Clinical Study Synopsis

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The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

Date of study report:	21 MAY 2007
Study title:	Phase II study of MS-275, a histone deacetylase inhibitor, comparing 2 dosage schedules in patients with metastatic melanoma
Sponsor's study number:	91410
NCT number:	NCT00185302
EudraCT number:	2004-002395-41
Sponsor:	Bayer HealthCare
Clinical phase:	Phase II
Study objectives:	Primary objective: To evaluate the efficacy of two different dosing schedules of MS-275 in subjects with metastatic melanoma Secondary objectives: To evaluate the safety and to assess the pharmacokinetic (PK) profile of MS-275 in subjects with metastatic melanoma
Test drug:	Histone Deacetylase Inhibitor, MS-275 (BAY 86-5274, ZK 244894)
Name of active ingredient(s):	Histone Deacetylase Inhibitor, MS-275
Dose:	Arm A: 3 mg (3 × 1 mg tablet) on Days 1 and 15 of a 4 week cycle Arm B: 7 mg (1 × 5 mg tablet + 2 × 1 mg tablet) on Days 1, 8, and 15 of a 4 week cycle
Route of administration:	Oral
Duration of treatment:	The subjects continued the treatment until disease progression or withdrawal of consent. The maximum number of 4 week treatment cycles completed was 15 in the 3 mg biweekly arm and 4 in the 7 mg weekly arm.
Reference drug:	Not applicable
Indication:	Stage III or IV non-resectable metastatic melanoma
Diagnosis and main criteria for inclusion:	• Adult subjects with Stage III or IV non-resectable nonuveal (cutaneous or mucosal) metastatic melanoma who had received at least one but no more than two previous systemic therapies (immunotherapy and/or chemotherapy) for metastatic disease and who had not responded to or who had progressed after their most recent therapy were eligible for enrollment. • Presence of at least one lesion fulfilling the minimum Response Evaluation Criteria in Solid Tumors (RECIST) size requirements for a target lesion • Able to undergo either contrast-enhanced computed tomography

(CT) scan or contrast-enhanced magnetic resonance imaging (MRI) scan for tumor assessment

- Life expectancy greater than 3 months
- Adequate organ and bone marrow functions as defined below: absolute neutrophil count (ANC) ≥ 1500 /µL, platelets ≥ 100,000 /µL, creatinine ≤ 1.5 × upper limit of normal (ULN) or measured creatinine clearance of ≥ 60 mL/min x 1.73 m^2 body surface area (BSA), total bilirubin ≤ 1.5 times ULN, aspartate aminotransferase (AST) or serum glutamic-oxalacetic transaminase (SGOT)/alanine aminotransferase (ALT) or serum glutamic-pyruvic transaminase (SGPT)* ≤ 2.5 times ULN
- Negative serum pregnancy test within 2 weeks prior to receiving the first dose of study drug in female subjects of childbearing potential. Agreement to use a highly effective method of birth control throughout the study period and 3 months thereafter for sexually active males and females of childbearing potential

Study design: The study was conducted in a multicenter, randomized, open-label, parallel-group design. The study design followed Simon's two-stage optimal design.

Methodology: The study comprised of the following visits:

- Screening/baseline evaluations
- On-study evaluations/measurements (during Cycles 1-14)
- End-of-treatment (EOT) evaluation
- 30 Day follow-up (F-up) evaluation
- Long-term disease progression follow-up

Evaluation of 6 month survival (6 Mo surv.) F-up did not require a subject visit.

The subjects received either 3 mg MS-275 orally biweekly (Days 1 and 15 of a 4 week cycle) or 7 mg MS-275 orally weekly (Days 1, 8, and 15 of a 4 week cycle) until disease progression or unacceptable toxicity. The maximum number of cycles planned was 14. In the case of sustained clinical benefit, subjects were allowed to continue to receive the study treatment after the completion of 14 cycles at the discretion of the investigator. These subjects were asked to sign a new informed consent form for the follow-up treatment.

Each subject visited the study site once weekly during the first cycle and every other week during the following cycles.

