obstruction	12 days	114	3	Y	def not	no action with test drug	recovered	
								Pulmonary Embolism	7 days	25	4	Y	poss	interrupted PRx	recovered
		1070	M	white	54	Treatment	28								
300 mg once daily x 7d/wk															
683801	1008	F	white	71	Treatment	204	Dehydration	4 days	227	3	Y	poss	interrupted PRx	recovered	
						227	Ischaemic Stroke	19 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	
300 mg once daily x 5d/wk															
683801	1044	M	white	81	Treatment	86	Squamous Cell Carcinoma	12 days	189	2	Y	def not	no action with test drug	recovered	
						204	Lung Neoplasm Squamous Cell Carcinoma	15 days	189	2	Y	prob not	no action with test drug	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
 Data Source: [16.4.2]

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Serious Laboratory Adverse Experiences

The following table summarizes specific *serious* laboratory adverse experiences by dose level. A single patient (AN1008: Stage III, Sezary syndrome) fell into this group. At dose level 300 mg daily, the patient had a blood creatinine 4.0 mg/dL. This was considered both serious and possibly drug-related by the investigator.

Table 235. Number (%) of Patients with Specific Serious Laboratory Adverse Experiences by Laboratory Test Category (Incidence >0%) (Applicant's Table)

	400 mg once daily x 7d/wk (N=74)		400 mg once daily x 5d/wk (N=1)		300 mg once daily x 7d/wk (N=9)		300 mg once daily x 5d/wk (N=2)		Total Patients (N=74)	
	n/m	%	n/m	%	n/m	%	n/m	%	n/m	%
Patients With One Or More Laboratory Adverse Experiences	0/74	(0.0)	0/1	(0.0)	1/8	(12.5)	0/2	(0.0)	1/74	(1.4)
Patients With No Laboratory Adverse Experiences	74/74	(100)	1/1	(100)	7/8	(87.5)	2/2	(100)	73/74	(98.6)
Blood Chemistry Test	0/74	(0.0)	0/1	(0.0)	1/8	(12.5)	0/2	(0.0)	1/74	(1.4)
Blood Creatinine Increased	0/74	(0.0)	0/1	(0.0)	1/8	(12.5)	0/2	(0.0)	1/74	(1.4)
Grade 3	0/74	(0.0)	0/1	(0.0)	1/8	(12.5)	0/2	(0.0)	1/74	(1.4)

n/m = number of patients with laboratory adverse experiences / number of patients for whom the laboratory test was recorded postbaseline.
 † indicates there was no associated laboratory test or there were no patients for whom the laboratory test was recorded postbaseline.
 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.

Data Source: [16.4.2]

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The following table lists and details the serious drug-related adverse experience.

Table 236. Details of Patients with Serious Laboratory Adverse Experiences by Dose Level (Applicant's Table)

Study Number	AN	Gender	Race	Age	Period	Rel Day of AE Onset	Adverse Experience	Rel Day of Drug Discon	Toxicity Grade	Serious	Drug Relation	Action Taken
300 mg once daily x 7d/wk												
683001	1698	F	white	71	Treatment	204	Blood Creatinine Increased	227	3	Y	poss	interrupted PRx
AN= Allocation number def = Definitely; def not = Definitely not; poss = Possibly; prob = Probably; prob not = Probably not PRx = prime therapy.												

Data Source: [15.4.2]

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Deaths

Three (3) deaths were reported during this study, the details are shown in the following table.

- Patient AN1048 was sent home with study medication, with the expectation that she would take the first dose at home with dinner. This patient was found dead the next day and the first responders discarded all study medication. No autopsy was performed on this patient. There is no way of verifying if this patient did or did not take a dose of Vorinostat.
- Patient AN1008 experienced a fatal stroke.
 - Both of these fatal adverse experiences were felt to be possibly related to study drug.
- AN1033 died due to disease progression.
 - This death was felt to be unrelated to study drug.

Table 237. Details of Patients with Clinical Adverse Experiences Resulting in Death 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
400 mg once daily x 7d/wk														
683001	1048	F	black	46	Treatment	2	Death	1 day	2	5	Y	poss	discontinued PRx	fatal
300 mg once daily x 7d/wk														
683001	1008	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 3.1
 Data Source: [16.4.2]

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Display and Analysis of Other Significant Adverse Experiences

No other significant adverse experiences were identified during the course of this study.

Adverse Experiences of Special Interest

No pre-specified adverse experiences of special interest were identified for this study.

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Clinical Evaluation of Laboratory Safety Tests

Evaluation of Each Laboratory Safety Test

Laboratory safety tests were collected and processed by the central lab (_____). Protocol specified pretreatment, treatment, and follow-up safety laboratory tests included: complete blood count with differential, platelet count, a comprehensive panel, PT/aPTT, thyroid function and urinalysis.

Listing of Specific Laboratory Safety Tests, Including Abnormal Laboratory Values, by Subject/Patient

Laboratory abnormalities by the highest CTCAE grade are summarized in the following table. These include all dose levels at any time during the study, including pre-dose abnormal baselines (Pre-existing laboratory abnormalities are not excluded from these analyses). Of note, urine protein was reported in 38/74 (51.4%) patients as a laboratory abnormality, however, these were not deemed by the investigators to be clinical or laboratory adverse experiences. Comparisons between laboratory abnormalities and baseline values are reported in the following section.

For blood chemistry laboratory tests performed in all 74 patients, the 3 most frequent abnormalities found were increased serum cholesterol (66.2%), increased serum triglycerides (66.2%), and increased serum glucose (63.5%).

The highest CTCAE grade reported for each of these abnormalities was Grade 3. The abnormalities may have occurred at any time during treatment. Baseline abnormality rates for increased serum cholesterol, increased serum triglycerides, and increased serum glucose were 55.4%, 29.7%, and 9.5% respectively. The highest CTCAE grade reported for each of these baseline abnormalities was Grade 2.

For hematology laboratory tests performed in all 74 patients the 2 most frequently reported laboratory abnormalities were decreased hemoglobin (54.1%) and decreased platelet count (41.9%). There were 4 patients, all with a reported adverse experience of anemia, who required the use of erythropoietic growth factors during the study. One patient who received erythropoietic growth factor therapy also required a transfusion.

Five (5) CTCAE Grade 4 laboratory abnormalities were reported. The abnormalities in these patients that were considered by the investigator to be drug-related were decreased neutrophil count and decreased platelet count.

Table 238. Laboratory Abnormalities by their Highest Grades (Applicant's Table)

Laboratory Test	400 mg qd x 7d-wk					Total n (%)
	N	Grades				
		1	2	3	4	
Blood Chemistry Test						
decreased serum calcium	74	7	1	0	0	8 (10.8)
decreased serum glucose	74	8	1	1	0	10 (13.5)
decreased serum potassium	74	10	0	1	0	11 (14.9)
decreased serum sodium	74	5	0	1	0	6 (8.1)
increased serum calcium	74	4	0	0	0	4 (5.4)
increased serum glucose	74	22	22	3	0	47 (63.5)
increased serum magnesium	7	5	0	0	0	5 (71.4)
increased serum potassium	74	1	2	1	0	4 (5.4)
serum alanine aminotransferase	74	11	0	0	0	11 (14.9)
serum albumin	74	4	2	0	0	6 (8.1)
serum alkaline phosphatase	74	13	1	0	0	14 (18.9)
serum aspartate aminotransferase	74	7	2	0	0	9 (12.2)
serum cholesterol	74	43	5	1	0	49 (66.2)
serum creatine kinase	3	3	0	0	0	3 (100.0)
serum creatinine	74	29	3	1	0	33 (44.6)
serum phosphorus	74	6	7	1	0	14 (18.9)
serum triglyceride	74	39	8	2	0	49 (66.2)
serum uric acid	74	4	0	0	2	6 (8.1)
total serum bilirubin	74	3	3	0	0	6 (8.1)
total serum carbon dioxide	74	23	5	0	0	28 (37.8)
Endocrine Test						
total serum thyroxine	1	0	1	0	0	1 (100.0)
Hematology Laboratory Test						
WBC count	74	10	7	1	0	18 (24.3)
absolute monocyte count	4	1	0	0	0	1 (25.0)
absolute neutrophil count	4	1	0	0	0	1 (25.0)
hemoglobin	74	33	6	1	0	40 (54.1)
lymphocyte count	74	4	16	9	1	30 (40.5)
mean corpuscular hemoglobin conc	10	1	0	0	0	1 (10.0)
mean corpuscular volume	12	2	0	0	0	2 (16.7)
neutrophil count	74	1	8	0	1	10 (13.5)
platelet count	74	25	1	3	1	31 (41.9)
Hemostatic Function Test						
APTT	20	2	1	0	0	3 (15.0)
INR	18	3	0	3	0	6 (33.3)
prothrombin time	20	0	1	0	0	1 (5.0)
Urinalysis Test						
calcium oxalate crystal	5	3	0	0	0	3 (60.0)
urine protein	73	31	7	0	0	38 (52.1)

N: number of patients who had the lab test during treatment.
 If a patient had more than one graded abnormality for a lab test, only the highest grade is counted.

Data Source: [16.4.2]

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Laboratory Values over Time

To assess whether laboratory abnormalities represented clinically meaningful changes from the baseline, a shift analysis was performed on laboratory abnormalities of the highest CTCAE grade noted in the study patients.

- A clinically meaningful shift is defined as a shift from a baseline value of less than CTCAE Grade 3 to any post-baseline value of CTCAE Grade 3, Grade 4, or Grade 5, or a shift from CTCAE Grade 0 to Grade 2 or higher.

The following table summarizes the shifts in pre-selected laboratory parameters from the baseline to the worst post-baseline to last value in the overall population.

- The laboratory parameters with clinically meaningful shifts from the baseline (with N indicating the number of patients) in more than 8 patients (or 10%) were: increased serum glucose (N=18), serum phosphorous (N=8), decreased lymphocyte count (N=19), and decreased neutrophil count (N=8).
- Exploratory analyses of the behavior of serum creatinine over time showed an initial rise in serum creatinine levels followed by a plateau and then recovery. This pattern was similar regardless of if the patient had normal or abnormal urine protein levels.
- The association between serum albumin and urine protein was also examined. No trend to decreased albumin levels was observed regardless of proteinuria.
- Additional analyses were performed for hemoglobin, platelet count, and serum glucose. Hemoglobin and serum glucose levels remained steady, platelet count showed an initial drop followed by a plateau.

