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 Advanced Malignant Pleural Mesothelioma	**CLINICAL STUDY REPORT SYNOPSIS**

PROTOCOL TITLE/NO.: A Phase III, Randomized, Double-Blind, Placebo-Controlled Trial of Oral Suberoylanilide Hydroxamic Acid (Vorinostat, MK-0683) in Patients With Advanced Malignant Pleural Mesothelioma Previously Treated With Systemic Chemotherapy — #014

INVESTIGATOR(S)/STUDY CENTER(S): Multicenter (125) in Australia, Belgium, Brazil, Canada, Chile, Croatia, Egypt, France, Germany, India, Israel, Italy, Japan, Mexico, the Netherlands, New Zealand, Portugal, South Africa, Spain, Sweden, Turkey, the United Kingdom, and the United States.

PUBLICATION(S):

1. Krug LM, Kindler H, Calvert H, et al. VANTAGE 014: Vorinostat (V) in patients with advanced malignant pleural mesothelioma (MPM) who have failed prior pemetrexed and either cisplatin or carboplatin therapy: A phase III, randomized, double-blind, placebo-controlled trial. Eur J Cancer. 2011; 47 Suppl 2:2-3.
2. Krug L, Baas P, Kindler H, et al. VANTAGE 014: Vorinostat in patients with advanced malignant pleural mesothelioma (MPM) previously treated with pemetrexed and either cisplatin or carboplatin: a phase III, randomized, double-blind, placebo-controlled trial**.** International Mesothelioma Interest Group Abstracts. 2010;(S10-1):135.
3. Krug LM, Arduino JM, Sun X, et al. Forced vital capacity (FVC) as a reproducible measure of pulmonary function (PF) in chemotherapy-pretreated patients with malignant pleural mesothelioma (MPM) [abstract]. J Clin Oncol. 2011;29 Suppl:7028.
4. Krug L, Baas P, Kindler H, et al. Vorinostat in patients with advanced malignant pleural mesothelioma (MPM) who have failed prior pemetrexed and either cisplatin or carboplatin therapy: A phase III, randomized, double-blind, placebo-controlled trial [abstract]. Presented at the IASLC 4th Latin American Conference on Lung Cancer, Buenos Aires, Argentina, Jul 2010.
5. Arduino JM, Kindler HL, Hollen PJ, et al. Confirmation of the reliability and validity of lung cancer symptom scale for patients with malignant pleural mesothelioma: comparison of chemotherapy-pretreated versus chemotherapy-naïve patient populations [abstract]. J Thorac Oncol. 2009;4(9 Suppl 1):S460.
6. Krug L, Marangolo M, Kindler H, et al. A phase III trial to investigate the effect of vorinostat in patients with advanced malignant pleural mesothelioma (MPM) previously treated with systemic chemotherapy (rationale and design) [abstract]. Presented at the 9th International Conference of the International Mesothelioma Interest Group, Amsterdam, The Netherlands, Sep 2008.

PRIMARY THERAPY PERIOD: 12-Jul-2005 to 13-Nov-2011. | **CLINICAL PHASE:** III

DURATION OF TREATMENT: Patients were treated until one of the following off-study criteria were met: disease progression; unacceptable adverse experiences (AEs); intercurrent events that, in the judgment of the Investigator, precluded further administration of study drugs; withdrawal of consent; pregnancy; patient non-compliance..

OBJECTIVE(S): Primary: To compare the overall survival associated with vorinostat plus best supportive care versus that associated with placebo plus best supportive care for the treatment of patients with advanced malignant pleural mesothelioma who have failed at least one prior chemotherapy regimen, and to determine the overall safety and toxicity of vorinostat in this population. **Secondary:** To compare between vorinostat plus best supportive care versus placebo plus best supportive care with respect to: 1) progression-free-survival; 2) overall objective response rate; 3) dyspnea score of lung cancer symptom scale modified for mesothelioma (LCSS-Meso) at Week 12; and 4) percent change from baseline in forced vital capacity (FVC) at Week 12..

MERCK RESEARCH LABORATORIES
MK-0683
vorinostat, Capsules
Advanced Malignant Pleural Mesothelioma

CLINICAL STUDY REPORT SYNOPSIS

STUDY DESIGN: Randomized, double-blind, placebo-controlled, multicenter Phase III study of oral vorinostat (MK-0683) plus best supportive care versus placebo plus best supportive care in patients with advanced malignant pleural mesothelioma previously treated with systemic chemotherapy.

SUBJECT/PATIENT DISPOSITION (as of 15 Jul 2011):

	Vorinostat (N=329)	Placebo (N=332)	Overall (N=661)
SCREENING FAILURES:			73
RANDOMIZED:	329	332	661
Male	283	270	
Female	46	62	
Age range	38.0 to 92.0	29.0 to 86.0	
CONTINUED	7	8	15
DISCONTINUED:	322	324	646
Clinical adverse experience	33	11	44
Death*	12	15	27
Progressive disease	251	281	532
Laboratory adverse experience	1	0	1
Lost to follow-up	0	1	1
Withdrew consent	15	10	25
Protocol deviation	1	1	2
Discontinued for other reasons	9	5	14

*Includes deaths that occurred on study drug or within 30 days after treatment termination.
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 latest discontinuation reason for that patient.

