Vorinostat for Treatment of Cutaneous Manifestations of Advanced Primary Cutaneous T-Cell Lymphoma

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Abstract

Purpose: To discuss vorinostat approval for treatment of cutaneous manifestations of advanced cutaneous T-cell lymphoma (CTCL).

Experimental Design: Data from 1 single-arm, open-label, multicenter pivotal trial and 11 other trials submitted to support the new drug application for vorinostat in the treatment of advanced primary CTCL were reviewed. The pivotal trial assessed responses by changes in overall skin disease score using a severity-weighted assessment tool (SWAT). Vorinostat could be considered active in CTCL if observed response rate was at least 20% and the lower bound of the corresponding 95% confidence interval (95% CI) excluded 5%. Patients reported pruritis relief using a questionnaire and a visual analogue scale.

Results: The pivotal trial enrolled 74 patients with stage IB or higher CTCL. Median number of prior treatments was 3, and 61 patients (82%) had stage IIB or higher disease. The objective response rate in the skin disease assessed by change in the overall SWAT score from the baseline was 30% (95% CI, 18.5 to 42.6) in patients with stage IIB or higher disease. Median response duration (end of response defined by 50% increase in SWAT score from the nadir) was 168 days. Median time to tumor progression was 148 days for overall population and 169 days for patients with stage IIB or higher disease. Assessment of pruritis relief was considered unreliable.

Conclusions: Vorinostat showed activity in CTCL, and skin responses were a clinical benefit. Vorinostat was approved for treatment of cutaneous manifestations of CTCL. A nonblinded, single-arm trial did not allow a reliable assessment of pruritis relief.

Background

Vorinostat or suberoylanilide hydroxamic acid is a histone deacetylase (HDAC) inhibitor; chemical name: *N*-hydroxy-*N*′-phenyloctanediamide. The drug product Zolinza (Merck & Co. Inc., Whitehouse Station, NJ) is an opaque white hard gelatin capsule containing 100 mg of vorinostat in an immediate-release formulation for p.o. administration. During early studies, vorinostat was found to be active in cutaneous T-cell lymphoma (CTCL), and further clinical development was planned.

CTCL is a rare disease (1). Approximately 1,000 to 1,500 new cases are reported each year in the United States. Clinical staging is based on the tumor-node-metastasis (TNM) system and circulating Sézary cells (2). Early disease may have symptoms, e.g., pruritis, but the clinical course is often indolent with minimal impact on overall survival (3). A variety of topical therapies is used. In many patients, the disease progresses, and lymph nodes and blood show the presence of malignant cells (1, 3). Advanced disease may become refractory to treatment, pruritis can be severe, and clinical complications may result, e.g., skin breakdown and local and systemic infections. A variety of agents are in use for the treatment of advanced disease, but better therapies are needed (3, 4).

The applicant (Merck & Co. Inc.) and the Food and Drug Administration (FDA) discussed the vorinostat clinical development program for advanced CTCL at an end of phase 2 meeting in September 2003. It was agreed that a well-conducted single-arm study might support the registration of vorinostat in CTCL patients who had failed two prior systemic therapies. Subsequently, in December 2003, the applicant submitted a proposal for a single-arm pivotal trial for a Special Protocol Assessment (SPA). Patients with advanced disease (stage IB or higher) that was progressive, persistent, or recurrent on or following two systemic therapies were eligible for the pivotal trial. One of the systemic therapies must have contained bexarotene, unless the patient was intolerant or not a candidate for bexarotene. It was recommended to enroll an adequate number of patients with stage IIB and higher disease and to analyze them separately from the patients with earlier stage disease. The primary end point of the study was overall response in the skin disease based on changes in the severity-weighted assessment tool (SWAT) scores. Additional supportive information was to be provided by standard sets of digital

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photographs and worksheets incorporating body diagrams. Vorinostat received fast-track designation in December 2003 and orphan drug designation in March 2004.

