# SYNOPSIS

| | |
|---|---|
| **Title of the study:** | A multinational, randomized, double-blind placebo controlled study of AVE8062 (25 mg/m²) administered every 3 weeks, in patients with advanced-stage soft tissue sarcoma treated with cisplatin (75 mg/m²) after failure of anthracycline and ifosfamide chemotherapies. (EFC 10145) |
| **Principal Investigators:** | [redacted] |
| **Study centers:** | 50 centers in Belgium, Brazil, France, Hungary, India, Italy, Serbia, Spain, United Kingdom, and USA |
| **Publications (reference):** | None |
| **Study period:** | |
| Date first patient enrolled: | 13Jun2008 |
| Primary data cut-off date: | 07Sep2012 |
| Final data cut-off date: | 17Apr2013 |
| **Phase of development:** | 3 |
| **Objectives:** | |
| Primary objective: | |
| To compare the progression-free survival (PFS) in the 2 treatment arms | |
| Secondary objectives: | |
| To compare the overall survival (OS) in the 2 treatment arms | |
| To compare the objective response rate (RR) in the 2 treatment arms | |
| To assess the safety profile of AVE8062 (in combination with the background cisplatin therapy) | |
| To assess the pharmacokinetics (PK) of AVE8062 and its main metabolite, RPR258063, using a population approach, in all patients enrolled in selected centers. | |
| **Methodology:** | |
| This was a multinational, prospective, double-blind, placebo-controlled, randomized, parallel group trial in patients with unresectable locally advanced or metastatic soft tissue sarcoma. Patients were randomized to ombrabulin (test arm) or placebo (control arm) in a ratio of 1:1. All patients received background chemotherapy with cisplatin. The combination therapy was to be administered every 3 weeks. | |
| Treatment allocation was performed centrally via an interactive voice response system (IVRS), using a permuted-block randomization stratified by histological soft tissue sarcoma (STS) subtype: (a) high-grade undifferentiated pleomorphic sarcoma (i.e. malignant fibrous histiocytoma including myxofibrosarcoma); (b) leiomyosarcoma; (c) liposarcoma; and (d) other types. | |
| **Number of** patients**:** | Planned: 350 patients (175 in each arm) |
| | Randomized: 355 |
| | Treated: 354 |
| **Evaluated:** | |
| | Efficacy: 354 |
| | Safety: 354 |
| | Pharmacokinetics: 246 |

**Diagnosis and criteria for inclusion:** •

Patients with advanced-stage STS: unresectable locally advanced STS or metastatic STS who have failed a previous anthracycline-based regimen administered at the recommended dose regardless of prior ifosfamide therapy and who had disease progression within 1 month before study randomization.

**Study treatments**

**Investigational medicinal product(s):** Ombrabulin (AVE8062)

Formulation: 25 mg/ mL solution

Route of administration: Intravenous (IV) infusion

Dose regimen: 25 mg/m$^2$, administered as a 30 minute IV infusion on Day 1 of each 21 day cycle

Batch numbers: [redacted]

**Noninvestigational medicinal product:** Placebo

Formulation: Sterile saline solution for injection 5 mL

Route of administration: IV infusion

Dose regimen: Administered as a 30 minute IV infusion on Day 1 of each 21 day cycle

Batch numbers: [redacted]

**Noninvestigational medicinal product:** Cisplatin

Formulation: Marketed formulation

Route of administration: IV infusion

Dose regimen: 75 mg/m², administered as a 2 hour IV infusion immediately after ombrabulin or placebo on Day 1 of each cycle

Batch number: Not applicable

**Pharmacokinetic/Pharmacodynamics sampling times and bioanalytical methods:** Blood samples were collected for PK on Day 1, cycle 1, just before the end of infusion, between 5 to 20 minutes, between 0.5 to 2 hours, between 4 to 8 hours, and 24 hours post end of infusion. The concentrations of ombrabulin and its metabolite RPR258063 in plasma were measured by a validated liquid chromatography with mass spectrometry method (limit of quantitation = 2 ng/mL for each analyte).

