SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: CAELYX®/ DOXIL® NAME OF ACTIVE INGREDIENT(S): Doxorubicin HCl	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Protocol No.: 30-57

Title of Study: A Phase 3, Randomized, Open-Label, Comparative Study of CAELYX® versus Paclitaxel HCl in Patients with Epithelial Ovarian Carcinoma Following Failure of First-Line, Platinum-Based Chemotherapy

Study Initiation/Completion Dates: 7 May 1997/12 April 2000	**Phase of development:** 3

Objectives: The objective of this study was to compare the efficacy and safety of DOXIL (CAELYX) versus paclitaxel HCl in subjects with epithelial ovarian carcinoma following failure of first-line, platinum-based chemotherapy.

Methodology: This was a randomized, open-label, comparative study of DOXIL and paclitaxel in the treatment of subjects with epithelial ovarian carcinoma following failure of first-line chemotherapy with a platinum-based regimen. Subjects entering the trial were stratified by platinum-sensitivity and bulky disease. Protocol-eligible subjects with measurable disease, who had received no more than 1 prior platinum-based regimen, were randomized in a 1:1 ratio within each stratum to receive either a 1-hour intravenous infusion of DOXIL 50 mg/m^2 every 28 days or paclitaxel 175 mg/m^2 as a 3-hour infusion every 21 days. Subjects were to have been treated for up to 1 year.

Subjects underwent appropriate radiologic imaging (x-ray, CT scan, MRI) to document baseline disease, as well as a chest x-ray and an assessment of left ventricular ejection fraction (LVEF) by multiple-gated acquisition scan within 30 days prior to the first dose of study drug. Subjects were followed weekly for hematologic toxicities. Radiologic imaging was repeated every 7 to 8 weeks to assess disease status. Subjects who achieved complete or partial response were reevaluated 4 weeks later to confirm the initial observation of response. All subjects were to have been followed for a minimum of 1 year for survival and disease progression.

The study was closed to new subjects on 31 August 1999, because of poor accrual after Taxol® (paclitaxel HCl) was approved for use in combination with platinum-based therapy for the first-line treatment of ovarian cancer by the European Agency for the Evaluation of Medicinal Products.

Criteria for Evaluation: The planned primary end point was time to progression following treatment with either DOXIL or paclitaxel. The planned secondary end points were response rates, time to response, duration of response, survival, and quality of life assessment following treatment with either DOXIL or paclitaxel. The study was terminated due to poor accrual after approximately 50% of the planned subjects had been entered. Therefore, efficacy analyses were limited to overall survival only, pursuant to an agreement with the Oncology Division.

Safety was assessed by examination of adverse events (AEs), clinical laboratory data, and vital signs. Data for all subjects in the ITT population and for whom an AE form was received prior to the database lock on 8 January 2004 were included in the safety analyses.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS: Demographic characteristics of the 216 subjects in the ITT population (108 DOXIL, 108 paclitaxel) were representative of subjects with advanced epithelial ovarian carcinoma and were similar between treatment groups. The ITT population ranged in age from 20 to 80 years, and the majority was white (97.2%).

For overall survival, the hazard ratio (HR) for paclitaxel relative to DOXIL was 0.931 (95% CI; 0.702, 1.234). The median overall survival was 46.6 weeks for DOXIL and 56.3 weeks for paclitaxel. In subjects with platinum-sensitive disease, the HR was 1.051 (95% CI; 0.663, 1.667). The median overall survival was 65.4 weeks for DOXIL-treated subjects and 57.0 weeks for paclitaxel-treated subjects. For subjects with platinum-refractory disease, the HR was 0.865 (95% CI; 0.605, 1.237). The median overall survival was 36.7 weeks for DOXIL-treated subjects and 54.3 weeks for paclitaxel-treated subjects.

SYNOPSIS (CONTINUED)

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SAFETY RESULTS: The most common treatment-related AEs are summarized by treatment and severity in Table 1. Treatment-related alopecia occurred more often in the paclitaxel-treated subjects (87.0%) than in DOXIL-treated subjects (43.5%). Treatment-related paresthesia and myalgia were also reported more often for paclitaxel-treated subjects (42.6% and 28.7%, respectively) than for DOXIL-treated subjects (13.0% and 2.8%, respectively). Treatment-related hand-foot syndrome (HFS) and stomatitis were reported more often for DOXIL-treated subjects (50.9% and 48.1%, respectively) than for paclitaxel-treated subjects (12.0% and 11.1%, respectively). Treatment-related fever and infection also tended to be more common for DOXIL-treated (12.0% and 11.1%) than for paclitaxel-treated (3.7% and 2.8%) subjects.