Tumor response to MS-275 was assessed radiographically after every 2 treatment cycles using CT/MRI scans and RECIST criteria. Each evaluation comprised of assessments of target lesions, non-target lesions, and new

	lesions. Based on these evaluations, the investigator assessed the overall response according to the RECIST directions: •Complete response (CR) •Partial response (PR) •Stable disease (SD) •Progressive disease (PD) •Not assessable (to be specified) Subjects were evaluated for disease progression according to local standards at the discretion of the investigator. Those who experienced CR, PR, or stable disease (SD) continued drug treatment until disease progression or unacceptable toxicity. Any PR or CR were to be confirmed by a repeated tumor assessment at least 4 and not more than 6 weeks after the first assessment documenting PR or CR. According to Simon's two-stage optimal study design, initially, 28 evaluable subjects (14 per treatment arm) were enrolled and treated (Stage 1). If no subject with partial or CR was observed, the enrollment was stopped. If 1 or more subjects with partial or CR was observed in one treatment arm, then an additional 33 evaluable subjects were enrolled (Stage 2) in this treatment arm. If 1 or more responses were observed in both treatment arms, then an additional 66 evaluable subjects were (Stage 2) in the study. If ≥3 of 47 subjects had a CR or PR, the drug was considered promising. All subjects who received at least one dose of study medication were to be assessed for response to treatment every 2 cycles until end of treatment and thereafter every 3 months until disease progression or withdrawal of consent. Tumor scans according to the RECIST was obtained at baseline (within 4 weeks prior to Day 1 Cycle 1) and repeated every 2 cycles until tumor progression between Day 22 of even-numbered cycles and Day 1 of subsequent odd-numbered cycle and also at EOT and F-up visit (at EOT and F-up visit tumor scans were not performed, if done less than 30 days previously). PK blood samples were collected pre-dose and up to 8 h post-dose on Day 1 of Cycle 1 and Cycle 2. Safety and tolerability of MS-275 were monitored throughout the study. Where applicable, toxicity severity was graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, (CTCAE), Version 3.0.
Study center(s):	The study was conducted at four centers in Germany.
Publication(s) based on the study (references):	None at the time of report creation
Study period:	**Study Start Date:** 13 DEC 2004 **Study Completion Date:** 27 JUL 2006

Early termination: Not applicable

Number of subjects:

Planned: Stage 1: 14 subjects in arm A and 14 subjects in arm B

Stage 2: 47 subjects in arm A and 47 subjects in arm B

Randomized Stage 1: 28 subjects

Stage 2: None

Analyzed: Stage 1: 14 subjects in arm A and 14 subjects in arm B

Stage 2: None

Criteria for evaluation

Efficacy: **Primary efficacy variable:**

Overall tumor response rate (the proportion of subjects with the best tumor response of PR or CR within the first 6 cycles of treatment)

Secondary efficacy variables:

- Tumor response rate at each tumor assessment time point (CR/PR/SD/PD/not assessable)
- Time to tumor progression (TTP), ie, time period between randomization and the first assessment of progressive disease
- Time to death
- Survival at 6 months

Safety: AEs, vital signs, electrocardiogram (ECGs), physical examinations, laboratory analyses

Clinical pharmacology: Pharmacokinetic parameters:

- C_{max}: Maximum drug concentration measured in plasma
- t_{max}: Time to reach maximum drug concentration
- C_{8h}: Drug concentration measured in plasma at 8 h after administration
- AUC(0-2h): Area under the drug concentration-time curve from administration up to 2 h
- C_{av}(0-2h): Average drug concentration from administration up to 2 h

Statistical methods: **Efficacy:**

Primary efficacy variable:

Simon's two-stage optimal design was applied to analyze "best overall response" at Cycle 6.

	Secondary efficacy variables: Kaplan-Meier estimates (TTP), frequency tables, and descriptive statistics were used for the other parameters. **Safety:** All AEs were coded using the Medical Dictionary for Regulatory Affairs (MedDRA). **Pharmacokinetics:** The PK parameters C_{max}, t_{max}, C_{8h}, AUC(0-2h), and C_{av}(0-2h) were tabulated per treatment arm for each subject with descriptive statistics (geometric mean, arithmetic mean together with their standard deviations and coefficients of variation as well as the median, range, and the upper and lower confidence limits of the 95% confidence interval of the geometric mean).
Substantial protocol changes:	Amendment 1 from 09 DEC 2005 introduced the following changes: • Subjects with sustained clinical benefits were allowed to remain in the study after the completion of 14 cycles without being transferred to a new protocol. A new informed consent was still required. • The number of visits was reduced after 14 cycles due to the mild toxicity profile. The radiological assessments were allowed to be performed according to local standards at the discretion of the investigator.

Subject disposition and baseline

A total of 31 subjects were recruited to the study. Two subjects did not meet the eligibility criteria (one due to brain metastasis and one due to thrombocytopenia) and did not receive the study drug. One subject withdrew consent before receiving study drug.

The remaining 28 subjects were randomized into two treatment arms: 14 subjects to receive 3 mg of MS-275 biweekly and 14 subjects to receive 7 mg of MS-275 weekly. All 28 subjects completed the study medication. These subjects either received study medication until progression of the disease or completed all 14 treatment cycles. The 30 days follow-up phase was completed by 12 subjects in the 3 mg biweekly arm and 11 subjects in the 7 mg weekly arm.