Pharmacology and toxicology. Vorinostat inhibits class 1 and class 2 HDACs. In the transformed cells, accumulation of hyperacetylated histones and inhibition of proliferation and induction of apoptosis are observed. The mechanism of antineoplastic activity of vorinostat has not been fully characterized, however.

Toxicology studies in rats and dogs were notable for gastrointestinal and hematologic effects; these were partially or completely reversible by 4 weeks of recovery. Reproductive toxicity studies in female rats showed increased peri- and postimplantation losses and decreased number of live fetuses per pregnant female. Transplacental transfer of vorinostat metabolites occurs, and developmental toxicities (decreased fetal weight and multiple skeletal abnormalities) were observed in rats and rabbits.

Pharmacokinetics. After p.o. administration of a single 400-mg dose of vorinostat to 24 patients in fasting state, the median time to the maximum concentration (T_{max}) was 1.5 h (range 0.5-10), the mean maximum serum concentration (C_{max}) was 1.2 μmol/L [coefficient of variation (CV), 29%], and the area under the curve (AUC) was 4.1 μmol/L h (CV 44%). When administered with a high fat meal, the median T_{max} was 4 h (range 2-10), the C_{max} was 1.15 μmol/L (CV, 47%), and the mean AUC was 5.5 μmol/L h (CV, 32%). The elimination half-life ($t_{1/2}$) of vorinostat averaged 2 h. No accumulation was noted upon chronic dosing for 28 days. Vorinostat is 71% bound to plasma proteins over serum concentrations of 2 to 200 μmol/L. It is predominantly eliminated via metabolism (glucuronidation and hydrolysis followed by β-oxidation), and <1% of the administered dose is recovered as unchanged drug in urine: renal excretion plays only a minor role in elimination of vorinostat. Biotransformation by cytochrome P450 is negligible. Details of the pharmacokinetics of p.o.–administered vorinostat in patients with advanced cancer, including effects of food and multiple dosing, have been published (5).

Materials and Methods

Review process. The FDA Division of Drug Oncology Products and Division of Biometrics 1 reviewed the clinical data from a single pivotal trial (Protocol 001) and a single supportive trial (Protocol 005) to evaluate the efficacy of vorinostat in the treatment of advanced CTCL. Data from these 2 and 10 other phases 1 and 2 clinical studies were reviewed to evaluate the safety of vorinostat. Additional data from a safety update of the pivotal trial, submitted to the FDA in July 2006, were reviewed. In its evaluation of safety and efficacy of vorinostat, the FDA also considered the applicant's oral presentation of vorinostat studies (June 2006) and the pertinent peer-reviewed publications. The FDA Division of Scientific Investigations provided on-site clinical inspections of selected study sites. The FDA Study Endpoints and Label Development Team evaluated the data submitted to support the patient-reported outcome of pruritis.

Study design. The pivotal trial (Protocol 001) was an open-label, single-arm, multicenter study. The supportive trial (Protocol 005) was an open-label, three-arm, nonrandomized, single-center study conducted before the pivotal trial. Details of the supportive trial are published (6).

Patient selection. Patients who were ≥18 years of old, with Eastern Cooperative Oncology Group performance status of 0 to 2 and life expectancy >3 months were eligible to participate in the pivotal trial (Protocol 001) after providing an informed consent if they had advanced CTCL with histologic diagnosis documented within 1 year before enrollment. Advanced disease was defined as stage IB or higher CTCL that was progressive, persistent, or recurrent on or following two systemic therapies, one of which must contain bexarotene, unless the patient was intolerant or not a candidate for bexarotene (described in the oral bexarotene package insert). Persistent disease was defined by the lack of at least 50% improvement on therapy for at least 3 months, unless the patient was intolerant to therapy because of the toxicities. Adequate bone marrow, hepatic, and renal functions were required. Concurrent chemotherapy, radiotherapy, PUVA, photopheresis, biological therapy, oral or topical retinoids, and investigational agents were not allowed during the study. Use of topical or systemic corticosteroids was not allowed on study except in Sezary syndrome patients who were on systemic steroids for at least 3 months or patients on a stable daily dose equivalent to ≤10 mg of prednisone for at least 4 weeks immediately before receiving study therapy or patients who had been on topical steroids for at least 3 months on a dose that did not exceed 0.1% triamcinolone acetonide cream or equivalent for at least 4 weeks immediately before receiving study therapy. Pregnancy, lactation, prior or current use of any HDAC inhibitor, acute infections requiring i.v. antibiotics or antifungal agents, HIV infection, and active hepatitis A, B, or C also excluded the patients from the study.

