This report may include approved and non-approved uses, formulations, or treatment regimens. The results reported may not reflect the overall profile of a product. Before prescribing any product mentioned in this report, healthcare professionals should consult local prescribing information for the product approved in their country.

2. Synopsis

MERCK RESEARCH LABORATORIES
MK-0683
vorinostat, Capsules
Diffuse Large B-Cell Lymphoma

CLINICAL STUDY REPORT SYNOPSIS

PROTOCOL TITLE/NO.: A Phase II Clinical Trial of Oral Suberoylanilide Hydroxamic Acid (MK-0683) in Patients With Relapsed Diffuse Large B-Cell Lymphoma (DLBCL) #013

INVESTIGATOR(S)/STUDY CENTER(S): Twenty-three (23) sites received IRB/ERC approval: 16 sites in the US, 3 sites in Canada, 2 sites in Belgium, 1 site in France, and 1 site in UK. Of these 23 sites, 21 were shipped clinical supplies.

PUBLICATION(S): None

PRIMARY THERAPY PERIOD: 13-May-2005 (first patient in) to 22-Aug-2006 (last patient out). Frozen File occurred 26-Feb-2007.

CLINICAL PHASE: IIb

DURATION OF TREATMENT: 24 weeks

OBJECTIVE(S): **Primary:** To determine the antitumor effectiveness of oral vorinostat (suberoylanilide hydroxamic acid, MK-0683) as measured by overall objective response rate (ORR) in patients with relapsed DLBCL (de novo or transformed). **Secondary:** To assess response duration (RD), progression-free survival (PFS), time to progression, time to response, and progression free survival rate at 3 months and 6 months; and to assess the safety of oral vorinostat in this patient population. [redacted]

STUDY DESIGN: This was an open-label, single-arm, multicenter, Phase II study. Patients were to receive 21-day cycles of outpatient treatment with oral vorinostat until disease progression, intolerable toxicity, withdrawal of consent, or if the Investigator determined that it was in the best interest of the patient to withdraw. Patients could be treated for up to 6 months on this protocol. Patients who demonstrated clinical benefit without intolerable toxicity after 6 months on this protocol were allowed to continue treatment under a separate continuation study (Protocol 007). For those who discontinued, a post-treatment follow-up visit was conducted within 4 weeks after the last study drug dose or prior to the initiation of new treatment. At screening, slides were required for pathology review. In addition, paraffin-embedded tissue blocks or a core needle biopsy, and blood (RNA) were requested for correlative studies. Selected sites also performed additional core needle biopsies at specified intervals for correlative studies.

SUBJECT/PATIENT DISPOSITION: 50 PLANNED, 18 ACTUAL PATIENTS

	Overall
SCREENING FAILURES:	7
ENROLLED:	18
Male (age range)	9 (64 – 86)
Female (age range)	9 (59 – 78)
Median Prior Systemic Therapies	2
COMPLETED:	2
DISCONTINUED:	16
Clinical adverse experience	1
Laboratory adverse experience	0
Progression	15
Other	0

DOSAGE/FORMULATION NOS.: No patients were treated with vorinostat 400 mg by mouth twice daily for 14 consecutive days followed by 7 days of rest under the original protocol. [redacted] 7 patients received 300 mg vorinostat by mouth twice daily for 14 consecutive days followed by 7 days of rest. [redacted] 11 patients received 300 mg vorinostat by mouth twice daily for 3 consecutive days, followed by 4 days of rest. This schedule was repeated weekly with 3 weeks (21 days) comprising one treatment cycle.

The drug was supplied in 100 mg capsules.

Drug	Potency	Formulation No.	Dosage Form	Control No.
Vorinostat	100 mg	[redacted]	Capsule	[redacted]
Vorinostat	100 mg		Capsule	
Vorinostat	100 mg		Capsule	
100-mg capsules: opaque white gelatin capsules (size 3) containing the following substances: vorinostat, microcrystalline cellulose NF, sodium croscarmellose NF, and magnesium stearate NF.				

DIAGNOSIS/INCLUSION CRITERIA: Eligible patients were ≥18 years of age with measurable relapsed DLBCL (de novo or transformed) following standard first-line chemotherapy and at least one systemic salvage therapy. Other eligibility criteria included: 3 months or longer without evidence of progression on the most recent treatment; Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 2; ≥4 weeks from prior chemotherapy, radiation therapy, major surgery, or any other investigational therapy; and adequate hematologic (absolute neutrophil count ≥1.0 x $10^3/mm^3$ platelets ≥75 x $10^3/mm^3$) hepatic and renal function.

EVALUATION CRITERIA: **Efficacy Measurements:** The primary efficacy endpoint was ORR based on FDG-PET and CT scan findings. Patients had to have 1 site of measurable disease defined as tumor that could be accurately measured in at least 1 dimension of ≥2 cm by conventional CT scan or ≥1 cm by spiral CT. **Safety Measurements:** Vital signs, physical examinations, ECOG performance status, electrocardiograms (ECGs), and laboratory safety tests (CBC, comprehensive chemistry panel, PT, INR, urinalysis) were obtained or assessed prior to drug administration and at designated intervals throughout the study. ECGs were interpreted by a central reader.

