SYNOPSIS

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

Protocol No.: 30-49

Title of Study: A Phase 3, Randomized, Open-Label, Comparative Study of DOXIL/CAELYX Versus Topotecan HCl in Patients With Epithelial Ovarian Carcinoma Following Failure of First-Line, Platinum-Based Chemotherapy

Coordinating Investigator: Alan Gordon, M.D. - [redacted]; USA

Publication (Reference): Gordon AN, Fleagle JT, Guthrie D, Parkin DE, Gore ME, Lacave AJ. Recurrent epithelial ovarian carcinoma: a randomized phase III study of pegylated liposomal doxorubicin versus topotecan. J Clin Oncol 2001;19(14):3312-3322.

Smith DH, Adams JR, Johnston SR, Gordon A, Drummond MF, Bennett CL. A comparative economic analysis of pegylated liposomal doxorubicin versus topotecan in ovarian cancer in the USA and the UK. Ann Oncol 2002;13(10):1590-1597.

Study Initiation/Completion Dates: 1 May 97 to 05 May 2003 (database lock) | **Phase of development:** 3

Objectives: The primary objective of this study was to compare the efficacy and safety of DOXIL to those of topotecan in subjects with epithelial ovarian carcinoma following failure of first-line, platinum-based chemotherapy. It was designed as a noninferiority study. The objective of the poststudy long-term follow-up analysis is to compare DOXIL versus topotecan HCl in terms of survival and PFS when approximately 90% of subjects have either died or are lost to follow-up.

Methodology: This was a Phase 3, parallel-group, randomized, multicenter, open-label, active-controlled study. Subjects were randomized in a 1:1 ratio stratified by platinum sensitivity and the presence or absence of bulky disease. The treatments were DOXIL 50 mg/m^2 via a 1-hour i.v. infusion every 4 weeks, or topotecan 1.5 mg/m^2 via a 30-minute i.v. infusion daily for 5 consecutive days every 3 weeks. Subjects who withdrew from the study were not replaced. Subjects underwent appropriate radiologic imaging (X-ray, computed tomography [CT] scan, magnetic resonance imaging [MRI]) to document baseline disease, as well as a chest X-ray within 30 days prior to the first dose of study drug. Left ventricular ejection fraction (LVEF) was to have been assessed by multiple-gated acquisition (MUGA) scan at baseline and at the end of the study for all subjects. For DOXIL-treated subjects, LVEF was also to have been assessed when the cumulative anthracycline dose reached 300 mg/m^2 and every 2 cycles thereafter. Subjects were followed weekly for hematologic toxicities. Disease status was assessed by radiologic imaging every 8 weeks. Subjects who achieved a complete or partial response had their radiologic imaging repeated at least 4 weeks later to confirm the initial observation of response.

Number of Subjects (planned and analyzed): To obtain 370 evaluable subjects, up to 460 subjects were to have been enrolled in the study. There were 481 women randomized, of whom 474 received at least a partial dose of study drug and comprise the intent-to-treat (ITT) analysis population.

Diagnosis and Main Criteria for Inclusion: Subjects had histologically proven epithelial ovarian carcinoma, with measurable disease or measurable and evaluable disease. They experienced either a recurrence of disease or disease progression indicative of failure of first-line, platinum-based chemotherapy. Their Karnofsky Performance Status (KPS) was 60% or higher. The minimum age was 18 years. All subjects had adequate bone marrow, renal, and liver function, and a left ventricular ejection fraction (LVEF) of 50% or higher. They were disease-free from prior malignancies for more than 5 years with the exception of curatively treated basal cell or squamous cell carcinoma of the skin or carcinoma in situ of the cervix.