Table 239. Summary of Shift in Laboratory Parameters from the Baseline to the Worst Post-baseline Value to Last Value (All Patients As Treated) (Applicant's Table)

Laboratory Test	N ¹⁾	Number(%) of subjects							
		Change in CTCAE grade from baseline to worst value postbaseline			Change in CTCAE grade from worst value postbaseline to last value postbaseline				
		Improved	Worsened	Clinically meaningful shift ²⁾	Consistent improvement from baseline ³⁾	Worsened and then improved ⁴⁾	No change ⁵⁾	Improved to Grade 0 or Grade 1 ⁶⁾	
WBC count	21	4(19.0)	17(81.0)	5(23.8)	1(4.8)	8(38.1)	8(42.9)	1(4.8)	8(38.1)
Hemoglobin	17	0(0.0)	17(100.0)	5(29.4)	0(0.0)	11(64.7)	16(95.3)	2(11.8)	9(52.9)
Lymphocyte count	24	2(8.3)	22(91.7)	19(79.2)	1(4.2)	17(70.8)	11(45.8)	1(4.2)	19(79.2)
Neutrophil count	19	1(5.3)	18(94.7)	8(42.1)	0(0.0)	4(21.1)	3(15.8)	0(0.0)	4(21.1)
Platelet count	31	0(0.0)	31(100.0)	6(19.4)	0(0.0)	24(77.4)	7(22.6)	2(6.5)	22(71.0)
Serum alanine aminotransferase	10	0(0.0)	10(100.0)	0(0.0)	0(0.0)	9(90.0)	1(10.0)	0(0.0)	9(90.0)
Serum albumin	5	1(20.0)	4(80.0)	2(40.0)	1(20.0)	3(60.0)	2(40.0)	0(0.0)	4(80.0)
Serum cholesterol	16	3(18.8)	13(81.2)	1(6.3)	0(0.0)	5(31.3)	8(50.0)	1(6.3)	4(25.0)
Serum creatinine	20	0(0.0)	20(100.0)	3(15.0)	0(0.0)	12(60.0)	18(90.0)	1(5.0)	11(55.0)
Serum glucose - decreased	4	0(0.0)	4(100.0)	1(25.0)	0(0.0)	3(75.0)	1(25.0)	0(0.0)	3(75.0)
Serum glucose - increased	40	0(0.0)	40(100.0)	18(45.0)	0(0.0)	33(82.5)	7(17.5)	5(12.5)	18(45.0)
Serum phosphorus	14	0(0.0)	14(100.0)	8(57.1)	0(0.0)	12(85.7)	3(21.4)	0(0.0)	12(85.7)
Serum potassium - decreased	10	1(10.0)	9(90.0)	1(10.0)	0(0.0)	7(70.0)	2(20.0)	0(0.0)	7(70.0)
Serum potassium - increased	4	0(0.0)	4(100.0)	3(75.0)	0(0.0)	4(100.0)	0(0.0)	1(25.0)	3(75.0)
Serum sodium - decreased	7	1(14.3)	6(85.7)	1(14.3)	0(0.0)	4(57.1)	2(28.6)	0(0.0)	4(57.1)
Serum triglyceride	14	2(14.3)	12(85.7)	1(7.1)	1(7.1)	11(78.6)	11(78.6)	1(7.1)	12(85.7)
Total serum carbon dioxide	23	0(0.0)	23(100.0)	3(13.0)	0(0.0)	19(83.0)	4(17.4)	0(0.0)	19(83.0)
Urine protein	20	1(5.0)	19(95.0)	5(25.0)	1(5.0)	18(90.0)	11(55.0)	3(15.0)	16(80.0)

¹⁾ Based on NCI CTCAE, Version 3.0
²⁾ A clinically meaningful shift in CTCAE grade was defined as a shift from less than Grade 3 to Grade 3 or 4 or 5 OR a shift from Grade 0 to Grade 2.
³⁾ Includes subjects from the column labeled "Improved".
⁴⁾ Includes subjects from the column labeled "Worsened".
⁵⁾ Includes subjects from the column labeled "Consistent improvement from baseline" and "Worsened and then improved".
⁶⁾ Denominator for each parameter = number of patients with at least 1 postbaseline value. Patients without any changes from baseline are excluded. A missing baseline value was set Grade 0.

Data Source: [16.4.2]

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Clinically Significant Laboratory Abnormalities

The following table summarizes the number of patients with clinically significant on-treatment laboratory abnormalities. The incidence of CTCAE Grade 3 and Grade 4 levels are shown by lab value.

- The only protocol specified CTCAE Grade 3 laboratory abnormalities experienced by more than one patient were increased serum glucose and decreased platelet count (both 3/74, 4.1%).
- The only protocol-specified CTCAE Grade 4 laboratory abnormality experienced by more than one patient was increased serum uric acid (2/74, 2.7%).

Table 240. Number of Patients with a Clinically Significant Laboratory Abnormality (CSLA) (Applicant's Table)

Laboratory Test	NCI Toxicity Grade 3 and 4	Patients With CSLA ≥50 mg qd x 7d wk n (%)
Blood Chemistry Test		
decreased serum glucose - mg/dL	39-49 <39	1/74 (1.4) 0/74 (0.0)
decreased serum potassium - mmol/L	2.5-3.0 <2.5	1/74 (1.4) 0/74 (0.0)
decreased serum sodium - mmol/L	120-130 <120	1/74 (1.4) 0/74 (0.0)
increased serum glucose - mg/dL	250-500 >500	3/74 (4.1) 0/74 (0.0)
increased serum potassium - mmol/L	6.0-7.0 >7.0	1/74 (1.4) 0/74 (0.0)
serum creatinine	3-6xULN >6xULN	1/74 (1.4) 0/74 (0.0)
serum phosphorus - mg/dL	1.0-2.0 <1.0	1/74 (1.4) 0/74 (0.0)
serum uric acid - mg/dL	ULN-10 >10	0/74 (0.0) 2/74 (2.7)
Hematology Laboratory Test		
hemoglobin - g/dL	6.5-8 <6.5	1/74 (1.4) 0/74 (0.0)
platelet count - /mm ³	25,000-50,000 <25,000	3/74 (4.1) 1/74 (1.4)
Hemostatic Function Test		
INR	>2xULN	3/18 (16.7)

Data Source: [16.4.2]

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Specific Abnormal Laboratory Values of *Clinical Relevance*

The 3 most frequent protocol-specific blood chemistry lab abnormalities were:

- Increased serum cholesterol 66.2%
- Increased serum triglycerides 66.2%
- Increased serum glucose 63.5%

The highest CTCAE grade reported for each of these abnormalities was Grade 3.

The 2 most frequently reported protocol-specific hematologic laboratory abnormalities were:

- Decreased hemoglobin 54.1%
- Decreased platelet count 41.9%

CTCAE Grade 4 laboratory abnormalities were reported in 5 patients.

The abnormalities in these patients that were considered by the investigator to be drug-related were decreased neutrophil count and decreased platelet count.

The frequency of clinically significant abnormalities for the laboratory tests examined was <10% for all of these tests.

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Vital Signs, Other Physical Observations, and Special Examinations Related to Safety

Summary statistics for ECOG and vital signs measured at baseline and during the treatment period are summarized in the following table. A reduction in weight and a rise in triglycerides were noted, however, no clinically relevant changes were seen.

Table 241. Mean (Standard Deviation) of Clinical Safety Measurements during the Study (Applicant's Table)

Treatment Visit	N ¹	ECOG	Temperature (C)	Respiration rate	DBP (mmHg)	SBP (mmHg)	Heart Rate (beats/min)	Weight (kg)	LDL (mg/dL)	HDL (mg/dL)	TG (mg/dL)
Baseline	74	0.6 (0.7)	36.6 (0.4)	16.3 (2.5)	76.9 (11.3)	131.0 (34.6)	76.9 (12.0)	78.4 (14.4)	113.7 (56.7)	46.4 (18.7)	265.7 (135.7)
Week 3	69	0.6 (0.7)	36.4 (0.5)	16.7 (2.9)	78.2 (11.5)	134.2 (18.1)	77.8 (12.0)	78.6 (14.4)	100.3 (27.5)	44.8 (14.6)	219.7 (154.6)
Week 5	70	0.6 (0.7)	36.5 (0.5)	16.4 (2.9)	76.5 (11.1)	135.0 (19.2)	79.3 (11.7)	77.7 (14.3)	95.2 (32.4)	45.6 (16.4)	228.7 (162.8)
Week 7	69	0.6 (0.7)	36.5 (0.4)	16.4 (3.2)	77.3 (10.7)	135.3 (19.5)	79.7 (12.7)	76.7 (14.2)	94.1 (30.4)	47.8 (17.7)	204.6 (123.3)
Week 9	63	0.6 (0.6)	36.4 (0.5)	16.0 (2.8)	76.3 (10.2)	131.7 (15.3)	77.5 (11.5)	76.8 (13.3)	96.0 (36.7)	46.7 (17.5)	221.6 (132.3)
Week 13	53	0.6 (0.7)	36.5 (0.5)	16.5 (2.6)	74.1 (8.3)	129.2 (14.6)	75.2 (11.8)	75.6 (14.2)	90.5 (32.8)	46.0 (18.2)	228.8 (134.5)
Week 17	41	0.5 (0.6)	36.5 (0.5)	16.8 (2.8)	75.3 (8.3)	125.8 (16.4)	75.0 (9.5)	76.0 (13.2)	93.5 (35.1)	44.1 (12.5)	263.6 (256.6)
Week 21	34	0.6 (0.9)	36.5 (0.4)	15.9 (2.9)	75.6 (10.0)	132.8 (13.4)	74.7 (15.6)	75.4 (12.2)	88.5 (35.4)	45.2 (11.7)	154.8 (152.2)
Week 25	23	0.6 (0.7)	36.5 (0.5)	15.8 (3.0)	73.9 (10.8)	132.1 (17.2)	72.6 (9.0)	72.1 (13.2)	87.5 (34.6)	43.8 (10.3)	264.6 (268.7)
Week 29	17	0.6 (0.7)	36.6 (0.4)	15.9 (3.3)	75.8 (10.3)	133.3 (17.9)	73.2 (10.4)	73.2 (11.2)	88.9 (35.3)	44.6 (13.8)	251.2 (184.1)
Week 33	10	0.3 (0.5)	36.5 (0.4)	15.8 (1.2)	75.7 (16.2)	133.1 (15.4)	70.7 (10.3)	71.9 (11.2)	90.7 (35.1)	45.4 (7.7)	196.6 (61.7)
Week 37	9	0.6 (0.5)	36.4 (0.3)	14.1 (2.3)	75.4 (18.3)	129.7 (18.6)	81.4 (14.3)	69.7 (11.7)	92.9 (38.4)	47.2 (9.2)	181.3 (85.7)
Week 41	5	0.4 (0.5)	36.5 (0.3)	15.8 (1.5)	73.6 (11.6)	130.0 (14.4)	70.4 (8.2)	76.3 (25.1)	98.8 (38.0)	53.4 (7.4)	186.2 (88.5)
Week 45	3	0.7 (0.6)	36.5 (0.4)	17.3 (1.2)	81.0 (7.9)	132.3 (11.7)	62.7 (8.1)	68.0 (16.3)	95.7 (38.0)	44.7 (11.0)	198.0 (56.5)
Week 49	1	1.0 (.)	36.8 (.)	18.0 (.)	90.0 (.)	135.0 (.)	68.0 (.)	52.0 (.)	102.0 (.)	44.0 (.)	155.0 (.)
Week 53	1	(.)	36.3 (.)	18.0 (.)	90.0 (.)	160.0 (.)	69.0 (.)	52.0 (.)	93.0 (.)	50.0 (.)	113.0 (.)

¹Number of patients with at least one clinical safety measurement. The last-value-carried-forward approach is used to impute missing measurements for those with incomplete data.
 DBP = Diastolic Blood Pressure
 SBP = Systolic Blood Pressure
 LDL = Low Density Lipoprotein
 HDL = High Density Lipoprotein
 TG = Triglyceride

Data Source: [16.4.1, 16.4.2]

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Drug related symptom complexes

A brief analysis of drug-related symptom complexes was performed. The following table summarizes 4 drug-related symptom complexes of adverse experiences most commonly observed: gastrointestinal symptoms (diarrhea, nausea, vomiting, weight loss, decreased appetite, and anorexia), constitutional symptoms (fatigue and asthenia), hematologic abnormalities (thrombocytopenia and anemia), and taste disorders (dysgeusia and dry mouth). The only symptom complex experienced by $\geq 50\%$ of the overall population was gastrointestinal symptoms (56/74, 75.7%).

Table 242. Number (%) of Patients with Specific Drug-related Clinical Adverse Experiences by Symptom Complexes (Incidence >0%) (Applicant's Table)

	400 mg once daily x 7d/wk (N=74)		Total Patients (N=74)	
	n	%	n	%
Gastrointestinal Symptoms	56	(75.7%)	56	(75.7%)
Constitutional Symptoms	35	(47.3%)	35	(47.3%)
Hematologic Abnormalities	19	(25.7%)	19	(25.7%)
Taste Disorders	23	(31.1%)	23	(31.1%)

Gastrointestinal Symptoms = diarrhea, nausea, vomiting, weight loss, decreased appetite, anorexia
 Constitutional Symptoms = fatigue, asthenia
 Hematologic Abnormalities = thrombocytopenia, anemia
 Taste Disorders = dysgeusia, dry mouth
 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

Data Source: [16.4.2]

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ECG

ECGs were examined at baseline and then every 4 weeks after starting study drug. Investigators were to report any clinically significant ECG finding post-baseline as an adverse experience.