Study treatment. The starting dose of vorinostat was 400 mg once daily, taken p.o., preferably with food. Two dose reductions were allowed for toxicity: 300 mg once daily or 300 mg once daily for 5 consecutive days per week, if necessary. Treatment was continued until progressive disease, unacceptable toxicity, lack of efficacy, or a patient's withdrawal of consent.

Study objectives and end points. The primary objective of the study was to determine response rate to oral vorinostat in the skin disease in advanced CTCL. Secondary objectives were assessments of time to objective response, response duration, time to progression, pruritis relief, and safety and tolerability of vorinostat. In eligible patients, the overall skin disease was assessed and scored at baseline and at scheduled follow-up visits using a SWAT. Abnormal skin not elevated from the normal skin was defined as patch, abnormal skin elevated from the normal skin by <5 mm was defined as plaque, and a plaque elevated ≥5 mm was considered as tumor. Percentages of the total body surface area involved with patch, plaque, and tumor were severity weighted by multiplying with factors of 1, 2, and 4, respectively, and summed to give an overall SWAT score. Response rate was based on assessment of the overall skin disease in patients with CTCL stage IIB and higher as measured by SWAT. A clinical complete response (CCR) required 100% improvement, with no evidence of the disease, and a partial response (PR) required at least 50% decrease in the SWAT score compared with the baseline, both required confirmation by 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 or ≯25% increase in the SWAT score compared with the baseline. Progressive disease (PD) required at least a 25% increase in the SWAT score compared with the baseline 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 with the baseline. Patients assessed to have PD must be taking the study drug actively and required confirmation of PD by a second assessment 1 to 4 weeks later whenever possible. Time to progression was measured from the start of treatment to when the criteria for progression were first met. Time to response was measured from the start of treatment to the time when criteria were first met for CCR or PR, whichever was recorded first. Duration of overall response was measured from the time when criteria were first met for CCR or PR to the time when an increase in the SWAT score was >50% of the difference between the baseline score and the nadir score, and if that magnitude of increase in the score was confirmed by a

second assessment at 1 to 4 weeks thereafter. Intensity of pruritus was evaluated using a patient-completed questionnaire at baseline and at each follow-up visit. A 10-point scale was used, and skin itch over the past week was assessed: 0 = no itching and 10 = itching as bad as it can be. A baseline pruritus score of ≥3 at baseline was required for assessment. A three-point decrease in pruritis intensity, without an increase in the use of antipruritic medications and confirmed by a second assessment at least 4 weeks later, was considered clinically significant.

Safety and tolerability of vorinostat was assessed by collecting data on the extent of exposure to vorinostat and the observed adverse events (AE) in the pivotal and supportive trials in the CTCL patients and 10 other trials which included vorinostat treatment in patients with other solid tumors and hematologic malignancies. The AEs were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events Version 3.0 (NCI CTCAE V 3.0). Relationship of the AE to vorinostat was categorized, by the investigator, as definitely related, probably related, possibly related, probably not related, or definitely not related to the test drug.

Follow-up visits and evaluations. After the first visit for baseline assessment, follow-up study visits were scheduled at weeks 2, 4, 6, and 8, and every 4 weeks thereafter until the patient discontinued from the study. Clinical evaluation at follow-up visits consisted of history and physical examination, electrocardiogram, and objective assessment of disease status by obtaining SWAT score. When applicable, a patient completed the pruritis questionnaire. Laboratory evaluation included monitoring of complete blood count, hepatic and renal functions, serum glucose, electrolytes, albumin, total proteins, lactic dehydrogenase, uric acid, calcium, magnesium, phosphorus, and lipids. All patients had computed tomography (CT) scans of chest, abdomen, and pelvis, and peripheral blood flow cytometry for Sézary cell count at baseline and, when abnormal, at follow-up visits. For each patient in the study, global half-body photographs and close-up photographs of distinct individual lesions were taken serially to document change in the skin disease. These photographs were supportive only and were not used to derive SWAT scores.