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Test Product, Dose and Mode of Administration, Batch No.: DOXIL was supplied by ALZA Corporation in sterile vials, each containing 20 mg doxorubicin HCl in a pegylated liposomal formulation at a concentration of 2.0 mg/mL. The study drug was refrigerated at 2°C to 8°C. Subjects randomized to DOXIL treatment received 50 mg/m^2 via a 1-hour i.v. infusion every 4 weeks. DOXIL dose modifications for hand-foot syndrome (HFS, also called palmar-plantar erythrodysesthesia or PPE), hematologic toxicity, elevated bilirubin, and stomatitis were recommended in the protocol. For all other Grade 3 and 4 events, a 25% reduction was recommended until the toxicity resolved to a severity of Grade 2 or lower. Both investigational and commercial lots of DOXIL were used. DOXIL lot numbers used were: 3DOX13, 4DOX01, 6DOX-3, 6DOX-5, 6DOX-6, 6DOX-8, 6DOX-11, 6DOX-13, 6DOX-14, 6DOX-16, 7DOX-01, 7DOX-03, 7DOX-07, 7DOX-14, 7DOX-15, 7DOX-18, 8DOX-16, 8DOX-20A, 8DOX-23.

Reference Therapy, Dose and Mode of Administration, Batch No.: Topotecan for injection was purchased commercially by study sites. Subjects randomized to topotecan treatment received 1.5 mg/m^2 via a 30-minute i.v. infusion daily for 5 consecutive days every 3 weeks, starting on Day 1 of a 21-day cycle (7.5 mg/m^2 every 3 weeks). Topotecan dose reductions were to be made for hematologic toxicity and renal function impairment. In the event of severe neutropenia during any cycle, the dose of topotecan was to be reduced by 0.25 mg/m^2 for subsequent cycles .

Duration of Treatment: Treatment with either drug was to be continued for up to 1 year in the absence of disease progression. Treatment could be extended as needed with sponsor consent if the investigator concluded that the subject continued to benefit from treatment. According to the standards of care for this patient population at many participating sites, subjects were given an option of discontinuing the study treatment after 6 months (6 cycles of DOXIL, 8 cycles of topotecan) and in such instances were considered to have completed the protocol.

Criteria for Evaluation:

Efficacy: Survival was the primary efficacy end point for this report. Other efficacy end points included progression-free survival, time to progression, response rate, time to response, and duration of response.

Safety: Safety was evaluated by adverse event reporting, MUGA scan or echocardiogram evaluation, and clinical laboratory tests (hematology, serum chemistry, and urinalysis). Vital sign measurements and physical examination results (including Karnofsky score) were also recorded.

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Statistical Methods: The ITT population (all subjects who were randomized and received at least a partial dose of study drug) was used for all safety and efficacy analyses in this report.

Survival time is defined as the time from the start of study drug administration to death. Progression-free survival (PFS) is defined as the time from the start of study drug administration to documented disease progression or death due to any cause. Overall survival (OS), PFS, and time to progression were estimated for each treatment using the Kaplan-Meier method. The 2 treatments were compared using the stratified log-rank test as a primary analysis. Hazard ratios with 2-sided 95% confidence intervals (CIs) were calculated. A hazard ratio (HR) greater than 1.0 indicates favorable efficacy for DOXIL relative to topotecan. To assess the potential influence of demographic and baseline disease characteristics, a Cox regression analysis was performed. Comparison of response rates (CR + PR) between the 2 treatment groups was conducted using a Cochran-Mantel-Haenszel analysis stratified by platinum-sensitivity and bulky disease. The response rates were also summarized using a 2-sided 95% CI for the difference between the 2 treatment groups. All statistical tests in these analyses were 2-sided. An overall 5% level of significance was used for treatment difference and a 10% level for interaction.

The Sponsor reviewed prior chemotherapy data (medications, start and end dates, and best response) and recurrence date to confirm that the investigators' assignments were made according to the protocol-specified criteria; fewer than 10% of subjects were reclassified. The primary efficacy analyses (OS) were repeated using the sponsor's classification.

For the end-of-planned-treatment report a quality-adjusted survival analysis (Q-TWiST) was used to compare the 2 treatments, taking into account both the quality and quantity of life. The analysis was not updated for this report.

Adverse events were summarized using a COSTART thesaurus. For each subject, multiple reports of adverse events mapped to a common COSTART term are presented as a single event, to which is assigned the greatest severity and strongest relationship to study drug observed among the multiple reports. NCI Common Toxicity Criteria were used to grade toxicities. The relationship to study drug was also assessed.