- Twenty-three (23) individual ECG adverse experiences were reported in 15 patients.
- Ten (10) of these patients had a history of cardiovascular disease or a baseline abnormal ECG. The only adverse experience Grade 3-5 was the myocardial infarction (Grade 4).
- None of the adverse experiences led to dose modification or discontinuation of Vorinostat treatment. QTc measurements were not specified to be collected as discrete data in this protocol.

The following table summarizes specific ECG findings reported as adverse experiences for the overall population broken down into 3 by classifications:

- Ischemic events (myocardial infarction, electrocardiogram ST or ST-T segment abnormal)
- Rhythm events (sinus bradycardia, electrocardiogram QT prolonged, ventricular extrasystoles, sinus arrhythmia, tachycardia, bundle branch block, electrocardiogram QT corrected interval prolonged)
- Other events (electrocardiogram T wave abnormal, electrocardiogram P wave abnormal, ventricular hypertrophy, electrocardiogram repolarization abnormality)

The only ECG adverse experience classification observed in ≥ 10% of the overall population was rhythm events (11/74, 14.9%).

Table 243. Number (%) Of Patients with Specific ECG Adverse Experiences by Classifications (Incidence >0% in One or More Dose Levels) (Applicant's Table)

	400 mg once daily x 7d/wk (N=74)		Total Patients (N=74)	
	n	%	n	%
Ischemic Events	5	(6.8%)	5	(6.8%)
Rhythm Events	11	(14.9%)	11	(14.9%)
Other Events	6	(8.1%)	6	(8.1%)

Ischemic events = myocardial infarction, electrocardiogram ST-T segment abnormal, electrocardiogram ST segment abnormal.
 Rhythm events = sinus bradycardia, electrocardiogram QT prolonged, ventricular extrasystoles, sinus arrhythmia, tachycardia, bundle branch block, electrocardiogram QT corrected interval prolonged.
 Other events = electrocardiogram T wave abnormal, electrocardiogram P wave abnormal, ventricular hypertrophy, electrocardiogram repolarisation abnormality.
 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

Data Source: [16.4.2]

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Exploratory analysis for patient and disease factors predictive of SAEs

Investigation of baseline characteristics including gender, age, baseline ECOG, normalized dose by body weight (mg/kg), serum lactate dehydrogenase (LDH), and disease stage on a multivariate logistic regression analysis did not reveal any factors that might be predictive of serious adverse experiences, whether or not considered drug-related.

These data are shown in the following two tables.

Baseline ECOG had a statistically significant effect on serious adverse experience at the 5% level (P = 0.023). A higher ECOG score was associated with a higher likelihood of having a serious adverse experience.

None of the other effects, including drug-related serious adverse experiences by baseline ECOG, were statistically significant at the 5% level.

The lack of weight effect suggests that the use of normalized dose by body weight for safety is not warranted.

Reviewer Comments: These analyses are exploratory and using unadjusted p value is misleading. The finding of higher ECOG score associated with a higher likelihood of having a serious adverse experience is unusual.

Table 244. Analyses of Factors Predictive to Serious Adverse Events (Exploratory Analyses – Logistic Regression) (Applicant's Table)

Variable/Covariate	Odds Ratio Estimate	p-Value
Gender (Male vs Female)	0.775	0.729
Age (>60 vs ≤ 60)	0.918	0.900
Baseline ECOG (0,1,2)	3.023	0.023
Normalized Dose By Body Weight (mg/kg)	1.179	0.630
LDH (<1 X normal vs ≥ 1 X normal)	1.707	0.499
CTCL Stage (III/IV vs I/II)	1.562	0.547

Data Source: [16.4.1; 16.4.2; 16.4.3]

Table 245. Analyses of Factors Predictive to Drug-related Serious Adverse Events (Exploratory Analyses – Logistic Regression) (Applicant's Table)

Variable/Covariate	Estimate	p-Value
Gender (Male vs Female)	1.047	0.961
Age (>60 vs ≤ 60)	0.485	0.447
Baseline ECOG (0,1,2)	2.629	0.158
Normalized Dose By Body Weight (mg/kg)	1.222	0.671
LDH (<1 X normal vs ≥ 1 X normal)	2.692	0.319
CTCL Stage (III/IV vs I/II)	7.045	0.104

Data Source: [16.4.1; 16.4.2; 16.4.3]

Subjects at Increased Risk, Pregnant Women and Other Potentially Vulnerable Subjects

- Not applicable to this study

Discussion and Conclusions

Discussion

This study was a multicenter, open-label, Phase II trial designed to provide an assessment of the efficacy and safety/tolerability of Vorinostat in patients with advanced CTCL who were refractory to or intolerant of other prior therapy.

In this study, Vorinostat provided clinically meaningful responses as determined by skin severity weighted assessment tool (SWAT) scores. The SWAT measurements were supported by annotated body diagrams and digital photographs. Pruritus was reduced as measured by serial pruritus scores provided by the patients. The safety profile of Vorinostat was acceptable for an agent used in the treatment of CTCL.

Unlike some cancers, durable complete remissions are unusual in advanced CTCL. This chronic relapsing and increasingly debilitating disease is currently treated with agents that produce transient reductions in disease manifestations and ameliorate disease-related symptoms. Clinical management of these patients requires a sequence of treatments that are capable of controlling the disease without inordinate irreversible side effects. Therefore patients with advanced CTCL require new therapies that can result in additional clinically beneficial responses. Choice of agents must balance the safety, tolerability, extent of response, and durability of response. Vorinostat should be judged based on its ability to produce responses in patients who have failed other therapies, as new treatments are greatly needed to re-induce responses in refractory patients. Furthermore, Vorinostat is well tolerated; there is no evidence of the irreversible toxicities sometimes associated with other salvage therapies. In this way, Vorinostat provides a valuable non-cross resistant treatment option for refractory and relapsed CTCL patients.

Efficacy

Vorinostat treatment resulted in a response rate of 29.5% (95% CI: 18.5%, 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.

The median response duration (defined as the time when criteria were first met for CCR or PR until the first date when a skin assessment by SWAT was greater than 50% of the difference between baseline score and nadir score and if the magnitude of increase in the score was confirmed by a second assessment 1 to 4 weeks thereafter) exceeds 4 months as the majority of patients who responded continued to respond at the time of data cut-off. Fifteen (15) patients continued on study therapy at the time of data cut-off.

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. Median time to progression had not been reached but is estimated to exceed 5 months.

Eighteen (18/59, 30.5%) patients with CTCL Stage IIB and higher had pruritus relief without an increase in the use of anti-pruritic medications.

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 pruritus relief or both.

In addition to the 22 patients who had demonstrated an objective response, 10 patients with Stage IIB or higher CTCL (AN1002, AN1021, AN 1026, AN1036, AN1045, AN1050, AN1052, AN1069, AN1076, and AN 1078) and one patient with Stage IB (AN1019) had experienced stable disease, defined as absence of disease progression or response, for 24 weeks. Therefore, 33/74 (44.6%) patients of all stages and 28/61 (45.9%) of patients Stage IIB or above CTCL demonstrated either objective response or 24 weeks of stable disease.

Among the patients continuing on the study, mean reduction in SWAT scores from the baseline was approximately 20% by Week 9 and continued to improve to approximately 35% at Week 25.

Response to Vorinostat was similar whether or not patients responded to previous 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 treatment 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 patients (35.0%) 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 demographics of the population in this study were consistent with the expected patient population. The median age of 60 years, 82.4% with clinical stage \geq IIB, and 51.4% male were representative of the CTCL population who would potentially use Vorinostat. This median time from diagnosis of 2.5 years, presence of clinically abnormal lymph nodes in 45.9% of patients, presence of Sezary syndrome in 40.5% of patients, a median of 3 prior systemic treatments for CTCL, a baseline median pruritus score of 6, and a median SWAT score of 74 suggests that this was a population with aggressive disease in need of new therapeutic options. Similar response rates were observed in all groups studied: 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 correlates with a more advanced stage of CTCL. The majority of Sezary syndrome patients had a greater than 25% reduction in Sezary cell count. Among patients without a cutaneous objective response the majority did show reduction in Sezary cell count. Some patients who had a cutaneous response did not have a reduction in Sezary cell count due to low circulating count at baseline. Reductions in Sezary cell count support the activity of Vorinostat in patients with advanced disease.

Patients with a tumor component also demonstrated responses on SWAT assessments. There is a $\geq 50\%$ reduction in the 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.

In addition to patients who met the criteria by SWAT score reduction for an objective response, 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, a rate of 17/74 (23.0%) was seen in the overall population. Improvement in skin disease, as measured in terms of best response, is attained in 60/74 (81.1%) patients treated with Vorinostat.

The symptom of pruritus significantly impacts the quality of life of CTCL patients. In this study, patients were asked to evaluate the severity of the symptom at each of their visits. Most patients presented at baseline with considerable pruritus as reflected by a mean baseline pruritus score of 6. Pruritus relief was rapid with nearly a 2 point decrease in mean pruritus score by Week 4. By Week 17, the mean pruritus score continued to decline to just above 3. Overall 23/72 (31.9%) patients had pruritus relief and 8/72 (11.1%) had complete resolution of their pruritus. 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 pruritus. A 3-point improvement in pruritus intensity was pre-specified as the minimally important difference based on the standard deviation (SD) of pruritus intensity at baseline among patients who had pruritus at study entry (N = 72 patients, SD = 2.5). This represents one SD, which is 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.

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 has not been reached and is estimated to exceed 5 months. Similarly, median response duration has not been reached and exceeds 4 months.

Safety

The median and mean duration of exposure to Vorinostat were 115 and 130 days. Thirty-eight (38/74, 51.4%) patients remained Vorinostat for more than 16 weeks and 20/74 (27.0%) patients remained on Vorinostat for more than 24 weeks.

Compliance with prescribed therapy as assessed by capsule count was greater than 80% in 65/74 (87.8%) patients and the median percentage of prescribed drug taken exceeded 98%.

Vorinostat therapy was generally well-tolerated. Although nearly all patients had one or more adverse experiences, only 9/74 (12.2%) patients discontinued study treatment due to adverse experiences. Only 10/74 (13.5%) patients had a dose modification.

Serious adverse experiences were reported in 16/74 (21.6%) patients and drug-related serious adverse experiences were reported in 8/74 (10.8%) patients.

Three (3) deaths were reported while on study, 2 of which were considered by the investigator to be possibly related to Vorinostat. Both of these drug-related deaths occurred at different times on study: one death occurred on Day 2 of study and was of unknown cause, and the other death was due to ischemic stroke that began on Day 227.

Of the 28 serious clinical adverse experiences reported, 13 were considered by the investigator to be related to study drug including: anemia, death, deep venous thrombosis, dehydration, ischaemic stroke, pulmonary embolism, streptococcal bacteremia, syncope, thrombocytopenia and gastrointestinal hemorrhage. Pulmonary embolism (4/74, 5.4%) was the only drug-related serious adverse experiences reported in more than one patient. There was one serious laboratory adverse experience of increased blood creatinine that was considered by the investigator to be related to study drug.

The most common drug-related adverse experiences could be classified into 4 symptom complexes: gastrointestinal symptoms (diarrhea, nausea, vomiting, weight loss, decreased appetite, anorexia), constitutional symptoms (fatigue, asthenia), hematologic abnormalities (thrombocytopenia, anemia), and taste disorders (dysgeusia, dry mouth).

