# SYNOPSIS

| NAME OF SPONSOR/COMPANY:<br>Johnson & Johnson Pharmaceutical Research & Development, L.L.C.<br>NAME OF FINISHED PRODUCT:<br>DOXIL®<br>NAME OF ACTIVE INGREDIENT(S):<br>Doxorubicin | INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER<br>Volume:<br>Page: | (FOR NATIONAL AUTHORITY USE ONLY) |
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**Protocol No.:** C-2000-003

**Title of Study:** A Multi-Center Randomized Study of Vincristine, DOXIL®, and Dexamethasone vs Vincristine, Doxorubicin, and Dexamethasone in Patients With Multiple Myeloma

**Principal Investigator:** Robert M. Rifkin, M.D., Rocky Mountain Cancer Center, US Oncology, Denver, CO

**Publication (Reference):** Rifkin RM, Gregory SA, Mohrbacher A, Hussein MA. Pegylated liposomal doxorubicin, vincristine, and dexamethasone provide significant reduction in toxicity compared with doxorubicin, vincristine, and dexamethasone in patients with newly diagnosed multiple myeloma: a phase III multicenter randomized trial. *Cancer.* 2006 Feb 15;106(4):848-858.

| **Study Initiation/Completion Dates:** First subject enrolled 11 January 2001; last subject off-study 12 June 2004. | **Phase of development:** 3 |
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**Objectives:** To compare the efficacy, clinical benefit, toxicity, and safety of the combination of vincristine, DOXIL and dexamethasone (VDD) to the standard regimen of vincristine, doxorubicin, and dexamethasone (VAD) in subjects with newly diagnosed multiple myeloma.

**Methodology:** This was a randomized, open-label, comparative study of VDD vs VAD in the treatment of subjects with newly diagnosed multiple myeloma.

**Number of Subjects (planned and analyzed):**

Planned: Approximately 200 male and female subjects were to be randomized 1:1 between the 2 study groups.

Analyzed: Ninety-five subjects were randomized to the VAD group and 97 to the VDD group. All subjects received study medication and are included in the intent-to-treat (ITT) analyses.

**Diagnosis and Main Criteria for Inclusion:**

Diagnosis: Newly diagnosed multiple myeloma.

Main Inclusion Criteria:

- Male and female subjects with an age ≥ 18 years.
- Untreated multiple myeloma requiring treatment (Durie-Salmon stage ≥ I).
- Total cumulative dose of prior doxorubicin cannot exceed 240 mg/m$^2$.
- Must have measurable disease defined as a quantifiable serum and/or urine M-component.
- Adequate bone marrow, liver, and renal function.

Main Exclusion Criteria:

- Pregnant or breast feeding.
- Life expectancy of ≤ 3 months.
- History of cardiac disease, with New York Heart Association Class II or greater, with congestive heart failure.
- Myocardial infarction within the last 6 months.
- Unstable angina, uncontrolled hypertension or cardiac arrhythmias, diabetes mellitus, or systemic infection.
- Nonsecretory myeloma, monoclonal gammopathy of unknown significance (MGUS), or smoldering myeloma.
- Prior chemotherapy for multiple myeloma.

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**Test Product, Dose and Mode of Administration, Batch No.:**

DOXIL 40 mg/m$^2$ intravenous (IV) infusion over 1 hour on Cycle Day 1.
Vincristine 1.4 mg/m$^2$ (maximum 2.0 mg) IV injection over approximately 5 minutes on Cycle Day 1.
Dexamethasone 40 mg/day orally (PO) on Cycle Days 1-4. A cycle was 28 ± 3 days.

DOXIL lot numbers: 0206627, 0106848, 0105596, 0003741, and 9915794.
Vincristine and dexamethasone: commercial drug used.

**Reference Therapy, Dose and Mode of Administration, Batch No.:**

Doxorubicin 9 mg/m$^2$/day continuous IV infusion per Cycle, Days 1-4.
Vincristine 0.4 mg/day continuous IV infusion per Cycle, Days 1-4.
Dexamethasone 40 mg/day PO on Cycle Days 1-4. A cycle was 28 ± 3 days

Doxorubicin, vincristine, and dexamethasone: commercial drug used.

**Duration of Treatment:**

Until any of the following points was reached:

- Disease progression.
- Unacceptable toxicity.
- Stable plateau disease, as defined by a stable monoclonal component over 2 additional cycles of therapy.
- Subjects eligible for bone marrow or hematopoietic stem cell transplantation who have demonstrated a response to either VDD or VAD could proceed to high-dose chemotherapy and transplantation following completion of the fourth cycle of VAD or VDD chemotherapy.

**Criteria for Evaluation:**

Efficacy: The primary efficacy parameter was the objective response rate (ORR), defined as the percentage of subjects who attained an objective status of complete remission (CR), remission (R), or partial remission (PR) according to the Southwest Oncology Group (SWOG) criteria as defined in the protocol. Objective response required a confirmatory assessment at a minimum of 6 weeks after the initial response assessment. Secondary efficacy parameters included time to progression, defined as the time from first study drug administration until documented disease progression or death due to any cause, and overall survival (OS).

Clinical benefit, defined as the incidence of any of the following: grade 3 or 4 neutropenia/neutropenic fever, documented sepsis, antibiotic treatment, or hospitalization for adverse events (AEs), was also a prespecified primary endpoint.

Safety: Safety and tolerability were assessed by monitoring AEs and laboratory abnormalities at each clinic visit. AEs and laboratory results were graded according to the National Cancer Institute (NCI) Common Toxicity Criteria (Version 2). Cardiac function was assessed by multiple gated acquisition scan/echocardiogram (MUGA/ECHO)-derived left ventricular ejection fraction (LVEF) measurements at baseline and every 2 cycles after subjects received 300 mg/m$^2$ cumulative anthracycline dosing.