Table 1: Most Frequently Reported Treatment-related Adverse Events: All Grades and at Least Grade 3 (Study 30-57; ITT Population)

	DOXIL (N=108)		Paclitaxel (N=108)	
Adverse Event	All Grades	Grade ≥3	All Grades	Grade ≥3
Hand-foot syndrome	55 (50.9%)	17 (15.7%)	13 (12.0%)	0
Nausea	53 (49.1%)	7 (6.5%)	47 (43.5%)	2 (1.9%)
Stomatitis	52 (48.1%)	11 (10.2%)	12 (11.1%)	1 (0.9%)
Alopecia	47 (43.5%)	3 (2.8%)[a]	94 (87.0%)	21 (19.4%)[a]
Asthenia	35 (32.4%)	4 (3.7%)	33 (30.6%)	5 (4.6%)
Paresthesia	14 (13.0%)	0	46 (42.6%)	4 (3.7%)
Myalgia	3 (2.8%)	0	31 (28.7%)	7 (6.5%)

[a] Investigators reported Grade 3 and 4 alopecia, although there are no criteria in the NCI-CTC for these grades.

Treatment-related HFS and stomatitis that were Grade 3 or higher in severity were more common for DOXIL-treated subjects (15.7% and 10.2%, respectively) compared with paclitaxel-treated subjects (0% and 0.9%, respectively). HFS and stomatitis were managed with dose modifications and rarely resulted in treatment discontinuation (HFS 0.9%; stomatitis 3.7%). Six DOXIL-treated subjects discontinued treatment due to treatment-related allergic or anaphylactic reactions reported as serious. One additional DOXIL-treated subject and 1 paclitaxel-treated subject had a treatment-related allergic reaction reported as an SAE. Of note, the protocol specified that all paclitaxel-treated subjects were to have been premedicated with corticosteroids, antihistamines, and H_2 antagonists prior to paclitaxel administration. Grades 3-4 anemia, leukopenia, and neutropenia were more often associated with paclitaxel than with DOXIL treatment. For the paclitaxel-treated group, anemia in 4 (3.7%) subjects was the most common treatment-related serious AE (SAE). The most common treatment-related SAEs for the DOXIL-treated group were fever and vomiting, each in 6 (5.6%) subjects, and abdominal pain, allergic reaction, and stomatitis, each in 4 (3.7%) subjects. There was no evidence of a direct relationship between cumulative DOXIL dose and change from baseline for left ventricular ejection fraction. No cases of clinical cardiotoxicity (signs and symptoms of congestive heart failure) occurred due to cumulative DOXIL exposure.

Twelve (11.1%) of the 108 DOXIL-treated subjects and 8 (7.4%) of the paclitaxel-treated subjects died within 30 days after the last dose of study drug. One hundred (92.6%) of the DOXIL-treated subjects and 101 (93.5%) of the paclitaxel-treated subjects died during treatment or the long-term follow-up period. The most common cause of death reported was disease progression, accounting for the deaths of 97 (89.8%) of the DOXIL-treated subjects and 96 (88.9%) of the paclitaxel-treated subjects. Adverse events unrelated to study drug were the primary cause of death for 3 (2.8%) of the DOXIL-treated subjects and 2 (1.9%) of the paclitaxel-treated subjects. One (0.9%) additional paclitaxel-treated subject died due to an AE of unknown relationship to study drug, and 2 (1.9%) died due to unknown causes.

CONCLUSION: In this population of women with epithelial ovarian cancer whose disease did not respond to or relapsed after first-line platinum-based therapies, overall survival appears to be similar for subjects treated with DOXIL or paclitaxel. DOXIL treatment was less often associated with alopecia and Grade 3-4 hematologic AEs than paclitaxel treatment. Grade 3-4 hand-foot syndrome and stomatitis were more frequently associated with DOXIL treatment. Change from baseline left ventricular ejection fraction shows no direct relationship with cumulative DOXIL dose, and there were no cases of clinical cardiotoxicity (signs or symptoms of congestive heart failure) due to cumulative DOXIL exposure.

Date of the report: 15 March 2004