The only symptom complex experienced by more than half the overall population was gastrointestinal symptoms (56/74, 75.7%). Gastrointestinal and constitutional symptoms along with taste disorders, anemia and thrombocytopenia were frequently observed but usually not severe enough to lead to discontinuation, interruption, or modification of Vorinostat treatment. Only diarrhea, fatigue and nausea were reported in more than one-third of the patients. Diarrhea, fatigue, nausea, anorexia, and dysgeusia were the 5 most commonly reported adverse experiences respectively, both drug-related and non drug-related. The severity of these symptoms was generally mild. Only fatigue (5/74, 6.8%) and pulmonary embolism (4/74, 5.4%) were reported at a severity of CTCAE Grade 3 or higher in more than 5% of patients. Twenty-nine (29/74, 39.2%) patients had any CTCAE Grade 3 or higher clinical adverse experience and 22/74 (29.7%) of patients had any CTCAE Grade 3 or higher drug-related adverse experience. Of particular note, only 2 patients experienced CTCAE Grade 3 and 1 patient experienced CTCAE Grade 4 thrombocytopenia.

Twenty two (22) patients had laboratory adverse experiences reported. The only laboratory adverse experience which was observed in more than 5% of patients was increased blood creatinine. This was noted in 12/74 (16.2%) patients and was clinically mild: Grade 1 in 9 patients, Grade 2 in 2 patients and Grade 3 in 1 patient. No patients were discontinued as a result of a laboratory adverse experience. A more comprehensive approach was to analyze all laboratory data by CTCAE Grade and evaluate shifts in values. The most common laboratory abnormalities in clinical chemistry parameters observed in more than 10% of patients during the study were increased serum glucose, decreased serum calcium, increased alkaline phosphatase, increased aspartate aminotransferase, increased serum cholesterol, increased serum triglycerides, total serum carbon dioxide, increased serum creatinine, decreased serum potassium, decreased serum phosphorus, increased serum alanine aminotransferase, and decreased serum glucose. The majority of these lab abnormalities were ≤ CTCAE Grade 2 severity. Of these more common laboratory abnormalities, CTCAE Grade 3 or CTCAE Grade 4 events were reported in more than one patient only for increased serum glucose and increased serum triglycerides.

A shift analysis was also performed. A clinically meaningful shift was defined as a shift from a baseline of less than CTCAE Grade 3 to any post-baseline value of CTCAE Grade 3 or higher; or a shift from CTCAE Grade 0 to CTCAE Grade 2. In this analysis, the only clinical chemistry

parameters with clinically meaningful shifts from baseline that occurred in more than 10% of patients were increased serum glucose in 18/74 (24.3%) patients and serum phosphorus in 8/74 (10.8%) patients. Although the increase in glucose was noted, there was not an increase beyond baseline in the number of patients who required treatment with insulin or other medications for diabetes mellitus. As well, there were no occurrences of renal failure reported during the study.

Hematologic laboratory data were also analyzed by CTCAE Grade. The most common hematology laboratory abnormalities observed in more than 10% of patients during the study were decreased hemoglobin, decreased lymphocyte count, decreased neutrophil count, decreased platelet count, and decreased WBC. The majority of these lab abnormalities were \leq CTCAE Grade 2 severity. Of these more common laboratory abnormalities, CTCAE Grade 3 or CTCAE Grade 4 events were reported in more than one patient only for decreased lymphocyte count (9/74, 12.2 %) and decreased platelet count (3/74, 4.1%). There were no reported serious adverse experiences attributable to a low platelet count. A shift analysis was performed on these laboratory values as well. In this analysis, the only hematology laboratory parameters with clinically meaningful shifts from baseline that occurred in more than 10% of patients were decreased lymphocyte count in 19/74 patients (25.7%) and decreased neutrophil count in 8/74 patients (10.8%).

The significance of the laboratory abnormality of decreased absolute lymphocyte count is uncertain when considered in the background of a disease in which the pathophysiology includes the lymphoid compartment.

Among the infrequent, although severe, adverse experiences, thrombotic experiences (deep venous thrombosis and associated pulmonary embolism) were noted in 4 patients in (AN1015, AN1058, AN1059 and AN1070). The clinical course for these 4 patients is detailed in the Narratives in the following section. In some instances, these patients had a history of prior thrombotic experiences and in addition to an underlying neoplastic process may have had lymphadenopathy that impinged on blood vessels and clinically significant edema in the extremities that may have predisposed them to thrombotic experiences. There is no common theme among these patients as to the timings of the events or locations. Venous thromboembolic events (VTEs) occur at increased frequency in cancer patients, cancer patients treated with chemotherapy, and lymphoma patients; incidences in some series as high as 30%.

The occurrence of venous thromboembolic events in any of the safety populations is not unexpected. VTEs are well documented to be associated with cancer. This association is further supported by the high rate of incident cancer detection or development in patients following identification of idiopathic thromboembolism. The pathogenesis of thrombosis in cancer patients is multifactorial. Tumors produce factors that may impair the anticoagulant and fibrinolytic mechanisms and induce a prothrombotic or hypercoagulable state. There is evidence to suggest that the risk of developing thromboembolic events depends on tumor type, the stage or extent of the cancer, and chemotherapy. Additional factors, such as previous history of thromboembolic event, age, immobilization, surgery and catheters, contribute to further increasing the risk.

The natural history for the development of thromboembolism in CTCL patients is currently unknown. Only rare case reports are published. The occurrence of thromboembolic events among CTCL patients in recent clinical studies is quite variable ranging up to 11% in the pivotal, phase

III trial of denileukin diftitox (ONTAK™; Ligand Pharmaceuticals, San Diego, CA). In a report of 10 CTCL patients treated with pegylated doxorubicin, one patient, with a complete response, died 12 months later from a pulmonary embolism that was determined not related to either treatment or disease. At least one case of pelvic thrombosis and pulmonary embolism was reported by the FDA in their medical review of bexarotene for CTCL. Fatal pulmonary embolism has also been reported in a retrospective series of CTCL patients.

A recent observational study noted a 12% incidence of venous thromboembolic events with a range from 2.7 – 72% depending on the presence of identified risk factors of inpatient treatment, prior DVT in medical history, family history of DVT, chemotherapy, fever and CRP elevation. A second observational study of cancer patients reported a 7.3% incidence of VTE during or within 3 months after chemotherapeutic treatment and an annual incidence was 10.9%. A third study reported an incidence of 7.8% for VTE in cancer patients.

Rates of VTE may be as high as 20% in advanced stage breast cancer or non-small cell lung cancer patients treated with chemotherapy. The reported rates range from 5% to 10% for Hodgkin's or non-Hodgkin's lymphoma patients and from 20% to 60% for patients with CNS lymphoma or high grade gliomas.

Patients in Vorinostat studies underwent routine scheduled evaluations to evaluate their tumor status. Incidental detection of pulmonary embolism was noted in at least one case. Two studies have estimated the frequency of incidental clinically silent pulmonary embolisms in cancer patients at 2.6 to 9%.

One unexplained death was observed in this study (AN1048). It is not known whether this patient took any Vorinostat, however an overdose cannot be ruled out. This patient's complicated clinical course prior to entering the study is detailed in the Narrative in the next section. Of note, this patient was hypokalemic the day before death and had a history of congestive heart failure. Her baseline ECG did not show any new ischemia or QT prolongation.

Fifteen (15) patients were reported as having clinically significant ECG changes. The only serious adverse experience reported was a non-fatal myocardial infarction which was considered by the investigator to be unrelated to the study drug. Two (2) patients had the ECG adverse experiences of QT prolonged and QT corrected interval prolonged, CTCAE Grade 2 and Grade 1 respectively. Both of these adverse experiences were felt to be possibly related to study drug.

Due to impairment of skin integrity, CTCL patients are at high risk for infection. Furthermore, prior cytotoxic chemotherapy may further impair these patients' immune defenses. Three (3) infections were reported as serious adverse experiences (sepsis, streptococcal bacteremia, and enterococcal infection). All required the patients to be hospitalized; however, only streptococcal bacteremia was considered drug-related. All of the reported infections eventually resolved.

Efficacy and Safety Conclusions

In this study of patients with advanced CTCL receiving Vorinostat, it can be concluded that:

1. Vorinostat provides clinically meaningful responses in a substantial proportion of patients with advanced CTCL (Stage IIB and higher), who have progressive, persistent, or recurrent disease on or

- following 2 systemic therapies. Prior therapy must have included bexarotene unless the patient is intolerant of or not a candidate for bexarotene therapy.
2. Vorinostat provides clinically meaningful responses in a substantial number of patients within the three prespecified subgroups: Sezary syndrome patients, T3 tumor patients, as well as in the overall population including lower clinical stage patients.
 3. The median duration of objective response and the median time to progression are clinically meaningful.
 - The median duration of objective response has not been reached, but exceeds 4 months.
 - The median time to progression has not been reached but is estimated to exceed 5 months.
 4. The median time to response is less than 2 months.
 5. Vorinostat provides clinically meaningful reduction in pruritus in a substantial number of symptomatic patients with CTCL refractory to or intolerant of at least 2 prior therapies including bexarotene.
 6. There was no discernable impact of response to last treatment or response to prior bexarotene treatment on subsequent efficacy of Vorinostat.
 7. Vorinostat has an acceptable safety profile and is generally well tolerated in this patient population.

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ON ORIGINAL**

Narratives

AN1004

Serious Adverse Experiences: Myocardial Infarction and Erythroderma

AN1004 a 50-year old black female entered the study with Stage IV cutaneous T-cell lymphoma diagnosed in 1992. The patient's pertinent medical history includes hypercholesterolemia, hypertension, coronary artery disease, and drug hypersensitivity to pentostatin. Prior oncologic treatment(s) mechlorethamine, bexarotene, interferon, doxorubion, cyclophosphamide, vincristine, pentostatin, radiation, and psoralen longwave ultraviolet radiation (PUVA). Concomitant medications include cholestyramine, lovastatin, topical fluocinonide, cetirzine, cephalexin, and folic acid.

The patient started treatment with Vorinostat 400 mg by mouth once a day on [redacted]

On [redacted] (Day 31), the patient experienced dyspnea and positional chest pain and was admitted to the hospital. Admitting chest x-ray was normal and laboratory results revealed creatine kinase of 469 IU/L, elevated high-density lipoprotein (HDL) (baseline 47) and low-density lipoprotein (LDL) (baseline 216) (laboratory results for [redacted] are not available) and an EKG with no changes. The patient was found to have complete occlusion of her circumflex artery that required a balloon angioplasty which was performed on [redacted]. The patient was diagnosed with a myocardial infarction and moderate coronary artery disease due to poorly controlled hyperlipidemia. The patient was placed on losartan, clopidogrel, lisinopril, atenolol, and aspirin. The patient recovered and was discharged from the hospital on [redacted].

Study therapy was interrupted on [redacted] due to concomitant and reinitiated on [redacted] due to a re-occurring non-serious adverse experience of hypertension.

On [redacted] (Day 140), the patient developed dyspnea and severe erythroderma and leg pain. The patient was unable to perform daily activities and was bed-ridden due to these events. The patient was admitted to the hospital. A chest x-ray and electrocardiogram was performed with normal results. Admitting laboratory results revealed Sezary panel (CD4+ CD26-) T-cell lymphocyte count 45% and blood cultures were normal. Results of a skin biopsy are unavailable. The patient was treated with prednisone and unspecified prophylactic antibiotics. The patient's symptoms improved, prednisone was discontinued and methotrexate and atenolol were initiated. Worsening of erythroderma and dyspnea improved with the initiation of prednisone. The patient was discharged from the hospital on [redacted]. Study therapy was discontinued on 07-Sep-2004 due disease progression.

In the opinion of the investigator, the serious adverse experience of Grade 4 myocardial infarction and Grade 3 worsening of erythroderma were considered not related to study therapy.