**Criteria for evaluation:**

Efficacy:

Primary efficacy endpoint:

- The primary efficacy endpoint is progression-free survival (PFS), defined as the time interval from the date of randomization to the date of occurrence of the first documented objective radiological tumor progression or death due to any cause, whichever comes first. Objective radiological tumor progressions were assessed by an independent review committee (IRC) blinded to the randomization arm and to the patient characteristics, according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria.

Secondary efficacy endpoints:

- Overall survival (OS), defined as the time from the date of randomization to the date of death due to any cause.
- Objective response includes complete response (CR) and partial response (PR), as assessed by the IRC according to RECIST criteria.

Safety:

Safety was assessed by collecting information about adverse events (AEs), clinical laboratory evaluations, physical examinations, vital signs measurements, electrocardiograms (ECGs), left ventricular ejection fraction (LVEF), concomitant medications, and Eastern Cooperative Oncology Group performance status. AEs were reported using Medical Dictionary for Regulatory Activities version 15.0. The National Cancer Institute Common Terminology Criteria for Adverse Event, version 3.0 was used in this study to grade the severity of AEs and assess laboratory abnormalities.

Pharmacokinetics:

At selected centers, a limited sampling strategy with 5 plasma samples collected per patient was implemented to assess the PK of ombrabulin and RPR258063, its main metabolite. A blood sample for genotyping drug metabolizing enzymes was collected before first infusion in patients who signed the genotype analysis consent form.

**Statistical methods:**

Analysis populations included 2 populations defined for the statistical analyses as follows:

- Intent-to-treat population (ITT) – all randomized patients who provided their informed consent; analyses were based on the treatment assigned by the IVRS.
- Safety population – subset of the ITT population that took at least one dose of study medication. Analyses were based on the treatment actually received

Efficacy: Analysis of all efficacy endpoints was performed based on the ITT population with the exception of objective response rate (ORR), which was analyzed in the ITT population with measurable disease.

The primary efficacy variable, PFS, was compared between the two treatments by the log-rank test procedure stratified by histological subtype of soft tissue sarcoma as specified at the time of randomization. The estimates of the hazard ratio and corresponding 95% confidence interval (CI) were provided using a Cox proportional hazard model stratified by histological subtype of soft tissue sarcoma as specified at the time of randomization. The PFS curves were estimated using Kaplan-Meier estimates.

The primary analysis of PFS was based on radiological progression events and deaths. In the absence of death and radiological documentation of progression, data on PFS were censored at the earliest date of last tumor assessment without evidence of progression and the study cut-off date. For purpose of sensitivity analysis, a secondary definition of PFS also included clinical progression/symptomatic deterioration as a PFS event, in absence of objective radiological documentation of tumor progression. The final analysis of PFS was conducted when at least 265 PFS events were observed. The one-sided nominal significance level that was used at the final analysis of PFS was 0.0248, as a penalty was applied to the overall significance level due to the interim analysis with a non-binding futility stopping rule.

Analyses of secondary efficacy variables included OS and objective response. OS was compared between the 2 treatments using log-rank test procedure, Cox model, and Kaplan-Meier estimates as described above. The cutoff for the final analysis of OS was the date when both approximately 260 deaths and 265 PFS events occurred, whichever was later. The final analysis of OS was conducted using a one-sided nominal significance level of 0.025. As a consequence, both PFS and OS endpoints were analyzed at the same time, when the targeted number of events was reached for both endpoints.

The objective response rate was estimated as the number of patients with objective response (CR+PR) divided by the number of patients in the population of interest. The 95% confidence interval was calculated in each treatment group. Objective response rates were compared between the two treatments using a Cochran-Mantel-Haenszel test stratified on histological subtype of soft tissue sarcoma as specified at the time of randomization.