STATISTICAL PLANNING AND ANALYSIS:

EFFICACY:

Efficacy was assessed by objective tumor response based on integrated CT and PET imaging findings. A listing of complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) for each patient is provided in this study report. Overall objective response rate along with its 95% exact confidence interval are also provided. Additionally, response duration, progression-free survival, time to progression, time to response, and progression free survival rate at 3 months and 6 months were analyzed.

SAFETY:

All 18 patients who received at least 1 dose of oral vorinostat were included in the safety analyses. Adverse experiences were recorded by body system and preferred term. The incidences of specific adverse experiences were reported for patients as a whole. Adverse experiences were listed and summarized for the overall population.

RESULTS:

EFFICACY:

Eighteen (18) patients with relapsed DLBCL (de novo or transformed) were enrolled. Seven (7) patients were initially treated with vorinostat at a dose of 300 mg twice daily for 14 consecutive days followed by 7 days of rest, and 11 additional patients were initially treated with a dose of 300 mg twice daily for 3 consecutive days followed by 4 days of rest. One (1) patient who received vorinostat at a dose of 300 mg twice daily for 3 consecutive days followed by 4 days of rest achieved a confirmed complete response (time-to-response [TTR] = 85 days; duration of response [DOR] = 91+ days) and the overall response rate (ORR) was 5.6% (1/18, 5.6%; 95% CI= 0.1, 27.3). One (1) patient who received initially 300 mg twice daily for 14 consecutive days followed by 7 days of rest, but eventually had the dose reduced to 200 mg twice daily for 14 consecutive days followed by 7 days of rest due to a dose limiting toxicity (DLT), had stable disease (SD) for 301 days. Fifteen (15) patients discontinued due to progressive disease (PD) and an additional patient discontinued due to PD-related adverse experiences; median time-to-progression (TTP) for all patients was 44 days. Median number of treatment cycles was 2 (range, 1-14+). Two (2) patients received study medication > 6 cycles (126 days).

SAFETY:

Oral vorinostat administered at 300 mg twice daily for 14 of 21 days was not well tolerated. Seven (7) patients were initially treated with this dose level, but 4 experienced DLTs (1 patient with Grade 3 muscle spasms; 2 patients with Grade 3 or 4 thrombocytopenia, 1 patient with Grade 4 thrombocytopenia and anemia). Of the 4 patients who developed DLTs, 3 had dose modified to 200 mg twice daily for 14 consecutive days followed by 7 days of rest and tolerated this dose. The protocol dose schedule was amended to 300 mg twice daily for 3 consecutive days followed by 4 days of rest and no other patient experienced a DLT.

All 18 patients experienced drug-related adverse experiences during the study. One patient was discontinued due to unrelated adverse experiences. Clinical adverse experiences are summarized below for the overall study population.

Clinical Adverse Experience Summary

	300 mg bid x 3d/wk (N = 11)		300 mg bid x 14d/3wk (N = 7)		Total (N = 18)	
	n	(%)	n	(%)	n	(%)
Number (%) of patients:						
With one or more adverse experiences	11	(100)	7	(100)	18	(100.0)
With no adverse experience	0	(0.0)	0	(0.0)	0	(0.0)
With drug-related adverse experiences†	11	(100)	7	(100)	18	(100.0)
With serious adverse experiences	3	(27.3)	4	(57.1)	7	(38.9)
With serious drug-related adverse experiences	1	(9.1)	2	(28.6)	3	(16.7)
Who died	2	(18.2)	0	(0.0)	2	(11.1)
Discontinued due to adverse experiences	0	(0.0)	1	(14.3)	1	(5.6)
Discontinued due to drug-related adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to serious adverse experiences	0	(0.0)	1	(14.3)	1	(5.6)
Discontinued due to serious drug-related adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)

† Determined by the investigator to be possibly, probably or definitely drug related.

The 5 most frequently reported adverse experiences by system organ class for the overall population were: Gastrointestinal Disorders (88.9%), General Disorders and Administration Site Conditions (72.2%), Blood and Lymphatic System Disorders (55.6%), Metabolism and Nutrition Disorders (55.6%), and Respiratory, Thoracic, and Mediastinal Disorders (44.4%). The 5 most common adverse experiences by preferred term regardless of grade for the overall population were diarrhea (61.1%), fatigue (50.0%), nausea (38.9%), anemia (33.3%), and vomiting (33.3%).

Common drug-related adverse experiences (AE; mostly ≤ Grade 2) were diarrhea (61.1%), fatigue (50.0%), nausea (38.9%), anemia (33.3%) and vomiting (33.3%). Drug-related AE ≥ Grade 3 included thrombocytopenia (3), asthenia (2), hyponatraemia (2), anaemia (1), fatigue (1), general physical health deterioration (1), hyperglycaemia (1), hypokalaemia (1), muscle spasms (1), and neutropenia (1). Drug-related clinical adverse experiences are summarized below for the overall study population.