AN1008

Serious Adverse Experiences: Dehydration, Blood Creatinine Increased and Ischemic Stroke

AN1008, a 71-year old white female entered the study with Stage IV cutaneous T-cell lymphoma diagnosed on 15-Feb-2001. The patient's pertinent medical history includes diabetes, hypertension, hyperglycemia, hyperlipidemia, weakness, dizziness, herpes simplex and confusion. Prior oncologic treatment(s) include interferon, bexarotene, alemtuzumab, dexamethasone, temozolomide, gemcitabine, doxorubicin, denileukin diftitox, and corticosteroids. Concomitant medications included metformin, quinapril, fentanyl, hydroxyzine, allopurinol, nystatin, megestrol and colchicine.

The patient started treatment with Vorinostat 400 mg by mouth once a day on [redacted]. Study therapy was interrupted on 19-Nov-2004 and reinitiated on 30-Nov-2004 due to non-serious adverse experience (NSAE) of Grade 1 thrombocytopenia. On 01-Dec-2004, study therapy was reduced to 300 mg by mouth once a day to due (NSAE) of thrombocytopenia. On 17-Feb-2005 study therapy interrupted and reinitiated on 24-Feb-2005 due to unexplained missed doses by patient.

On [redacted] (Day 204), the patient tripped and fell hitting her head. She was taken to the emergency room. At the hospital, the patient's blood pressure was 96/58, (pulse and temperature not available) and she complained of a sore neck and occipital area, although she was able to move all extremities. A CT scan of the head revealed no evidence of a subdural hematoma and a chest x-ray performed was normal. Admitting laboratory results revealed hemoglobin blood urea nitrogen 56 mg/dL (baseline 22 mg/dL), creatinine 4.0 mg/dL (baseline 2.2 mg/dL) and creatine kinase (CK) 600 IU/L (baseline value unavailable). Electrolyte laboratory values are not available. The patient reported that over the past two weeks she was unable to eat, but was drinking water. No decrease in urine output was reported. The patient was diagnosed with dehydration and increased creatinine. Treatment included rehydration with intravenous fluids. Laboratory results on [redacted] revealed creatinine at 1.6 mg/dL. The patient was considered recovered and discharged to home. Study therapy was interrupted on [redacted] and reinitiated on [redacted].

On [redacted] (Day 227), the patient was brought to the emergency room after sustaining a fall. She collapsed suddenly, but was alert. She did not respond to oral commands and was aphasic. Vital signs in emergency room temperature 36.6°C, blood pressure 146/61 mmHg, respiration rate 20 breaths/min, pulse 70 beats/min, pulse oxygen 99% on room air. The patient appeared lethargic, opened her eyes, and responded to painful stimuli, both pupils pinpoint and reactive to light. Neurological findings could not assess strength, though right side more flaccid and hypotonic than the left side. Cranial nerves could be assessed, Babinski positive on right side and head CT scan revealed decreased attenuation on the right occipital region, cerebral/cerebellar atrophy, enlarged ventricles with prominent sulci. There was no hemorrhage, hematoma or mass lesions evident and midline shift or extra cerebral collection of fluids. No additional head CT/MRI were performed. EEG findings were abnormal with generalized slowing, slightly more predominant on the left side. ECG findings indicated normal sinus rhythm, T wave abnormal. Anterolateral ischemia was considered. A neurology consult concluded that the patient present with a complete stroke. Admitting laboratory results revealed white blood cell count 33.9 x10³/microL (baseline 52.3 x10³/microL), hemoglobin 11.1 gm/dL (baseline 12.3 gm/dL), platelets 106 x10³/microL (baseline 105x10³/microL), prothrombin time (PT) 11.6 sec (baseline 10.4 sec), blood urea nitrogen 30 mg/dL (baseline 15 mg/dL), carbon dioxide 18 mEq/L (baseline 19 mEq/L), and creatinine 2.1 mg/dL (baseline 1.3

mg/dL). The patient received nasogastric feeding tube and was transferred to a hospital close to her home. The patient's status declined and she was transferred to a nursing home on _____ and on _____ she patient died. It was noted by the investigator the complications of stroke and cutaneous T-cell lymphoma (CTCL) are probable causes of death. Study therapy was discontinued on 05-May-2005.

In the opinion of the investigator, the serious adverse experience of Grade 3 blood creatinine increased and Grade 3 dehydration were considered related to study therapy. Grade 4 ischemic stroke was considered possibly related to study therapy.

AN1012

Serious Adverse Experience: Sepsis

AN1012, a 74-year old white female entered the study with Stage IV cutaneous T-cell lymphoma diagnosed in 1992. The patient's pertinent medical history includes urinary tract infection, pollakiuria, pruritus, peptic ulcer, arthralgia, osteoporosis, cardiac murmur, hypothyroidism, anisocytosis, left arterial enlargement, and diverticulum. The patient entered the study with a urinary tract infection (50-100 white blood cells in urine) treated with ciprofloxacin. Prior oncologic treatment(s) include radiotherapy, psoralen long-wave ultraviolet radiation (PUVA), mechlorethamine, bexarotene, interferon, denileukin difitox, fluorouracil, methotrexate, gemcitabine, and carmustine. Concomitant medications included hydroxyzine, levothyroxine, oxycodone, enoxolone and hyaluronate, and epoetin alfa.

The patient started treatment with Vorinostat 400 mg by mouth once a day on _____

On _____ (Day 27), the patient experienced sepsis and was admitted to the hospital. Labs results from _____, hemoglobin 11.1 gm/dL (baseline 11.6 gm/dL), absolute lymphocyte count $0.5 \times 10^3/\text{microL}$ (baseline $0.81 \times 10^3/\text{microL}$), absolute neutrophil count $9.9 \times 10^3/\text{microL}$ (baseline $4.45 \times 10^3/\text{microL}$), blood urea nitrogen 21 mg/dL (baseline 16 mg/dL), creatinine 1.2 mg/dL (baseline 0.9 mg/dL), glucose 151 mg/dL (baseline 95 mg/dL), sodium 129 mg/dL (baseline 140 mg/dL), protein 100 mg/dL (baseline negative), blood culture revealed *Staphylococcus aureus*, and urine culture mixed bacterial organism suggestive of contamination. Chest x-ray results were consistent with chronic obstructive pulmonary disease (COPD) without acute cardiopulmonary disease. The patient was treated with intravenous vancomycin. On 30-Nov-2004, the patient received two units of platelets due to count decrease on 29-Nov-2004 of $59 \times 10^3/\text{microL}$ (baseline $379 \times 10^3/\text{microL}$). The patient was discharged from the hospital on _____ it was reported that the patient recovered from sepsis and laboratory tests on 04-Dec-2004 were normal. The patient was seen in the clinic for her next scheduled visit and blood cultures were repeated since the patient felt poorly and experienced chills. Laboratory results for 04-Dec-2004 are not available. On 14-Dec-2004 laboratory results revealed hemoglobin at 11.09 gm/dL, platelet count $124 \times 10^3/\text{microL}$, absolute neutrophil count $0.4 \times 10^3/\text{microL}$, and lymphocyte count $4.1 \times 10^3/\text{microL}$ and study therapy was discontinued. The patient subsequently discontinued from the study due to disease progression. In the opinion of the investigator, the serious adverse experience of Grade 3 sepsis was considered not related to study therapy.

AN1015

Serious Adverse Experiences: Deep Vein Thrombosis and Pulmonary Embolism

AN1015 a 42-year old black women entered the study with Stage IV cutaneous T-cell lymphoma diagnosed on 15-Jun-2001. The patient's pertinent medical history includes depression, hypertension, pruritus, left leg pain, inguinal mass, diverticulosis, upper respiratory tract infection, and fibrocystic breast disease. Prior oncologic treatment(s) include psoralen long-wave ultraviolet radiation (PUVA), bexarotene, methotrexate, interferon, unspecified investigational drug, cyclophosphamide and doxorubin and prednisone and vincristine (CHOP), gemcitabine. Concomitant medications included hydrochlorothiazide, sertraline, and topical triamcinolone.

The patient started treatment with Vorinostat 400 mg by mouth once a day on [redacted]

On [redacted] (Day 56), the patient was admitted to the emergency room with left thigh swelling that had progressed over the past 2 days accompanied by subjective fevers and significant pain (pain scale: 9/10 burning) with no chest pain. Upon physical exam, the left thigh was grossly edematous down the calf without specific mass and several areas of chronic ulceration on the thigh. There were good pulses on all extremities, no extremity tenderness, and pitting edema to the left hip. An ultrasound of the left lower extremity was performed and the patient was diagnosed with an occlusive expansile deep vein thrombosis (DVT) from the femoral vein to trifurcation and non-occlusive clot in the greater saphenous vein, and left arterial descending coronary vein in the groin. The radiologist noted that the ultrasound had multiple large heterogeneous abnormal appearing lymph nodes in the left groin. These could represent nodes involved with tumor and infection cannot be entirely excluded. Laboratory results on [redacted] were within normal limits. The patient was diagnosed with deep vein thrombosis (DVT) and admitted to hospital for observation and treatment with enoxaparin and hydromorphone. On [redacted] the patient was discharged to home with enoxaparin, oxycodone, and warfarin. Study therapy was discontinued on [redacted].

On [redacted] (Day 63), the patient reported that she had had 3-4 episodes of midsternal chest pressure, shortness of breath, burning chest pain, and left thigh with +2 edema and tenderness. She was sent to the emergency room for further evaluation for possible pulmonary embolism. Laboratory results were within normal limits with the exception of hemoglobin 11.8 gm/dl (baseline 13.3 gm/dL), prothrombin time was slightly increased at 13.9 sec (baseline 9.5 sec), and an under-therapeutic range INR 1.2 (baseline 0.9). Electrocardiogram and pulse oximetry were unremarkable. She was placed on a cardiac monitor. Ventilation perfusion scan results were high probability scan for pulmonary embolism. The patient was admitted to the hospital with a diagnosis of a pulmonary embolism. The patient was continued on enoxaparin. By [redacted] the patient was discharged from the hospital and it was noted the patient had not recovered. On 31-Jan-2005 the patient recovered from the deep vein thrombosis and pulmonary embolism. A follow-up evaluation on 01-Feb-2005 revealed that the patient's disease was "flaring" and a recommendation for radiation oncology and stem cell transplant was made. However, the patient was discontinued from the due to this adverse experience.

In the opinion of the investigator, the serious adverse experience of Grade 4 deep vein thrombosis and Grade 4 pulmonary embolism were considered to be related to study therapy.

AN1027

Serious Adverse Experience: Squamous Cell Carcinoma

AN1027 a 70-year old white male entered the study with Stage IV cutaneous T-cell lymphoma diagnosed on 15-Jun-2001. The patient's pertinent medical history includes squamous cell carcinoma, basal cell carcinoma, lung nodule, pre-auricular skin cancer, and onychomycosis. Prior oncologic treatment(s) include interferon and bexarotene. Concomitant medications include atorvastatin.

The patient started treatment with Vorinostat 400 mg by mouth once a day on 21-Dec-2004.

On 07-Sep-2005 (Day 261), the patient had a 4 mm papule on his left cheek and underwent a biopsy which revealed squamous cell carcinoma in situ. On 05-Oct-2005, an excision was performed and was found to have clear margins. The patient recovered and no action was taken with study therapy.

In the opinion of the investigator, the serious adverse experience of Grade 2 squamous cell carcinoma was considered not related to study therapy.

AN1030

Serious Adverse Experience: Squamous Cell Carcinoma

AN1030, a 70-year old white male entered the study with Stage IV cutaneous T-cell lymphoma diagnosed on 16-Feb-2002. The patient's pertinent medical history includes colon and gastric cancer, dysuria, partial colectomy, and gastrectomy. Prior oncologic treatment(s) include psoralen long-wave ultraviolet radiation, bexarotene, chlorambucil, methotrexate and prednisone. Concomitant medications included minoxidil.

The patient started treatment with Vorinostat 400 mg by mouth once a day on 30-Dec-2004.