Statistical methods. The primary efficacy end point of this study was the proportion of patients with stage IIB or higher disease with an objective response in the overall skin disease. Determination of sample size was based on the assumptions that the highest theoretical spontaneous response rate in patients with CTCL stage IIB or higher who had received at least two systemic therapies was estimated to be 5%, and that oral vorinostat could be considered active for treatment of such patients if the observed response rate in the overall skin disease was at least 20% and the lower bound of the corresponding 95% confidence interval (95% CI) excluded 5%. Enrollment of 50 to 70 patients with stage IB and higher disease was planned to ensure that there were at least 50 evaluable patients with stage IIB and higher disease. The observed response rate and the corresponding 95% CI were calculated. Summary statistics were provided for secondary efficacy end points: duration of response, time to progression, relief of pruritis, and time to objective response. Efficacy analyses were also done in three prespecified subgroups: Sézary syndrome patients, patients with T3 tumor disease, and 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.

Results

The pivotal trial (Protocol 001), conducted by 18 centers in the United States and Canada, opened for accrual on the March 17, 2004, and enrolled 74 patients who had stage IB or higher advanced CTCL. The initial New Drug Application submission in April 2006 contained data collected until the November 23, 2005, and an update submitted in June 2006 included the data collected until the April 11, 2006. Patient and disease characteristics at baseline are shown in Table 1. Notably, the median age of the study population was 60 years; 61 (82%) had stage IIB or higher CTCL, and about a third of the patients were on concomitant therapies for other diseases. Previous CTCL therapies had included bexarotene 71 (96%), IFN 47 (64%), photopheresis 27 (37%), methotrexate 26 (35%), denileukin diftitox 23 (31%), glucocorticoids 18 (24%), doxorubicin 13 (18%), gemcitabine 12 (16%), cyclophosphamide 9 (12%), and chlorambucil 7 (10%). The median number of days on protocol treatment was 118. During the study, 10 patients required one or more dose modifications, and 9 patients discontinued study treatment due to AEs. By the November 23, 2005 data cutoff date, 16 patients had continued or completed study treatment and 58 had discontinued: 25 due to progressive disease, 9 due to clinical AEs, and 24 due to lack of efficacy, withdrawal of consent, or unacceptable toxicity.

Analysis of efficacy. Objective responses to vorinostat by all patients as treated and by per-protocol analysis are shown in Table 2. Median times to response were 55 and 56 days, respectively, in the overall and stage IIB or higher disease patients. All responses except one were partial. In all of the

Table 1. Patient and disease characteristics at baseline (Protocol 001, *N* = 74)

Age (y)	
Median (range)	60 (39-83)
Gender	
Male	38 (51)
Female	36 (49)
CTCL stage	
IB	11 (15)
IIA	2 (3)
IIB	19 (26)
III	22 (30)
IVA	16 (21)
IVB	4 (5)
Racial origin	
Asian	1 (1.4)
Black	11 (15)
Other	1 (1.4)
White	61 (83)
Time from initial CTCL diagnosis (y)	
Median (range)	2.6 (0-27)
Clinical characteristics for exploratory analysis	
Presence of clinically abnormal lymph nodes	34 (46)
Presence of histologically involved lymph nodes	19 (26)
Presence of skin tumor	22 (30)
Presence of Sézary syndrome	30 (40)
Number of prior systemic treatments, median (range)	3 (1-12)
Body surface area involvement (%), median (range)	
Patch	16 (0-100)
Plaque	6% (0-98)
Tumor	0% (0-92)
SWAT score	
Mean (SD)	82 (70)
Median (range)	75 (1.5-366)
Pruritis score	
Mean (SD)	6 (2.5)
Median (range)	6 (0-10)

NOTE: Values in table are expressed as *n* (%), unless otherwise noted.