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CLINICAL STUDY REPORT SYNOPSIS

DOSAGE/FORMULATION NOS.:

Vorinostat (300 mg) or matching placebo was administered orally twice daily for 3 consecutive days every 7 days. A cycle consisted of 21 days, including 9 days of dosing.

Drug	Potency	Formulation No.	Dosage Form	Control No.	Clinical Batch No.
Vorinostat	100 mg	[redacted]	Capsule	[redacted]	[redacted]
Vorinostat	100 mg		Capsule		
Vorinostat	100 mg		Capsule		
Vorinostat	100 mg		Capsule		
Vorinostat	100 mg		Capsule		
Vorinostat	100 mg		Capsule		
Vorinostat	100 mg		Capsule		
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Vorinostat	100 mg		Capsule		
Vorinostat	100 mg		Capsule		
Vorinostat	100 mg		Capsule		
Vorinostat	100 mg		Capsule		
Placebo	Not applicable		Capsule		
Placebo	Not applicable		Capsule		
Placebo	Not applicable		Capsule		
Placebo	Not applicable		Capsule		
Placebo	Not applicable		Capsule		
Placebo	Not applicable		Capsule		
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Placebo	Not applicable		Capsule		
Placebo	Not applicable		Capsule		

MK-0683 Prot. No. 014
MK-0683 in Patients With Advanced Malignant Pleural Mesothelioma

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CLINICAL STUDY REPORT SYNOPSIS

DIAGNOSIS/INCLUSION CRITERIA: This study enrolled patients with malignant pleural mesothelioma whose disease had progressed or relapsed following treatment with at least one prior chemotherapy regimen; regimen must have included pemetrexed and either cisplatin or carboplatin in countries where pemetrexed was an approved mesothelioma treatment. Eligibility requirements included the following: ≥18 years of age; had received no more than 2 prior systemic therapy regimens; had an area of pleural rind thickness measured by meso-modified Response Criteria in Solid Tumors (RECIST) that was at least 1.0 cm in line-length on a spiral computerized tomography scan; Karnofsky performance scale status of ≥70; adequate bone marrow function without current use of colony stimulating factors; adequate coagulation, liver, and renal function; ≥4 weeks from previous chemotherapy or radiotherapy before drug administration (6 weeks for nitrosoureas or mitomycin C) and had recovered from any treatment-related toxicities.

EVALUATION CRITERIA: Primary: overall survival. Secondary: progression-free survival (the time from randomization to the time of disease progression or death); objective response (the evaluation of measurable lesions using a modification of RECIST created and validated for pleural mesothelioma); LCSS-Meso (patient-reported outcome measures of disease-related symptoms, symptom distress, activity level and global quality of life); and percent change from baseline in FVC at Week 12.

Safety measurements: History and physical examination, vital signs, EKG, laboratory testing - CBC, comprehensive metabolic profile, urinalysis.

STATISTICAL PLANNING AND ANALYSIS: Approximately 660 patients were planned to be enrolled to achieve a total of 540 events for the survival analysis. This study was event-driven, and was planned to complete after 540 deaths occurred. With 540 deaths, this study had 90% power at the 4% significance level (two-sided) to demonstrate a hazard difference of 25% (e.g., median survival 6 months versus 8 months). The primary efficacy measurement, overall survival, was calculated from the time of randomization until death. Patients who did not die on study were to be censored from the analysis at the time of the final visit. Secondary efficacy measurements included progression-free-survival (defined as the time from randomization to the time when the meso-modified RECIST criteria for disease progression were first met or when death from any cause occurred) and objective response. Response in this study was evaluated using a modification of the Response Criteria in Solid Tumors (RECIST), created and validated for pleural mesothelioma, in which disease measurement is more complicated than in most other solid tumors. Measurable lesions were evaluated according to these modified criteria. Complete response was defined as the disappearance of all target lesions with no evidence of tumor elsewhere; partial response was defined as at least a 30% reduction in the total tumor measurement; progressive disease was defined as at least a 20% increase in the total tumor measurement over the nadir measurement or the appearance of 1 or more new lesions; and stable disease was defined as neither sufficient shrinkage to qualify for a PR nor sufficient growth to qualify for PD. Non-measurable lesions were considered non-target lesions, and were evaluated according to RECIST.

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CLINICAL STUDY REPORT SYNOPSIS

RESULTS:

EFFICACY

Primary Efficacy Objective:

Overall Survival (OS)

• The median OS time was 30.7 weeks in the vorinostat arm and 27.1 weeks in the placebo arm. The hazard ratio between the vorinostat arm and the placebo arm was 0.98 with a 95% confidence interval (CI) as 0.83 to 1.17. The two-sided p-value was 0.858, failing to meet the pre-specified criterion for this endpoint.