On 19-May-2005 (Day 141), the patient had scaly plaque on the left side of the near and neck. It was considered these lesions were present previously but were not specifically noted due to concurrent cutaneous T-cell lymphoma. With the improvement of his cutaneous T-cell lymphoma it became more noticeable and suspicious for squamous cell carcinoma or basal cell cancer. Both lesions were biopsied and the pathology report showed squamous cell carcinoma in situ. The patient has a definitive re-excision on 02-Jun-2005. It was noted that the patient had chronic sun damage to his skin as well as a history of psoralen long-wave ultraviolet radiation which are believed the likely causative of events. The patient recovered and no action was taken with study therapy.

In the opinion of the investigator, the serious adverse experience of Grade 2 squamous cell carcinoma was considered not related to study therapy.

AN1033

Serious Adverse Experience: Worsening of Cutaneous T-cell Lymphoma

AN1033, a 75-year old black female entered the study with Stage IV cutaneous T-cell lymphoma diagnosed on 01-Sep-2002. The patient's pertinent medical history includes systolic murmur, hyperthyroidism, abnormal electrocardiogram, and Sezary syndrome. Prior oncologic treatment(s) include radiotherapy, triamcinolone, bexarotene and interferon. Concomitant medications included doxepin and cephalexin.

The patient started treatment with Vorinostat 400 mg by mouth once a day on _____

On 16-Feb-2005 study therapy was reduced to 300 mg by mouth once a day due to a non-serious adverse experience (NSAE) of increased blood creatinine.

On _____ (Day 43), the patient was discontinued from the study due disease progression. The patient had been in a hospice and on _____ (Day 52), the patient died due to a worsening of the cutaneous T-cell lymphoma.

In the opinion of the investigator the serious adverse experience Grade 5 worsening of cutaneous T-cell lymphoma was not related to study therapy.

AN1040

Serious Adverse Experience: Worsening of Cutaneous T-cell Lymphoma

AN1040, a 53-year old white female entered the study with Stage IV cutaneous T-cell lymphoma diagnosed on 18-Feb-2004. The patient's pertinent medical history includes muscle cramps, pruritus, edema lower extremity, nausea, fatigue, skin fissuring, hypothyroidism, intestinal obstruction, dyspnea on exertion, anemia, and pseudomonas infection. Prior oncologic treatment(s) include bexarotene, interferon, alemtuzumab, cyclophosphamide, doxorubicin and vincristine. Concomitant medications included hydroxyzine, mupirocin, quinine, dapsone, trimethoprim, doxepin, oxycodone, paroxetine, furosemide, levothyroxine, megestrol, methylphenidate, meperidine, hydromorphone, voriconazole, azithromycin, methylprednisone, and dexamethasone.

The patient started treatment with Vorinostat 400 mg once a day on _____. Study therapy was interrupted on _____

On _____ (Day 54) the patient was admitted to the hospital with symptoms upon admission of fatigue, rhinorrhea, anorexia, nausea, constipation, chest tightness with pain radiating to the right arm 10 days prior to admission, trouble opening jaw due to enlarged lymph nodes, burning and painful skin, occasional numbness of hands and feet, and dysuria related to painful and thickened labia. Study therapy was interrupted. Her oxygen saturation was 93% on room air with desaturations to 87% on exertion. Bilateral breath sounds were normal with poor air entry in general. A CT scan of the chest, abdomen and pelvis revealed interval development of bilateral diffuse predominately lower lung nodular opacities with diffuse interlobular septal thickening and ground glass opacification. She had bilateral bulky axillary, inguinal and right iliac lymphadenopathy. The impression and plan included pulmonary-consult for atypical lung process since patient was on multiple prophylactic

antibiotics and differential diagnosis included mycobacterial, fungal (*aspergillosis*, *coccidiomycosis*), *pneumocystis carinii* infection, (community acquired pneumonia), or lymphoma. Laboratory results on 1- revealed white blood cell count $13.1 \times 10^3/\text{microL}$ (baseline $8.4 \times 10^3/\text{microL}$), absolute lymphocyte count $0.71 \times 10^3/\text{microL}$ (baseline not available), and absolute neutrophil count $9.9 \times 10^3/\text{microL}$ (baseline not available). The patient had a bronchoscopy with bronchial alveolar lavage and transbronchial biopsy on — All the cultures were negative. The non-diagnostic transbronchial biopsy contained no lung tissue; however, the cytometry on the bronchial, alveolar lavage fluid revealed malignant T-cells. Therefore the diagnosis of progressive T-cell lymphoma with lung involvement was confirmed on flowcytometry and did contribute to the patient's chief complaint of dyspnea on exertion. The patient was treated with fluticasone, albuterol, fentanyl, and supplemental oxygen. The patient required persistent oxygen supplementation during hospitalization. Duonebs were recommended for dyspnea to improve breathing. On — the patient was discharged home. The patient discontinued from study on 19-Apr-2005 due to disease progression.

In the opinion of the investigator, the serious adverse experience Grade 3 worsening of cutaneous T cell lymphoma was not related to study therapy.

AN1044

Serious Adverse Experiences: Gastrointestinal Hemorrhage, Streptococcal Bacteremia, Anemia, Thrombocytopenia, Squamous Cell Carcinoma and Lung Neoplasm

AN1044, an 83-year old white male entered the study with Stage IV cutaneous T-cell lymphoma diagnosed on 15-Feb-2005. The patient's pertinent medical history includes mastoiditis, leg edema, granuloma, hepatic lesion, renal cysts, cervical radiculopathy, hyperthyroidism, anemia, chronic obstructive pulmonary disease (COPD), lung nodule, bacteremia, aortic calcification, arterial calcification, arterial disorder, right bundle block pattern, convulsion disorder, prostate cancer, malignant melanoma, and squamous cell carcinoma. Prior oncologic treatment(s) include triamcinolone, methotrexate, and bexarotene. Concomitant medications included triamcinolone, aspirin, polysaccharide iron complex, darbepoetin alfa, timolol, bimatoprost, econazole, nystatin, cephalexin, cyanocobalamin, cefpodoxime proxetil, fluconazole, levothyroxine, valproic acid, esomeprazole, fluocinolone, itraconazole, furosemide, ceftriaxone, lansoprazole, levetiracetam, divalproex, and oxcarbazepine.

The patient started treatment with Vorinostat 400 mg by mouth once a day on ' — . On 28-Jun-2005 study therapy dose returned to 300 mg by mouth once a day.

On — (Day 27), the patient had an episode of decreased consciousness when exiting a car. He was subsequently hospitalized for gastrointestinal bleeding (source unknown), *viridians streptococcus* bacteremia, anemia and thrombocytopenia. Upon arrival to the emergency room, he was lethargic and poorly responsive with little verbalization, afebrile, blood pressure was 97/53 mmHg, respiratory rate 60 beats/min, oxygen saturation was within normal limits on room air. A chest x-ray showed no acute changes, and stool was reddish on rectal exam. Blood cultures were positive for *viridiansstreptococcus* group. Laboratory results from 28-MAR-2005 revealed hemoglobin (HGB) 6.8 gm/dL (baseline 12.9 gm/dL), platelets $9 \times 10^3/\text{microL}$ (baseline $151 \times 10^3/\text{microL}$), absolute neutrophil count $2.5 \times 10^3/\text{microL}$ (baseline $7.36 \times 10^3/\text{microL}$), blood urea nitrogen (BUN) 49 mg/dL (baseline 20 mg/dL) albumin 2.7 gm/dL (baseline 3.6 gm/dL), sodium 128

mEq/L (baseline 141 mEq/L), calcium 7.8 mg/dL (baseline 9.3 mg/dL), plasma protein 5.9 g/dl (baseline not available), alanine aminotransferase (AST) 13 IU/L (baseline 12 IU/L), creatine kinase 52 IU/L (baseline not available), and serum lipids normal. The remainder of chemistry panel was noted to be normal. Study therapy with Vorinostat was interrupted. The patient's treatment included intravenous fluids, oxygen supplementation, and intravenous vancomycin. Due to drug sensitivity vancomycin was changed to ceftriaxone. The patient was also received a red blood cell transfusion and a platelet transfusion. Laboratory results on 29-MAR-2005 revealed hemoglobin 10.3 gm/dL, platelets $148 \times 10^3/\text{microL}$, prothrombin time (PT) 15.2 sec (baseline 1.07 sec), partial thromboplastin time (ATTP) 27 sec (baseline 31 sec), international normalization ratio (INR) 1.20 (baseline 1.1) and plasma fibrinogen was high at 526 mg/d (no baseline available). On 31-MAR-2005, an upper endoscopy was performed and revealed petechiae and erosions which the gastroenterologist reported may have been the site of the patient's gastrointestinal bleeding. It was noted that the patient not hemorrhaging at time of the upper endoscopy. The patient was treated with a total of five units packed red blood cells and three platelet transfusions and esomeprazole. On 03-APR-2005 Laboratory tests revealed blood urea nitrogen 14 mg/dL; creatinine 0.9 mg/dL; and sodium 132 mEq/L. Cardiac enzymes and thyroid function tests were normal and valproic acid level was 79. The patient was considered recovered from anemia, thrombocytopenia, and *streptococcus viridians* bacteremia and was discharged from the hospital. On 06-APR-2005, follow-up laboratory results revealed (WBC) $12.5 \times 10^3/\text{microL}$, platelet $301 \times 10^3/\text{microL}$, and HGB 11.3 g/dl. It was reported that the patient recovered from gastrointestinal hemorrhage on 10-Apr-2005.

On (Day 45), a shave biopsy on the right elbow was taken with a diagnosis of squamous cell carcinoma in-situ. On 26-Apr-2005 study therapy was reduced to 300 mg by mouth once day.

On (Day 80), the patient had a biopsy measuring 0.9 x 0.7 x 0.1 cm of another lesion on the right elbow with a diagnosis of squamous cell carcinoma. On 06-May-2005 study therapy was changed to 300 mg by mouth once a day for five consecutive days every seven days due to a non-serious adverse experience (NSAE) of confusion. It was reported that the subject recovered from both events of squamous cell carcinoma. Subsequently the patient discontinued from the study on 08-Sep-2005.

On (Day 205), the patient developed a neoplasm on his left dorsal wrist. A shave biopsy was performed. The results revealed a squamous cell skin cancer. Excision of the lesion via Moh's micrographic was performed on an unspecified date. The patient subsequently recovered. On , a follow-up computed axial tomography (CT) revealed interval development of a new 1.3 x 1.2 cm spiculated nodule in the lower lobe of the right lung, and a new 0.9 x 0.8 cm nodule in the middle lobe of the right lung. Both of the lesions were suspicious for malignant neoplasm. The indeterminate nodules described in a prior CT scan were stable. As per the recommendation of the patient's oncologist, and request of the patient's family, no biopsy or pursuit of a definitive diagnosis was planned. Therefore, the etiology of the pulmonary nodules could not be determined. The patient's pulmonary nodules persisted.

In the opinion of the investigator, the serious adverse experience of Grade 3 gastrointestinal hemorrhage, Grade 4 anemia, Grade 3 streptococcal bacteremia and Grade 4 thrombocytopenia were considered related to study therapy. However, the patient had a history of melena, and had been on aspirin treatment. The patient's primary care physician stated that the patient had a stool guaiac test

performed, and that the result was positive. Although the source of bleeding had not been identified, gastrointestinal bleed was felt to be caused by combination of thrombocytopenia, dysfunctional platelets, and other unknown factors.

It was noted that the patient was taking valproic acid (500 mg twice a day) for seizure history since June 2003 and continued while on study drug. It was further noted that valproic acid was considered a "HDAC inhibitor and it may also interfere with SAHA metabolism." The reporting investigator felt that the exact role of valproic acid in this adverse event could not be clearly defined. The serious adverse experiences of Grade 2 squamous cell carcinoma and Grade 2 lung neoplasm were not related to study therapy.