As no major protocol violations occurred, all 28 subjects were included in the full analysis set (FAS), safety analysis set (SAF), per-protocol set (PPS), and primary analysis set (PAS). The PK study was also performed for all 28 subjects.

The median (min-max) age of the subjects was 63.0 (30-73) years in the 3 mg biweekly arm and 55.5 (42-78) years in the 7 mg weekly arm.

All subjects in the study had received prior therapy for their disease.

Baseline findings were detected in 14 subjects of the 3 mg biweekly arm and 13 subjects in the 7 mg weekly arm. Abnormal physical examination findings were recorded in 13 subjects of the 3 mg biweekly arm and 13 subjects in the 7 mg weekly arm at baseline.

Efficacy evaluation

None of the subjects achieved CR or PR as best overall response. Hence the estimated response probability was 0 for both dosing schedules. Confidence intervals could not be calculated for the response rates nor for the difference of response rates between the two dosing schedules. Consequently, Stage 2 of the study was not performed.

SD was the best overall response for 4 (28.6%) subjects in the 3 mg biweekly arm and for 3 (21.4%) subjects in the 7 mg weekly arm. All the remaining subjects had PD as best overall response. An overall estimate for the median TTP was comparable in the treatment arms: 55.5 days in the 3 mg biweekly arm and 51.5 days in the 7 mg weekly arm. In the 3 mg biweekly arm, 2 subjects had disease stabilization for approximately 13 and 14 months, while in the 7 mg weekly arm, the maximum disease stabilization was approximately 3 months. Data for the survival at 6 months was available for 12 subjects in the 3 mg biweekly arm and 14 subjects in the 7 mg weekly arm. Altogether 8 (57.1%) subjects in the 3 mg arm and 10 (71.4%) subjects in the 7 mg weekly arm were alive at 6 months after start of the study medication.

The sample size remained too small to present meaningful results on time to death.

Safety evaluation

A total of 13 (92.9%) subjects in the 3 mg biweekly arm and 14 (100.0%) subjects in the 7 mg weekly arm reported at least 1 AE during the study. Most of the subjects (17; 60.7%) experienced at least 1 drug-related AE. These were slightly more frequent in the 7 mg weekly arm compared to the 3 mg biweekly arm occurring in 11 (78.6%) and 6 (42.9%) subjects, respectively. The investigators assessed most AEs as grade 2 events, which occurred in 5 (35.7%) subjects in the 3 mg biweekly arm and in 8 (57.1%) subjects in the 7 mg weekly arm. Grade 3/4/5 AEs were reported altogether in 7 (50.0%) subjects in the 3 mg biweekly arm and 5 (35.7%) subjects in the 7 mg weekly arm.

The most frequently reported AEs among all subjects were nausea in 11 (39.3%) subjects, hypophosphatemia in 8 (28.6%) subjects, pain in extremity in 6 (21.4%) subjects, diarrhea in 5 (17.9%) subjects, and back pain in 5 (17.9%) subjects. All of these belong to the expected AEs, ie, they have been frequently detected in subjects treated with MS-275 in earlier clinical studies. The occurrence of the most common AEs was similar in both treatment arms. In most cases, the common AEs were grade 1 or 2 events. Two subjects with grade 3 hypophosphataemia, 1 subject with grade 3 pain in the extremity, and 1 subject with grade 3 back pain were reported. None of the most common AEs was of grade 4 or 5 severity.

All cases of hypophosphatemia were considered as drug-related. Similarly, all 5 occurrences of nausea in the 7 mg weekly arm were assessed as drug-related. However, in the 3 mg biweekly arm, nausea was considered to be drug-related in only 1 of 6 subjects. Also most cases with diarrhea (3 [21.4%] subjects in the 7 mg weekly arm) were assessed as being related to the study drug. Neither back pain nor pain in the extremity was related to the study drug in any of the cases.

Serious AEs (SAEs) were reported for 2 (14.3%) subjects in the 3 mg biweekly arm and 3 (21.4%) subjects in the 7 mg weekly arm. None of the SAEs were related to the study drug. All except 1 SAE were considered as manifestations of progressive melanoma. One subject in the 7 mg weekly arm had grade 2 peripheral edema from which the subject recovered.

Two subjects died during the treatment phase of the study, one in each treatment arm. Six subjects died during the 6 months survival follow-up phase, 3 in each treatment arm. All deaths were due to disease progression.

Laboratory evaluations consisted of hematology and serum chemistry. Most of the subjects with abnormal laboratory findings including low hemoglobin, low hematocrit, low erythrocyte, and low lymphocyte values had them already at the baseline. However, shifts in monocyte and alkaline phosphate values from normal baseline to higher values were detected in both treatment arms during the study medication cycles. Additionally, for some subjects the levels of leukocytes, platelets, and neutrophils had shifted from normal at baseline to low during the treatment, occurring more frequently in the 7 mg weekly arm.