Table 2. Objective response rates to vorinostat

Patient populations	All patients as treated			Per-protocol analysis		
	n	Responders, *n* (%)	95% CI	*n*	Responders, *n* (%)	95% CI
All patients	74	22 (30)	19.7-41.5	65	21 (32)	21.2-45.1
Stage IIB or higher	61	18 (30)	18.5-42.6	54	17 (32)	19.5-45.6
Patients with Sézary syndrome	30	10 (33)	17.3-52.8	27	9 (33)	16.5-54.0
Patients with T3 tumor disease	22	5 (23)	7.8-45.4	20	5 (25)	8.7-49.1

analyzed subsets, the response rate was about 30%. The observed response rate in patients with IIB or higher stage disease was 30% (95% CI, 18.5-42.6) on the all-patients-as-treated analysis and 32% (95% CI, 19.5-45.6) on the per-protocol analysis. This showed the activity of vorinostat in advanced CTCL. Patients who had failed bexarotene had response rate of 31% (5/16). This rate was similar to the rate (29%, 2/7) observed in the patients who had earlier responded to bexarotene. Median response duration had not been reached at the time of analysis and was estimated to be >6 months using the applicant's definition of response duration. Defining end of response by a 50% increase in the SWAT score from the nadir, the FDA estimated median response duration as 168 days. Median times to tumor progression were estimated as 148 days for the overall population and 169 days for the patients with stage IIB or higher disease.

Analysis of safety. Exposure and AE data from the pivotal and supportive trials and 10 other trials, which included vorinostat treatment, were reviewed for assessment of safety. The latter trials included patients with advanced solid tumors and hematologic malignancies who differed from the CTCL patients by the natural histories of their diseases, extent of visceral and bone marrow involvement, and past treatments. Data from these trials were reviewed in detail and considered in assessment of vorinostat safety. Because the AE profiles in patients with different disease (CTCL versus other malignancy) were noted to be different, and vorinostat was dose dependent, only the AEs seen in the pivotal trial are presented here. In the pivotal trial, all patients received 400 mg of vorinostat p.o. daily.

Clinical AEs were reported by the majority of the patients: 70/74 (95%). However, serious clinical adverse experiences were reported by 16 (22%) patients only, 8 of these were classified by the investigators as drug related, and 9 (12%) patients discontinued study therapy due to a clinical AE. Specific clinical AEs of all grades with incidence of ≥10% reported during the study period are shown in Table 3. It is notable that the vast majority of the AEs reported for this study were considered drug related by the investigators. In addition, four cases of pulmonary embolism and one each of deep venous thrombosis, myocardial infarction, ischemic stroke, syncope, dehydration, gastrointestinal hemorrhage, sepsis, streptococcal bacteremia, and enterococcal infections were reported. Three deaths were reported on the study. One was attributed to ischemic stroke, one was attributed to progressive disease, and for one, the cause was reported as unknown.

Laboratory abnormalities, at baseline and at anytime during the study, were seen in a large number of patients. Table 4 shows the number of patients who had post-baseline changes in hematology and chemistry laboratory tests, whether these were worse or improved, and whether these were clinically meaningful. A clinically meaningful change was a change from a baseline value of <CTCAE Grade 3 to any post-baseline value of ≥CTCAE Grade 3, or a change from CTCAE Grade 0 to ≥Grade 2.

Discussion

CTCL is a rare disease with a relatively long clinical course: 5-year survival can be as high as 65% in patients with stage IIB

Table 3. Clinical AEs reported by ≥10% patients (*N* = 74)