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**Statistical Methods:**

Two 1-sided tests were performed with $\alpha = 0.025$ for determining therapeutic equivalence between the 2 treatment groups VDD and VAD, on the ORR. The 2 treatment groups were considered therapeutically equivalent if the corresponding 2-sided 95% confidence interval (CI) for the difference in ORR fell within ± 20%. All statistical tests for the other variables were performed at the $\alpha = 0.05$ significance level, 2-sided, with the exception of the analysis of baseline data, which was at the $\alpha = 0.10$ significance level. A sample size of approximately 100 subjects per group provided 80% power to demonstrate therapeutic equivalence for objective response of the 2 treatment groups as defined above, assuming that the ORR would be approximately 50% in each treatment group. This sample size provided greater than 80% power to detect a 20% difference in clinical benefit parameters. Statistical comparisons between treatment groups for response rate and clinical benefit were performed using the 2-sided Fisher's exact test. Progression-free survival (PFS) and OS were estimated using the Kaplan-Meier method. For the PFS analysis, subjects undergoing bone marrow or stem cell transplantation were censored at the date of transplant. A data sweep was conducted in April 2004 to update disease progression and survival status on all available subjects. Hazard ratios were calculated for PFS and OS with values > 1 favoring the VDD group.

**Summary – Conclusions:**

Efficacy Results:

The primary efficacy measure, ORR, was similar between the 2 treatment groups (VDD: 39.2%; 95% CI: 29.5%-48.9% and VAD: 35.8%; 95% CI: 26.1%-45.4%). The 95% CI for the treatment difference in objective response was –17.1 to 10.3%; $P = 0.652$, thus satisfying the protocol-specified criteria for therapeutic equivalence. No significant differences were seen in either PFS (hazard ratio = 1.11; $P = 0.69$) or OS (hazard ratio = 0.884; $P = 0.67$) between treatment groups. With respect to clinical benefit, the VDD treatment group had a significantly lower incidence of grade 3/4 neutropenia than the VAD treatment group: 10.3% vs 24.2% ($P = 0.0128$). In addition, there was a nonsignificant trend toward lower incidence of documented sepsis in the VDD group vs the VAD group: 3.1% vs 8.4% ($P = 0.1314$). The other measures of clinical benefit, including incidence of antibiotic treatment as well as incidence and duration of hospitalization for AEs, did not differ between the treatment groups.

Safety Results:

The most frequent treatment-related AEs reported in both treatment groups included asthenia, followed by nausea, constipation, anemia, and pain. Alopecia, although common in the VAD group (44%), was seen in only 20% of subjects in the VDD group, and pronounced or total hair loss (grade 2) was experienced by 20% of subjects in the VAD group as compared to only 4% of subjects in the VDD group. In addition to alopecia, AEs with a large between-group difference (≥ 8% absolute difference) included anemia (44% vs 36%) and leukopenia (30% vs 18%), which were more common in the VAD group, and hand-foot syndrome (26% vs 1%), dyspepsia (21% vs 13%), stomatitis (31% vs 21%), and vomiting (24% vs 15%), which were more common in the VDD group. Consistent with the lower incidence of myelosuppression, fewer subjects treated with VDD required growth factor support compared to those treated with VAD (22% vs 36%). Hand-foot syndrome, a well-described side effect of DOXIL therapy, was reported in 26% of VDD subjects, but most were of mild-moderate severity (4% grade 3; 0 grade 4) and only 2 subjects discontinued VDD due to hand-foot syndrome. With respect to cardiotoxicity, treatment with VAD was associated with grade 3/4 congestive heart failure in 2 subjects, whereas no subjects treated with VDD experienced grade 3/4 heart failure. Similarly, the mean absolute decrease in LVEF from baseline was greater for the VAD group than the VDD group (–4.5 vs –2.3).

Ninety serious AEs (SAEs) were reported by 34 subjects in the VAD group and 109 SAEs were reported by 36 subjects in the VDD group during this study. Sepsis was reported more often in the VAD group (7% vs 3%) while 4 SAEs were reported more often in the VDD group: pneumonia (9% vs 4%), dehydration (6% vs 0%), asthenia (5% vs 0%), and nausea (5% vs 0%). The difference between groups was ≤ 9% for all preferred terms. Otherwise, no individual SAEs appear to have been concentrated in a particular treatment group

Hepatic and renal function, assessed throughout the study by monitoring of laboratory values for aspartate aminotransferase (AST)/total bilirubin, and serum creatinine, respectively, indicated that for both treatment groups neither hepatic nor renal toxicity occurred over the course of the study and, in fact, renal function may have shown a slight improvement. However individual elevations in total bilirubin and serum AST levels were more likely to occur in the VAD group than in the VDD group (5% vs 1% for elevated AST, 11% vs 2% for elevated bilirubin).

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Conclusions:

- Therapeutic equivalence between the VDD and VAD regimens, as prospectively defined in the protocol, was demonstrated.
- The incidence of grade 3 or 4 neutropenia, a prespecified clinical benefit parameter, was significantly lower for VDD compared to VAD, although no significant difference in other measures of clinical benefit was demonstrated between the 2 groups.
- There were no instances of grade 3/4 congestive heart failure in the VDD group.
- Other safety advantages of VDD as compared to VAD included less alopecia, less effect on cardiac function, fewer incidents of sepsis, and lower growth factor support use. However, treatment with VDD was associated with a higher incidence of hand-foot syndrome (26% vs 1%), a common but reversible DOXIL-associated toxicity, as well as stomatitis (31% vs 21%).

**Date of the report:** 20 October 2006

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