Clinically relevant changes in the laboratory parameters were reported in both treatment arms at baseline and throughout the study. The most frequent investigators' comments for the changes included hypophosphatemia (9 subjects), anemia (6 subjects), lymphocytopenia (6 subjects), leukocytopenia (4 subjects), and neutropenia (4 subjects).

There were no notable differences in vital signs (including blood pressure, heart rate, and weight) during the study. No relevant trends or changes were seen in ECG examinations. The Eastern Cooperative Oncology Group (ECOG) performance status of the subjects was slightly lower toward the end of the study, which most likely reflected progression of the underlying disease.

Clinical pharmacology evaluation

Pharmacokinetic evaluation:

In this study, the PK variables C_{max} as well as C_{av}(0-2h) and C_{8h} as indices of the systemic exposure to MS-275 were determined during the initial phase and during the terminal elimination phase. Each of the investigated parameters increased dose-dependently.

The C_{max} and C_{av}(0-2h) values showed considerable variability, while the C_{8h} value was less variable. The mean plasma concentrations on Day 1 of Cycle 2 were slightly lower compared to those on Day 1 of Cycle 1 after administration at 3 mg flat dose biweekly, while similar mean plasma concentrations were observed between Day 1 of Cycle 1 and Day 1 of Cycle 2 after administration at 7 mg flat dose given weekly. However, individual change in systemic exposure between Day 1 of Cycle 1 and Cycle 2 had no trend for time-dependent decrease or increase in either regimen.

Mean PK parameters of biweekly regimen are reported in Table 1.

Table 1: Mean pharmacokinetic parameters of MS-275 in plasma obtained at Day 1 of Cycle 1 and Cycle 2 after oral administration of 3 mg MS-275 on Days 1 and 15 of a 4 week cycle

Parameters unit	C_{max} [ng/mL]	t_{max} [hr]	AUC(0-2hr) [ng*h/mL]	C_{av}(0-2hr) [ng/mL]	C_{8hr} [ng/mL]
Day 1 of Cycle 1 (N=13)	6.46 (130%)	0.5 (0.5-2)	7.66 (124%)	3.83 (124%)	1.22 (56.3%)
Day 1 of Cycle 2 (N=10-11)	4.56 (169%)	0.5 (0.5-2)	5.44 (145%)	2.72 (145%)	0.860 (40.0%)
Ratio Cycle 2/Cycle 1 (N=9-10)	0.650 (156%)	1 (0.25-4)	0.682 (139%)	0.682 (139%)	0.751 (34.1%)

C_{max} = maximum plasma concentration
t_{max} = time to reach C_{max}
AUC(0-2hr) = area under the plasma concentration-time curve up to 2 hr after administration
C_{av}(0-2hr) = average plasma concentration up to 2 hr after administration
C_{8hr} = plasma concentration at 8 hr after administration
N = number of patients taken for the calculation of the geometric mean and CV
Values are shown as geometric mean with geometric coefficient of variation (%) in parenthesis, except for t_{max}, which are shown as median with range in parenthesis.

Mean PK parameters of weekly regimen are reported in Table 2.

Table 2: Mean pharmacokinetic parameters of MS-275 in plasma obtained at Day 1 of Cycle 1 and Cycle 2 after oral administration of 7 mg MS-275 on Days 1, 8, and 15 of a 4 week cycle

Parameters unit	C_{max} [ng/mL]	t_{max} [hr]	AUC(0-2hr) [ng*h/mL]	C_{av}(0-2hr) [ng/mL]	C_{8hr} [ng/mL]
Day 1 of Cycle 1 (N=11-13)	18.5 (123%)	0.5 (0.5-0.5)	22.8 (107%)	11.4 (107%)	1.79 (31.8%)
Day 1 of Cycle 2 (N=10-11)	23.3 (174%)	0.5 (0.333-2)	26.4 (167%)	13.2 (167%)	2.05 (45.0%)
Ratio Cycle 2/Cycle 1 (N=9-11)	1.18 (267%)	1 (0.667-4)	0.866 (206%)	0.866 (206%)	1.12 (27.8%)

Overall conclusions

- Considering the long-term tumor stabilization seen in 2 subjects and the remarkably mild toxicity profile, the histone deacetylase inhibitor MS-275 is an interesting partner for combination regimens in the treatment of metastatic melanoma.
- MS-275 treatment was well-tolerated in both treatment arms.
- The PK data indicated an increase in plasma drug concentration with increasing dose and no considerable accumulation with either regimen.