Safety: Descriptive analyses of AEs, vital signs, ECG, and laboratory data were performed by treatment arm in the safety population. The primary analysis of safety was based on the “treatment-emergent” principle, with treatment emergent adverse events (TEAEs) summarized in terms of incidence, intensity/severity, seriousness and relationship.

**Summary:**

**Population characteristics:**

A total of 355 patients with soft tissue sarcoma were randomized to receive cisplatin in combination with placebo (179 patients) or ombrabulin (176 patients). Patients had a median age of 52 years and 51.5% were male. While most baseline characteristics were generally balanced between treatment groups, differences were noted for patients between 40 and 49 years (14.5% and 26.7% in the placebo and ombrabulin arms, respectively), time from first diagnosis to randomization (median 19.5 versus 24.9 months), and diameter of the largest lesion (≥5 cm in 53.8% versus 63.3%). Overall, 26.8% of patients had the histological subtype leiomyosarcoma, 13.8% pleomorphic sarcoma, 13.5% liposarcoma, and 45.9% other. In the stratum other, patients with synovial sarcoma represented 14.6% of the total population. The treatment groups were well balanced with regard to the stratification based on sarcoma histology type.

**Efficacy results:**

The primary endpoint in the study was PFS and the primary analysis was to be performed when 265 PFS events had occurred. The primary PFS analysis showed a statistically significant difference in favor of ombrabulin over placebo (stratified log rank test 2-sided p=0.0302). Median PFS was 1.41 months (95% CI: 1.38 to 1.58) in the placebo arm and 1.54 months (95% CI: 1.45 to 2.69) in the ombrabulin arm corresponding to a 4 day improvement and an hazard ratio (HR) of 0.76 (95% CI: 0.59 to 0.98).

In the analysis of PFS by histology strata, a numerical improvement favoring ombrabulin was observed in 3 of the 4 defined strata: liposarcoma median PFS was 1.31 months in the placebo arm versus 2.86 months in the ombrabulin arm, corresponding to an improvement of 47 days and an HR of 0.53 (95% CI: 0.26 to 1.05); leiomyosarcoma median PFS was 1.61 months in the placebo arm versus 2.73 months in the ombrabulin arm, corresponding to an improvement of 34 days and an HR of 0.70 (95% CI: 0.43 to 1.13); stratum other median PFS was 1.38 months in the placebo arm versus 1.48 months in the ombrabulin arm, corresponding to an improvement of 3 days and an HR of 0.67 (95% CI: 0.47 to 0.97). For pleomorphic sarcoma, median PFS was 1.48 months in the placebo arm versus 1.35 months in the ombrabulin arm, corresponding to a 4 day difference in favor of placebo and an HR of 1.92 (95% CI: 0.99 to 3.70).

No significant improvement in OS was observed for ombrabulin over placebo. The median OS was 9.33 months (95% CI: 7.95 to 12.06) in the placebo arm versus 11.43 months (95% CI: 9.79 to 14.49) in the ombrabulin arm, corresponding to a difference of 63 days; the HR was 0.85 (95% CI: 0.67 to 1.09; stratified 2-sided log rank p=0.197).

Two patients in the placebo arm had a PR versus 6 in the ombrabulin arm. The incidence of stable disease was higher in the ombrabulin arm than in the placebo arm (42.6% versus 34.5%).

**Safety results:**

Patients received a median of 7.4 weeks of treatment in the placebo arm and 7.0 weeks in the ombrabulin; a total of 653 and 741 cycles, respectively, were administered (median 2.0 cycles in both arms).

The overall incidence of TEAEs, (all grade, regardless of relationship), was similar between the placebo and ombrabulin arms (96.0% and 96.6%, as was the incidence of grade 3-4 TEAEs (49.7% and 54.2%), serious adverse events (SAEs) (31.6% and 28.8%), and discontinuations due to TEAEs (15.3% and 17.5%).