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SUMMARY – CONCLUSIONS

EFFICACY RESULTS: There was an observed benefit in OS for DOXIL-treated subjects over topotecan-treated subjects as indicated by a HR of 1.216 (95% CI; 1.000, 1.478). The median overall survival was 62.7 weeks for DOXIL and 59.7 weeks for topotecan. For subjects with platinum-sensitive disease, there was an even greater observed benefit in OS for DOXIL over topotecan: HR of 1.432 (95% CI; 1.066, 1.923). The median OS was 107.9 weeks for DOXIL and 70.1 weeks for topotecan. These differences were sustained in 2-year and 3-year survival rates.

Overall Survival: Stratified Logrank Test
(Study 30-49; ITT Population)

ITT Set Treatment	N	% Censored	Median (weeks)	Range	P Value	Hazard Ratio[a]	95% CI for HR
All							
DOXIL	239	16.7	62.7	1.7 – 258.3	0.050	1.216	1.000, 1.478
Topotecan	235	8.9	59.7	1.6 – 247.1+	---	---	---
Platinum-sensitive							
DOXIL	109	22.0	107.9	6.9 – 258.3	0.017	1.432	1.066, 1.923
Topotecan	110	10.9	70.1	1.6 – 247.1+	---	---	---

[a] Hazard ratio (HR) >1 favors DOXIL.
+ indicates a censored observation.

For subjects with platinum-refractory disease, survival was similar for DOXIL-treated subjects and topotecan treated-subjects as indicated by a HR of 1.069 (95% CI; 0.823, 1.387).

Adjusted for possible prognostic factors, the HR for DOXIL relative to topotecan for OS is 1.189, similar to that for the primary analysis, thereby indicating that the overall results favoring DOXIL treatment demonstrated in the primary analysis were not affected by the influence of prognostic factors. Analyses of overall survival without taking strata into consideration, or using the sponsor's reclassification of strata, gave results similar to analyses using the investigator's classification of strata.

There was a trend toward benefit in PFS for DOXIL over topotecan: HR of 1.118 (95% CI; 0.928, 1.347). The median PFS was 16.1 weeks for Doxil and 16.9 weeks for topotecan. There was a trend toward benefit in PFS for DOXIL-treated subjects in the platinum-sensitive subgroup (HR=1.287; 95% CI; 0.977, 1.694). There was no difference in PFS between the treatment groups (HR=0.992; CI, 0.770, 1.279) in the platinum-refractory subgroup. Adjusted for possible prognostic factors, the HR for PFS is 1.07, similar to that for the primary analysis.

The time to progression for the ITT population did not differ between the treatments as indicated by a HR of 1.053 (95% CI; 0.841, 1.319). The objective response rate was similar for the 2 treatment groups: 19.7% for DOXIL and 17.0% for topotecan. For responding subjects, median time to response was the same for the 2 treatment groups (8.1 weeks), with a range of 4.0 to 28.4 weeks for DOXIL and 5.6 to 44.1 weeks for topotecan. The median duration of response was 30.1 weeks for DOXIL (range, 5.0+ to 93.1) and 25.7 weeks for topotecan (range 7.0+ to 93.9+).

The quality-adjusted survival analysis (end-of-planned-treatment) shows that when quality of life outcomes such as toxicity and progression are also taken into account, DOXIL is always preferred over topotecan.

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SUMMARY – CONCLUSIONS (cont'd)

SAFETY RESULTS: The most common treatment-related AEs for the DOXIL-treated subjects were HFS (50.6%), stomatitis (40.6%), nausea (36.8%), leukopenia (36.4%), anemia (36.0%), neutropenia (35.1%), and asthenia (32.6%). The most common treatment-related AEs for the topotecan-treated subjects were neutropenia (81.3%), anemia (71.9%), thrombocytopenia (64.7%), leukopenia (63.4%), nausea (54.9%), alopecia (52.3%), asthenia (44.3%), and vomiting (34%). Drug-related hematologic AEs (neutropenia, anemia, thrombocytopenia, and leukopenia) and alopecia were experienced by a higher percentage of topotecan-treated than of DOXIL-treated subjects. HFS and stomatitis were experienced by a higher percentage of DOXIL-treated subjects