AN1048

Serious Adverse Experience: Death

AN1048, a 46-year old black female entered the study with Stage IV cutaneous T-cell lymphoma diagnosed on 15-May-2003 with bone and node metastases. The patient's pertinent medical history includes hypothyroidism, benign thyroid nodule, mitral regurgitation, fungal pneumonia, hypertension, ureteropelvic junction obstruction, cardiomegaly, aortic valve insufficiency, tachycardia, atrial fibrillation, congestive heart failure, diastolic heart failure, potassium, magnesium, and candidiasis. Prior oncologic treatment(s) include radiotherapy, mechlorethamine, triamcinolone, bexarotene, interferon, pentostatin and gemcitabine. Concomitant medications included furosemide, ciclopirox, ramipril, digoxin, carvedilol, voriconazole, diflucan, and levothyroxine.

The patient started treatment with Vorinostat 400 mg by mouth once a day on 16-Mar- 2005.

On 09-Nov-2004, the patient had a transesophageal echo performed and the results revealed the left atrium was severely dilated, elevated left atrial pressure, and moderate mitral regurgitation. It was noted the patient was seen at the Dermatology clinic on 02-Mar-2005. An EKG on 02-Mar-2005 showed normal sinus rhythm, rate 83 with left atrial enlargement and anterior infarct. Chest x-ray revealed multiple fluffy nodules present throughout the lung fields associated with mediastinal and hilar adenopathy. These nodules probably represent pulmonary parenchymal. Laboratory tests revealed LDH 418 U/L and potassium 3.9 mEq/L. It was also noted the patient received her last radiation treatment to the localized axillary lymph nodes on 01-Mar-2005 due to rapid progression of disease.

A CT scan on 04-Mar-2005 revealed progressive retroperitoneal and pelvic lymphadenopathy, and new bilateral lung nodules and masses which are concerning for lymphoma. It was also reported that the patient was short of breath and had cough. There were bibasilar rales that do not clear with cough.

On 06-Mar-2005, at the patient's screening visit she reported a cough that productive with whitish sputum which grew *Candida albicans*, decreased taste after radiation, and had difficulty breathing, and she had been out of her furosemide for about a week. Her lungs revealed bibasilar rales and she had a mitral valve regurgitation murmur. Laboratory test results revealed a magnesium count of 1.5 MEq/L (baseline value not available).

On [redacted] the patient stated that she “is feeling well”. She also reported that she did not get her carvedilol refilled and had stopped taking the medication after the initial month. The patient was restarted on ramipril at 10 mg and it was recommended that she is likely to need a mitral valve replacement.

On [redacted] (Day 1), the patient “felt bad” but did not go to the emergency room and was found dead in her bed the next morning on [redacted]. It was noted that emergency personnel threw out all the patient’s medications and it is unknown if the patient had actually taken study therapy. An autopsy was not performed. It was noted that on [redacted] the patient was seen by her cardiologist and was cleared prior to starting study therapy. The cardiologist had restarted the patient on ramipril. On [redacted] unsuccessful attempts were made to contact the patient’s family. Laboratory values early in the day on [redacted] revealed a potassium count of 3.0 mEq/l and LDH count 573 U/L.

In the opinion of the investigator, although it was not confirmed, it was “assumed that the patient took study therapy as instructed”, therefore the investigator considers the serious adverse experience Grade 5 death was possibly related to study therapy.

AN1057

Serious Adverse Experience: Syncope

AN1057, a 67-year old white male entered the study with Stage IV cutaneous T-cell lymphoma diagnosed on 27-Jan-2001. The patient’s pertinent medical history includes coronary artery disease, hypertriglyceridemia, hypothyroidism, and pollakiuria. Prior oncologic treatment(s) include radiotherapy, triamcinolone, hypersensitive to bexarotene, and denileukin diftitox. Concomitant medications included atenolol, prednisone, methotrexate and atrovastatin.

The patient started treatment with Vorinostat 400 mg once a day on [redacted].

On [redacted] (Day 27), the patient was alert and oriented x 4 and ambulatory. At the clinic, during the skin assessment, the patient had a syncopal episode from a sitting position. The patient was placed in Trendelenburg position but was unresponsive for 20- 30 seconds. Vitals signs during episode included BP 120/90 mmHg, pulse 64 beats/min, respiratory rate 14 breaths/min, and temperature 36.6°C. The patient aroused on his own and was placed on a bradycardia-SR monitor. The patient was treated with intravenous saline and supplemental oxygen and was transported to the emergency department and admitted for inpatient observation. The patient reported a good appetite and no recent weight loss. No previous syncopal episodes were reported. The patient recalled the event and was alert and oriented. A neurological work up was not performed. Troponin levels were negative x 3. An ECG showed sinus arrhythmia and bradycardia at a rate of 50, normal intervals and non-specific ST-T wave changes. There was no significant ischemia or infarct patterned noted. The patient denied nausea, vomiting or diarrhea and did not feel dehydrated the day of the syncope. The discharge impressions included no evidence of dehydration, marked bradycardia since starting beta blocker in January 2005, no evidence of ischemia, tachyarrhythmia, angina or dyspnea on exertion, nothing to suggest a neurological cause and the incident was a combination of bradycardia and questionable vaso vagal reaction. The patient was discharged to home with a recommendation to follow up with a cardiologist in one week. Study therapy was discontinued on 03-May- 2005.

In the opinion of the investigator, the serious adverse experience Grade 4 syncope was considered related to study therapy.

AN1058

Serious Adverse Experience: Pulmonary Embolism

AN1058, a 57-year old white male entered the study with Stage IIB mycosis fungoides diagnosed on 22-Aug-2003. The patient's pertinent medical history includes anxiety disorder, hypertension, pruritus, and menopause. Prior oncologic treatment(s) include mechlorethamine, bexarotene and acitretin. Concomitant medications included conjugated estrogens, citalopram, hydrochlorothiazide, topical dexoximetasone, and paroxetine.

The patient started treatment with Vorinostat 400 mg by mouth once a day on 22-Mar-2005.

On 09-Aug-2005 (Day 141), chest computed axial tomography (CT) with contrast was performed on the patient as part of the study procedure. The chest CT revealed stable mediastinal lymphadenopathy, right lower lobe sub-segmental pulmonary embolus, and tiny pulmonary nodules, compatible with previous granulomatous disease. The patient did not report shortness of breath, leg pain or leg swelling. On 10-Aug-2005, a repeat chest CT performed on the patient demonstrated no pulmonary embolus. Subsequently, another chest CT was requested to confirm the findings. On 12-Aug-2005, a chest CT with contrast revealed no significant interval change from the chest CT performed on 09-Aug-2005. On [redacted], the patient was hospitalized for the treatment of pulmonary embolus with intravenous heparin. On [redacted], the patient was placed on warfarin therapy for anticoagulation. No action was taken with study therapy. Conjugated estrogens (HRT) were considered a contributor to this event and on [redacted] her (HRT) were reduced from 1.25 mg to .625 mg. By [redacted] the patient recovered and was discharged from the hospital on enoxaparin and warfarin. It was reported that there was no evidence of the R506Q or G20210A mutation. Follow-up information received reported that the patient appeared well and laboratory results for protein C, protein S, lupus anticoagulant and factor V mutation tests did not yield any positive findings. No further imaging studies have been performed and the patient remains under treatment for this experience. The investigator felt the pulmonary embolus may have been caused by several risk factors which included hormone replacement therapy (HRT); presence of lymphoma; and/or recent motor vehicle accident on 13-Jun-2005.

In the opinion of the investigator, the serious adverse experience Grade 4 pulmonary embolism was possibly related to study therapy.

AN1059

Serious Adverse Experience: Pulmonary Embolism

AN1059, a 64 year-old white male entered the study with Stage IV cutaneous T-cell lymphoma diagnosed on 23-Aug-1995. The patient's pertinent medical history includes pruritus, melanoma in situ, and umbilical hernia. Prior oncologic treatment(s) includes radiotherapy, psoralen long-wave ultraviolet radiation (PUVA), mechlorethamine, fluocinolone, interferon, denileukin diftitox,

corticosteroids, bexarotene, and methotrexate. Concomitant medications included temazepam, lorazepam, atorvastatin, and topical triamcinolone.

The patient started treatment with Vorinostat 400 mg by mouth once a day on _____

On _____ (Day 185), the patient experienced chest pain on inspiration, back pain, difficulty unclenching his left hand and dyspnea and was hospitalized. The patient's vital signs were temperature 36.6°C; pulse 87 beats/min; blood pressure 118/75 mmHg, and oxygen saturation 93% on room. Respiratory rate not provided. The patient's electrocardiogram (EKG) was normal. Elevated D-Dimer was 2.6. A ventilation perfusion (VQ) scan was performed showing bilateral non-matching defects with a definite segment defect on the right and a probable defect on the left was abnormal as evidenced by 1 definite segmental sized mismatch and another probable mismatch. A chest CT scan revealed an occlusive embolus in the posterior medial basal segment of the right lower lobe with pulmonary infiltrate, non-occlusive thrombus in the posterior basal segment of the right lower lobe, posterior basal segment of the left lower lobe. A bilateral femoral-popliteal duplex revealed no evidence of deep vein thrombosis (DVT) within either common femoral-popliteal venous system. The patient was diagnosis with bilateral pulmonary emboli and resultant pulmonary infarct and treated with enoxaparin and warfarin. Study therapy was discontinued on _____ due to this adverse experience. Laboratory results on _____ revealed a white blood cell count of $9.3 \times 10^3/\text{microL}$ (baseline $7.3 \times 10^3/\text{microL}$) and International Normalized Ratio (INR) 0.99 (baseline 1.1). On _____, the patient was discharged to home with an INR of 0.99. Therapy with enoxaparin was to be continued until the patient's INR was greater than 2. The patient's vital signs upon discharge were temperature 36.5°C; pulse 72; respirations 20; and blood pressure 95/61.

On 14-OCT-2005, the patient's INR was 2.1 and there were no risk factors noted in the patient's medical history for pulmonary embolism. Additionally, imaging tests and physical exam did not suggest the pulmonary embolism was related to the patient's cutaneous T-cell lymphoma. No genetic tests were performed and no further imaging studies expected. In follow-up, the investigator reported that the expected duration for "this type of" adverse event would be 6 to 8 weeks. The patient's bilateral pulmonary emboli persisted.

In the opinion of the investigator, the serious adverse experience Grade 4 pulmonary embolism was possibly related to study therapy.

AN1063

Serious Adverse Experience: Spinal Cord Injury

AN1063, an 80-year old white female entered the study with Stage IV cutaneous T-cell lymphoma diagnosed on 19-Dec-2001. The patient's pertinent medical history includes herniated disc, hypertension, high cholesterol, diabetes, shingles, cardiac murmur, edema lower limb, abnormal electrocardiograms, and back pain. Prior oncologic treatment(s) include psoralen long-wave ultraviolet radiation (PUVA), bexarotene, denileukin diftitox, triamcinolone, and prednisone. Concomitant medications included lisinopril, furosemide, glyburide, atorvastatin, hydroxyzine, amlodipine, tinzaparin, insulin (unspecified), enoxaparin, gabapentin, oxycodone, and tramadol.