TEAEs reported in ≥10% of patients in either arm were nausea, asthenia, vomiting, neutropenia, decreased appetite, constipation, weight decreased, tinnitus, dyspnea, headache, abdominal pain, fatigue, cough, diarrhea, thrombocytopenia, pyrexia, back pain, edema peripheral, weight increased, and pain in extremity. With the exception of neutropenia and thrombocytopenia, these events were generally reported at a similar incidence in both treatment arms and most of events were grade 1-2. The most common grade 3-4 TEAEs were neutropenia and thrombocytopenia; both neutropenia (19.2% and 31.1% in the placebo and ombrabulin arms; grade 3-4: 7.9% and 19.2%) and thrombocytopenia (8.5% and 12.4%; grade 3-4: 3.4% and 8.5%) occurred more frequently with ombrabulin. TEAEs related to investigational product (IP) were generally the most frequently reported events.

A total of 135 (76.3%) patients in the placebo arm and 128 (72.3%) patients in the ombrabulin arm died during both the treatment and post-treatment periods. TEAEs (including those reported in the setting of disease progression) led to death more frequently in patients in the ombrabulin arm compared with the placebo arm (18 patients versus 10 patients). TEAEs leading to death reported in more than 1 patient were general disease progression (8 patients) and dyspnea (4 patients) in the ombrabulin arm and disease progression (3 patients) in the placebo arm. Of the deaths due to AEs, 1 patient in the placebo arm died of pulmonary embolism (reported more than 30 days from last study treatment) considered related to IP and 1 patient in the ombrabulin arm died of atrial flutter considered related to IP.

SAEs reported more frequently in the ombrabulin arm (2 or more patients in the ombrabulin arm compared to the placebo arm) were disease progression 9 versus 5 patients), dyspnea (7 versus 0 patients), pulmonary embolism (5 versus 3 patients), neutropenia (4 versus 2 patients), back pain (3 versus 0 patients), and sciatica (2 versus 0 patients).

Overall, 15.3% and 17.5% of patients in the placebo and ombrabulin arms, respectively, discontinued due to TEAEs; of these 9.6% and 12.4% of patients, respectively, had grade 3-4 TEAEs. The most common TEAEs (>2% of patients) leading to discontinuation in the ombrabulin arm were neutropenia, pulmonary embolism, peripheral neuropathy, and decreased creatinine clearance. These were all reported more frequently in the ombrabulin compared to the placebo arm.

Overall, the safety analysis at the final database cut-off did not lead to any change in the safety conclusions from the primary analysis.

Grade 3-4 hematologic abnormalities (primarily decreased leukocytes, neutropenia and thrombocytopenia) occurred more frequently in the ombrabulin arm than in the placebo arm (there was only one event of febrile neutropenia reported in the study (in the placebo arm)). For other clinical laboratory parameters, grade 3-4 abnormalities occurred either in only one patient or the incidence was equal or higher with placebo than ombrabulin.

Dose reductions and treatment delays were most frequently due to neutropenia and thrombocytopenia, both of which occurred most frequently in the ombrabulin arm.

Potentially significant changes in systolic blood pressure occurred with similar incidence between the two treatment arms.

Decreases from baseline in absolute LVEF ≤10% to values below the lower limit of normal (LLN) (8 versus 4 patients) and decreases >20% to within and below the LLN (3 versus 1 patient) were reported more frequently with ombrabulin than placebo respectively. There was one event of grade 2 left ventricular dysfunction in the placebo group and 1 event of grade 3 cardiac failure in the ombrabulin treatment group.

The overall safety profile demonstrated with ombrabulin in combination with background chemotherapy was generally consistent with the safety profile of the background chemotherapy alone when administered to the targeted population with the exception of increased myelosuppression and a trend toward decreased LVEF (measured as per protocol) in the ombrabulin arm; the adverse reactions associated with ombrabulin were comparable to those observed in previous clinical studies and were also manageable.

**Pharmacokinetic results:** AVE8062 and RPR258063 concentrations were determined in 2382 human plasma samples that included 124 patients in the ombrabulin treatment arm.

**Conclusions:**

[redacted]

**Date of report:** 14-Nov-2013