Selected Treatment-related Adverse Events: All Grades and at Least Grade 3
(Study 30-49; ITT Population)

	DOXIL (N=239)		Topotecan (N=235)	
Preferred term adverse event	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)
Neutropenia	84 (35.1%)	29 (12.1%)	191 (81.3%)	180 (76.6%)
Anemia	86 (36.0%)	12 (5.0%)	169 (71.9%)	66 (28.1%)
Thrombocytopenia	31 (13.0%)	3 (1.3%)	152 (64.7%)	80 (34.0%)
Leukopenia	87 (36.4%)	24 (10.0%)	149 (63.4%)	117 (49.8%)
Alopecia	45 (18.8%)	3 (1.3%)[a]	123 (52.3%)	15 (6.4%)[a]
HFS	121 (50.6%)	57 (23.8%)	2 (0.9%)	0
Stomatitis	97 (40.6%)	20 (8.4%)	35 (14.9%)	1 (0.4%)

[a] Investigators reported Grade 3 alopecia even though the NCI CTC lists criteria only for Grade 1 and 2.

Treatment-related hematologic toxicities Grade ≥3 were more often associated with topotecan than with DOXIL (neutropenia 76.6% vs. 12.1%, leukopenia 49.8% vs. 10.0%, thrombocytopenia 34.0% vs. 1.3%, and anemia 28.1% vs. 5.0%, respectively). The need for hematologic growth factor was substantially higher with topotecan than with DOXIL (G-CSF/GM-CSF 29.5% vs. 4.6%, epoetin alfa 23.1% vs. 6.3%), as was the requirement for blood product transfusions (57.8% vs. 15.0%). Sepsis was reported as a reason for discontinuation for 5 topotecan-treated subjects, 2 of who died due to this complication. No DOXIL-treated subjects discontinued due to sepsis. Treatment-related alopecia was observed in 52.3% of topotecan-treated subjects compared with 18.8% incidence with DOXIL.

Most drug-related adverse events associated with DOXIL were Grade 1 or 2, with the exceptions of HFS (Grade 3 in 23.0%, Grade 4 in 0.8%) and stomatitis (Grade 3 in 7.9%, Grade 4 in 0.4%). HFS and stomatitis were managed with dose modifications and rarely resulted in study discontinuation (3.3% of the DOXIL-treated subjects discontinued due to HFS alone and 0.8% discontinued due to HFS and stomatitis). There was no evidence of a relationship between cumulative DOXIL dose and reduction from baseline for left ventricular ejection fraction (LVEF). No cases of clinical cardiotoxicity occurred due to cumulative DOXIL exposure.

Fifteen (6.3%) of the 239 DOXIL-treated subjects and 28 (11.9%) of the 235 topotecan-treated subjects died within 30 days after the last dose of study drug. No cause of death was specified for 1 DOXIL-treated and 5 topotecan-treated subjects. The most common cause of death reported was carcinoma (disease progression), accounting for the deaths of 3 DOXIL-treated subjects and 6 topotecan-treated subjects. Fatal heart arrest, hepatic failure, and shock, respectively, occurred in 3, 2, and 2 DOXIL-treated subjects. Fatal heart arrest and sepsis, respectively, occurred in 4 and 3 topotecan-treated subjects. No unusual or unexpected serious adverse events were reported.

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CONCLUSION: This analysis of long-term follow-up data confirms that in this population of subjects with ovarian cancer, whose disease does not respond to or relapses after platinum-based therapy, DOXIL treatment provides a survival advantage when compared with topotecan treatment. The pronounced survival advantage for DOXIL-treated subjects with platinum-sensitive disease is confirmed by this long-term follow-up analysis. Survival was comparable for the treatments in subjects with platinum-refractory disease. The Q-TWiST analysis showed that when QOL outcomes such as toxicity and progression are also taken into account, DOXIL is preferred over topotecan. DOXIL treatment is less often associated with hematologic AEs, dose modifications, and life-threatening sequelae than topotecan treatment. Date of the report: 06 October 2006		