The patient started treatment with Vorinostat 400 mg once a day on _____

Study therapy was discontinued on 13-Aug-2005. On [redacted] (Day 124), the patient tripped and fell. The fall resulted in a spinal cord injury and the patient was hospitalized. The patient did not experience a loss of consciousness, but did strike her head resulting in a small left frontal contusion. She immediately felt numbness and tingling in her arms and legs and was unable to move. Upon admission to the hospital, the patient did not have a fever, headache, dizziness, chest pain, shortness of breath or wheezing. The patient did report dysuria and her vital signs were stable. She was awake, alert, oriented and her speech was clear and fluent. At the hospital, a head CT scan was negative for hemorrhage. A CT scan of the cervical spine revealed multiple level degeneration with cervical stenosis and the MRI showed severe stenosis at C4-C5, C5-C6, with chronic spondylotic changes and probable soft disk herniation at C4-C5 with severe underlying cord contusion and questionable disk disruption at C5-C6. No cord hemorrhage was identified. The overall impression was a dense incomplete upper cervical cord injury secondary to stenosis at the above levels. On [redacted], the patient underwent an intra-cervical discectomy and fusion C4-C5 and C5-C6 with allograft and plate. The patient presented with upper extremity weakness, lower extremity paralysis and dysphagia. On 15-Aug-2005, a repeat CT scan of the patient's cervical spine revealed anterior cervical fusion of C4-C6. A chest X-ray, also performed on [redacted] revealed a stable lung nodule at left lateral base that likely represents a calcified granuloma; enlargement of the pulmonary arteries bilaterally, suggestive of pulmonary hypertension with no acute process identified. On [redacted] an extremity venous ultrasound with Doppler revealed no evidence of deep vein thrombosis (DVT) in either lower extremities; no sonographic evidence of DVT in the upper extremities. However, the upper extremity exam was limited in that the internal jugular veins were not able to be scanned bilaterally. On [redacted], the patient was transferred from an acute care hospital to a long-term care facility. On 19-Aug-2005, the patient was discontinued from the study due to intercurrent illness.

In the opinion of the investigator, the serious adverse experience Grade 3 spinal cord injury was considered definitely not related to study therapy.

AN1064

Serious Adverse Experiences: Ureteric Obstruction, Pelvi-Ureteric Obstruction, and Enterococcal Infection

AN1064, a 52-year old male entered the study with Stage IV cutaneous T-cell lymphoma diagnosed in 08-Sep-2004. The patient's pertinent medical history includes hypertension, nephrolithiasis, and Islets of Langerhan's hyperplasia. Prior oncologic treatment(s) include bexarotene and methotrexate. Concomitant medications included amlodipine, lisinopril, nitroglycerin, famotidine, heparin, oxycodone, cefazolin, phenazopyrine, oxybutynin, meclizine, amoxicillin and clavulanate potassium, potassium citrate, and tamsulosin.

The patient started treatment with Vorinostat 400 mg by mouth once a day on [redacted].

On 25-MAY-2005, the patient experienced heartburn and developed a non-serious adverse experience (NSAE) of diarrhea, subsequently, the patient's study therapy was down titrated to 200 mg by mouth twice a day to alleviate nausea and diarrhea. On [redacted] (Day 59) study therapy was held, as the patient underwent extracorporeal shock wave lithotripsy to the right side for renal

stones. Study therapy was reinitiated on 16-Jul-2005. The patient continued to experience renal colic associated with increased nausea and vomiting over the next two days. On 17-Jul-2005, study therapy was interrupted due to the increased nausea and vomiting.

On [redacted] (Day 62), the patient's nausea and vomiting persisted and hospitalized. The patient was placed on therapy with ondansetron and morphine for renal colic was reinstated. Computed axial tomography (CT), revealed multiple kidney stones partially obstructing the patient's right ureter. The patient was diagnosed with ureteric obstruction.

On [redacted], the patient underwent a percutaneous nephrostomy and several kidney stones were removed. The patient was discharged with the nephrostomy tube in place and study therapy was reinitiated at a reduced dose of 300 mg, once day, five days per week.

It was reported that on [redacted] (Day 76), the patient underwent lithotripsy to the left side and placement of a urethral stent, which was planned to be removed within 2 to 3 weeks. The right sided nephrostomy tube was removed and an ultrasound showed no evidence of renal obstruction. It was also reported that the patient may undergo a kidney biopsy. Since the patient's creatinine was noted to be 2.6 mg/dL (baseline 1.2 mg/dL), it was planned to check the patient's serum creatinine on a weekly basis, and hydration was encouraged. The patient developed an (NSAE) of nausea and study therapy was interrupted. The nausea resolved the same day and study therapy was reinitiated. As of 05-Aug-2005 on 400 mg of Vorinostat, the patient had recovered from renal obstruction, and study therapy was increased to 400 mg by mouth once a day. On 17-AUG-2005, the patient's creatinine was 1.2 mg/dL, and the patient was being followed closely by his urologist.

On [redacted] 5, the patient's ureteral stent was removed. However, later that day, the patient complained of flank pain similar to his previous renal colic and he was treated with oxycodone. The patient developed a fever 38.8°C and chills and was hospitalized for urosepsis. Treatment with intravenous cefepime was initiated. On 23-AUG-2005, a CT scan was performed, which revealed multiple renal calculi at the left ureterovesicular junction, and the patient underwent percutaneous nephrostomy tube placement. Cultures obtained from the patient's nephrostomy tube revealed growth of *enterococcus faecalis*. Treatment with amoxicillin and clavulanate potassium for 14 days was initiated on 25-Aug-2005. The patient was also placed on therapy with tamsulosin, and oxycodone as needed. On [redacted], the patient was discharged from the hospital with the nephrostomy tube in. On 30-Aug-2005, the patient's nephrostomy tube was removed after a radiographic study showed only one small stone in the left kidney. The patient was placed on therapy with potassium citrate, citrate levels might have been contributing to the formation of the patient's stones. Results from analysis of previous kidney stones were outstanding. On an unspecified date, the patient recovered from the renal obstruction. By 05-Sep-2005, the patient resumed study therapy at a reduced dose of 300 mg by mouth, five days per week. On 09-Sep-2005, study therapy was discontinued and the patient was discontinued from the study due to unacceptable toxicity.

In the opinion of the investigator the serious adverse experience Grade 2 ureteric obstruction, Grade 3 pelvi-uerteric obstruction and Grade 3 *enterococcal* infection were not related to study therapy.

AN1070

Serious Adverse Experience: Pulmonary Embolism

AN1070, a 55-year old white male entered the study with Stage IV cutaneous T-cell lymphoma diagnosed 01-Jul-1999. The patient's pertinent medical history includes swelling of left leg, foot drop, fasciotomy, arthroscopic surgery left knee, pain left calf, history of lower extremity edema, and shingles. Prior oncologic treatment(s) include carmustine, clobetasol, mechlorethamine, denileukin difitox, bexarotene, and psoralen long-wave ultraviolet radiation (PUVA). There were no significant concomitant medications.

The patient started treatment with Vorinostat 400 mg by mouth once a day on

On — (Day 28) the patient had been experiencing chest pain and inspiration with cough and was sent to the emergency room for evaluation. A CT angiogram revealed evidence of pulmonary embolism and the patient was hospitalized for anticoagulation. Upon admission, the patient was treated with enoxaparin, intravenous fluids, ceftriaxone and levofloxacin. Study therapy was interrupted on — due to this adverse experience. On 07-Jul-2005, the patient's leg became swollen and red and he received increased doses of intravenous fluids and dopamine for blood pressure support. A CT scan of the left leg showed extensive cellulitis with no signs of fasciitis and imipenem and cilastatin was added to the antibiotic regimen. The redness, swelling and tenderness subsided and the patient was treated with warfarin and INR became therapeutic on 12-Jul-2002. The patient recovered and was discharged to home on — and to remain on warfarin. The investigator believed the pulmonary embolus was most likely related to venous compression secondary to large inguinal lymphadenopathy. The swelling in the leg was likely from what was a DVT that was to be seen by an ultrasound, and was most likely in the pelvis. It was noted that the patient had a history of lower extremity edema and while on study therapy, had two lower extremity ultrasounds (25-May-2005 and 06-June-2005 prior to study treatment) that were negative for deep vein thrombosis (DVT). The patient was discontinued from the study on 04-Aug-2005 due to disease progression.

In the opinion of the investigator, the serious adverse experience of Grade 4 pulmonary embolism was considered possibly related to study therapy.

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10.2 Line-by-Line Labeling Review

- Labeling Review is scheduled for a later date.

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/s/

Bhupinder Mann
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Rajeshwari Sridhara
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John Johnson
9/9/2006 10:43:16 AM
MEDICAL OFFICER

EXPERT OUTSIDE CONSULTANT REVIEW OF THE NDA
PHOTOGRAPHS

NDA 21991
DRUG Vorinostat
APPLICANT Merck
CONSULTANT Mark Pittelkow, M.D.
Professor of Dermatology
Mayo Clinic College of Medicine
Rochester, Minnesota, USA

DATE OF CONSULTATION August 21, 2006

In study 001 there were 74 Cutaneous T-cell Lymphoma (CTCL) patients. The Applicant reported objective tumor responses in 18 of 61 patients with Stage IIB or greater disease and 4 of 13 patients with less than Stage IIB disease.

Dr Pittelkow examined the digital photographs of all 22 of the CTCL patients with reported tumor responses.

In the 18 reported tumor responders with Stage IIB or greater disease Dr. Pittelkow scored 7 patients as responders, 4 patients as equivocal responders, 3 patients as not responding, and 4 patients as un-evaluable (due to poor quality or missing photographs).

In the 4 reported tumor responders with less than Stage IIB disease (all Stage IB) Dr. Pittelkow scored 1 patient as a responder, 1 patient as equivocal, and 2 patients as not responding.

Dr. Pittelkow was requested to review the photographs only. He did not review the NDA and did not have much information on Vorinostat safety. Thus he did not make a recommendation regarding approval of the NDA. But he indicated he was not very favorably impressed with the photographs he reviewed. He believes only a small fraction of CTCL patients would benefit from Vorinostat and usually for a relatively short

period of time. He does not believe Vorinostat, as a single agent, would be a significant addition to the treatment armamentarium for CTCL

John R. Johnson, M.D.
Clinical Team Leader Oncology Drugs

Bhupinder Mann, M.D.
Medical Officer Oncology Drugs

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John Johnson
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Clinical Team Leader Review of NDA

NDA 21991

APPLICANT Merck and Co, Inc.

STAMP DATE 4/7/06

REVIEW COMPLETION DATE 9/18/06

DRUG Established Name Vorinostat
 (Proposed) Trade Name Zolinza™

THERAPEUTIC CLASS Histone deacetylase inhibitor

FORMULATION 100 mg capsules for oral administration

DOSING REGIMEN 400 mg orally once daily with food

PROPOSED INDICATION Zolinza™ is indicated —

EFFICACY

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. Patients have progressive, persistent, or recurrent disease on or following two systemic therapies, one of which must contain bexarotene unless the patient is intolerant to or not a candidate for bexarotene therapy.

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

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)

All tumor responses except one were partial responses.

- 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.

SAFETY

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. Seven 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.

Specific Laboratory Abnormalities in CTCL monotherapy patients at 400 mg dose:

- The most common laboratory abnormalities seen in the patients assigned to Vorinostat monotherapy at a dose of 400 mg once daily, when *all grades* are included, occurring in at least 10% of patients:
- | | |
|---|-------|
| ○ Increased serum glucose in 60 of 87 patients | 69.0% |
| ○ Increased serum cholesterol in 49 of 74 patients | 66.2% |
| ○ Increased serum triglycerides in 49 of 74 patients | 66.2% |
| ○ Increased serum creatinine in 39 of 87 patients | 44.8% |
| ○ Decreased total serum carbon dioxide in 28 of 74 patients | 37.8% |

- Increased serum alkaline phosphate in 18 of 87 patients 20.7%
- Decreased serum phosphorus in 17 of 87 patients 19.5%
- Increased serum aspartate aminotransferase in 14 of 87 patients 16.1%
- Decreased serum potassium in 14 of 87 patients 16.1%
- Increased serum alanine aminotransferase in 13 of 87 patients 14.9%
- Decreased serum calcium in 13 of 87 patients 14.9%
- Decreased glucose in 10 of 87 patients 11.5%

CONCLUSION

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.

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.

**APPEARS THIS WAY
ON ORIGINAL**

John R. Johnson, M.D.
Clinical Team Leader
Division Drug Oncology Products
September 18, 2006

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