Secondary Objectives:

(1) Progression-Free Survival (PFS) –Based on Independent Radiologist's Review

• The median PFS time based on independent radiology review was 6.3 weeks in the vorinostat arm and 6.1 weeks in the placebo arm. The hazard ratio between the vorinostat arm and the placebo arm was 0.75 (95% CI: 0.63 to 0.88) with two-sided p-value < 0.001, favoring the vorinostat arm. It passed the pre-specified criterion for this endpoint (i.e., p-value<0.0012).

(2) Overall Objective Response (OOR)

• There were 2 (0.63%) patients determined by the independent radiologist as responders in the vorinostat arm and 1 (0.31%) patient in the placebo arm. The difference in OOR between the two arms was 0.3% (95% CI: -1.18 to 1.97) with two-sided p-value=0.621, favoring the vorinostat arm. This result did not meet the threshold for statistical significance.

(3) Modified Lung Cancer Symptom Scale (LCSS-Meso)

• The mean percent change from baseline in LCSS-Meso dyspnea score at Week 12 was 141.8% for the vorinostat arm versus 174.7% for the placebo arm, with a difference of -52.4% (95% CI: -143.5% to 38.6%) favoring the vorinostat arm. The associated two-sided p-value=0.259, which did not meet the pre-specified threshold for statistical significance.

(4) Forced Vital Capacity (FVC)

• The mean percent change from baseline in FVC at Week 12 was -6.0% for the vorinostat arm versus -5.6% for the placebo arm, with a difference of -0.06 (95% CI: -4.61 to 4.49) and an associated two-sided p-value=0.979; the marginal difference was not statistically significant.

SAFETY (Co-primary Objective):

A summary of the clinical adverse experiences (AEs) in the All Patients as Treated population is shown below.

	Vorinostat (N=329)		Placebo (N=329)	
	n	(%)	n	(%)
Number (%) of patients:				
With one or more adverse experiences	327	(99.4)	311	(94.5)
With no adverse experience	2	(0.6)	18	(5.5)
With drug-related adverse experiences[†]	287	(87.2)	204	(62.0)
With serious adverse experiences	133	(40.4)	131	(39.8)
With serious drug-related AEs	40	(12.2)	13	(4.0)
Who died[‡]	60	(18.2)	64	(19.5)
Discontinued due to adverse experiences	60	(18.2)	49	(14.9)
Discontinued due to drug-related AEs	20	(6.1)	2	(0.6)
Discontinued due to serious AEs	41	(12.5)	41	(12.5)
Discontinued due to serious drug-related AEs	8	(2.4)	1	(0.3)

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

[‡] Includes deaths that occurred on study drug or within 30 days after treatment termination.

• The primary safety endpoint was grade 3-5 or serious AEs. There were no statistically significant differences in the percentage of patients with grade 3-5 or serious clinical or laboratory AEs during the treatment between the two arms.
• The most common AEs (occurring in >30% patients) in the vorinostat arm were nausea (58.7%), fatigue (48.0%), diarrhoea (42.9%), decreased appetite (40.4%), vomiting (40.4%), and dyspnea (30.4%), while in the placebo arm they were fatigue (39.2%), dyspnea (34.0%), and nausea (31.6%).
• The grade 3-5 clinical AEs occurring in >10% patients in the vorinostat arm were pleural mesothelioma malignant advanced (15.8%), fatigue (14.3%) and dyspnoea (10.6%), while in the placebo arm they were pleural mesothelioma malignant advanced (19.1%), tumour pain (12.2%), and dyspnea (13.7%). The most common grade 3-5 drug-related clinical AE in the vorinostat arm was fatigue (9.7%).
• Most of the deaths were reported as not drug-related; 3 deaths (one each from pneumonia, renal failure acute, and renal impairment) in the vorinostat arm and 1 death in the placebo arm (using the term death) were reported as drug-related.
• The median number of days on study was 47 for the vorinostat arm and 43 for the placebo arm.

CONCLUSIONS: MK-0683, when administered at 300 mg b.i.d. for three days out of seven days plus best supportive care, did not extend the overall survival of patients as compared to placebo plus best supportive care. An improvement in PFS by MK-0683 based on assessment from independent radiology review met the pre-specified criterion for this endpoint. MK-0683 was relatively well-tolerated in this population of patients with advanced malignant pleural mesothelioma.

The treatment effect on the primary endpoint of overall survival inexplicably reversed its direction after Interim Analysis 3, when approximately 60% of the total planned patient population for the study had enrolled. A testing of the interaction between the survival effect and the time of enrollment (before Interim Analysis 3 or after) shows a two-sided p-value of 0.019. However, extensive investigation has not revealed any apparent cause in the reversal of the treatment effect after Interim Analysis 3.

AUTHORS: [redacted]

REPORT DATE: **18-MAR-2015**