	All reported AEs, *n* (%)		AEs classified as drug related by the investigator, *n* (%)	
	All grades	Grades 3-5	All grades	Grades 3-5
Diarrhea	38 (51)	0	36 (49)	0
Fatigue	38 (51)	5 (7)	34 (46)	4 (6)
Nausea	32 (43)	3 (4)	32 (43)	3 (4)
Anorexia	20 (27)	2 (3)	19 (26)	2 (3)
Dysgeusia	20 (27)	0	18 (24)	0
Weight loss	15 (20)	1 (1)	14 (19)	1 (1)
Alopecia	14 (19)	0	13 (18)	0
Chills	13 (18)	1 (1)	9 (12)	1 (1)
Constipation	12 (16)	0	8 (11)	0
Muscle spasms	12 (16)	2 (3)	12 (16)	2 (3)
Dizziness	11 (15)	1 (1)	5 (7)	1 (1)
Vomiting	11 (15)	1 (1)	9 (12)	0
Pruritis	10 (14)	1 (1)	1 (1)	0
Headache	9 (12)	0	4 (6)	0
Peripheral edema	9 (12)	0	2 (3)	0
Upper respiratory tract infection	9 (12)	0	2 (3)	0
Dry mouth	8 (11)	0	8 (11)	0

Table 4. Patients with post-baseline changes in hematology and chemistry laboratory tests (N = 74)

Laboratory test	Patients with a change in the post-baseline test, *n* (%)*	Improved	Worsened	Clinically meaningful change, *n* (%)†
Hematology				
Platelet count	31 (42)	0	31	6 (8)
Hemoglobin	27 (36)	0	27	5 (7)
WBC count	21 (28)	4	17	6 (8)
Neutrophil count	10 (14)	1	9	8 (11)
Chemistry				
Hyperglycemia	40 (54)	0	40	18 (24)
Hypertriglyceridemia	34 (46)	2	32	2 (3)
Creatinine increased	30 (41)	0	30	3 (4)
Proteinuria	30 (41)	1	29	3 (4)
Total CO_2	23 (31)	0	23	5 (7)
Hypercholesterolemia	16 (22)	3	13	1 (6)
Phosphorus	14 (19)	0	14	8 (11)
Hypokalemia	10 (14)	1	9	1 (1)
Alanine aminotransferase increased	10 (14)	0	10	0 (0)
Hyponatremia	7 (9)	1	6	1 (1)
Hyperkalemia	4 (5)	0	4	3 (4)
Hypoglycemia	4 (5)	0	4	1 (1)

*Number of patients with at least one post-baseline value. Patients without any change from the baseline are excluded.
†From <CTCAE Grade 3 to ≥CTCAE Grade 3 or from CTCAE Grade 0 to ≥CTCAE Grade 2.

and 15% in patients with stage IVB disease. This makes conduct of adequately powered, randomized, controlled clinical trials using survival-based end points impractical. Accordingly, response rate has been the basis for approval of treatments in this disease.

Denileukin diftitox, a recombinant fusion protein designed to direct cytotoxic action of diphtheria toxin to cells expressing interleukin-2 (IL-2) receptor, received accelerated approval in February 1999 for 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, two doses of denileukin diftitox (9 or 18 μg/kg/day) were administered i.v. Tumor response rate assessed using 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 for an overall tumor response rate of 30%: 7 CRs and 14 PRs in 71 patients.

Bexarotene received approval in December 1999 based on two-multicenter, open-labeled, historical-control studies. In 62 patients with early- and advanced-stage disease refractory to at least one prior systemic therapy, bexarotene given 300 mg/m^2/day p.o. produced an overall response rate of 32%: 1 CR and 19 PRs. Responses were evaluated by the Composite Assessment of Index Lesion Disease Severity. Over a median follow-up duration of 21 weeks, the relapse rate was 30% in the 20 responding patients.

The response rate of 30% with median response duration of 168 days observed in heavily pretreated advanced CTCL patients on treatment with vorinostat was considered a clinical benefit. Accordingly, vorinostat was approved for the treatment of cutaneous manifestations in patients with CTCL who have progressive, persistent, or recurrent disease on or following two systemic therapies.

The pivotal trial was a single-arm and open-label study with a small number of patients and did not provide adequate data to reliably define correlations between lymph node or Sézary cell responses and the responses noted in the skin disease. Assessment of clinical benefit measured as pruritis relief in this single-arm, nonblinded trial was considered unreliable, and the results were not included in the label.

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