Number (%) Of Patients With Specific Drug-related Clinical Adverse Experiences by Preferred Term (Incidence > 10% in Overall Population)

	300 mg bid x 3d/wk (N=11)		300 mg bid x 14d/3wk (N=7)		Total Patients (N=18)	
	n	%	n	%	n	%
Diarrhoea	4	(36.4)	7	(100)	11	(61.1)
Fatigue	6	(54.5)	3	(42.9)	9	(50.0)
Nausea	5	(45.5)	2	(28.6)	7	(38.9)
Anaemia	3	(27.3)	3	(42.9)	6	(33.3)
Vomiting	4	(36.4)	2	(28.6)	6	(33.3)
Anorexia	1	(9.1)	4	(57.1)	5	(27.8)
Thrombocytopenia	1	(9 1)	4	(57.1)	5	(27.8)
Asthenia	3	(27.3)	1	(14.3)	4	(22.2)
Abdominal Pain	2	(18 2)	0	(0.0)	2	(11.1)
Alopecia	1	(9.1)	1	(14.3)	2	(11.1)
Constipation	0	(0.0)	2	(28.6)	2	(11.1)
Contusion	0	(0.0)	2	(28.6)	2	(11.1)
Dizziness	0	(0.0)	2	(28.6)	2	(11.1)
Dyspepsia	1	(9.1)	1	(14.3)	2	(11.1)
Hyperglycaemia	2	(18.2)	0	(0.0)	2	(11.1)
Hyponatraemia	1	(9.1)	1	(14.3)	2	(11.1)
Muscle Spasms	0	(0.0)	2	(28.6)	2	(11.1)
Pyrexia	2	(18.2)	0	(0.0)	2	(11.1)
Weight Decreased	0	(0.0)	2	(28.6)	2	(11.1)

A patient is counted only once within a System Organ Class category, even if more than one adverse experience with specific preferred terms occurred. Only the highest grade of a given adverse experience is counted per treatment group for the individual patient.

Adverse experience terms are from MedDRA Version 9.1

During the study, 15 serious adverse experiences were reported in 7 patients, of whom, 4 patients experienced 5 drug-related serious adverse experiences. Drug-related serious adverse experiences are summarized below.

Number (%) Of Patients With Specific Serious Drug-Related Clinical Adverse Experiences by Preferred Term (Incidence > 0% in One or More Treatment Groups)

	300 mg bid x 3d/wk (N=11)		300 mg bid x 14d/3wk (N=7)		Total Patients (N=18)	
	n	%	n	%	n	%
Thrombocytopenia	0	(0.0)	2	(28.6)	2	(11.1)
Anaemia	0	(0.0)	1	(14.3)	1	(5.6)
General Physical Health Deterioration	1	(9.1)	0	(0.0)	1	(5.6)
Hyponatraemia	1	(9.1)	0	(0.0)	1	(5.6)

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 9.1

Laboratory adverse experiences were reported for 4 patients. These laboratory adverse experiences included blood creatinine increased (2), blood phosphorus decreased (1), alkaline phosphatase increased (1), blood carbon dioxide decreased (1), lymphocyte count decreased (1) and monocyte count decreased (1). With the exception of blood phosphorus decreased and alkaline phosphatase increase, all laboratory adverse experiences were drug-related. Drug-related laboratory adverse experiences $\geq$ Grade 3 were blood phosphorus decreased (1) and monocyte count decreased (1). No serious laboratory adverse experience was reported.

To assess whether laboratory abnormalities represented clinically meaningful changes from baseline, a shift analysis was performed for each laboratory parameter. In this analysis, a clinically meaningful shift is defined as a shift from baseline less than CTCAE Grade 3 to any post-baseline value of CTCAE Grade 3 or 4, or a shift from CTCAE Grade 0 to Grade 2. The laboratory parameters with clinically meaningful shifts from baseline included: decreased WBC count, decreased hemoglobin, decreased lymphocyte count, decreased absolute neutrophil count, decreased platelet count, increased serum alanine aminotransferase, decreased serum albumin, increased serum calcium, increased serum creatinine, increased or decreased serum glucose, increased serum phosphorus, decreased serum sodium, increased total serum bilirubin, increased total serum carbon dioxide and increased urine protein.

Two (2) patients died on study of causes unrelated to study medication. [redacted]

CONCLUSIONS: In this study, 1) vorinostat at the doses and schedules used in this study did not meet the pre-specified definition of anti-tumor activity that warrants further investigation in the treatment of DLBCL; 2) the response duration (RD) was 91+ days in the one patient who responded, the median progression-free survival (PFS) was 44 days, median time to progression (TTP) for all patients was 44 days, time to response was 85 days for the one patient who responded, and progression free survival rate at 3 months was 16.7% and at 6 months was 11.1%; 3) vorinostat at a dose of 300 mg twice daily for 14 consecutive days followed by 7 days of rest was not tolerable for patients with relapsed DLBCL, although 300 mg twice daily for 3 consecutive days followed by 4 days of rest was tolerable; 4) the nature, frequency and severity of adverse events noted with this regimen in patients with DLBCL are similar to those noted in other vorinostat single agent studies.

AUTHORS: [redacted]