SYNOPSIS

Name of Sponsor/Company	Janssen Research & Development*
Name of Active Ingredient(s)	R031059 (doxorubicin HCL liposome injection)

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Status: Approved

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Prepared by: Janssen Research & Development, LLC

Protocol No.: DOXILNAP1004

Title of Study: A Pivotal Bioequivalence Study of DOXIL®/CAELYX® Manufactured at a New Site in Subjects with Advanced or Refractory Solid Malignancies

EudraCT Number: 2013-004641-16

NCT No.: NCT02081495

Clinical Registry No.: CR103500

Principal Investigator(s): Emiliano Calvo, MD - Centro Integral Oncológico Clara Campal, [redacted] Spain

Study Center(s): The study was conducted in Belgium (2 sites), Canada (1 site), Spain (2 sites), and the United States (US) (1 site).

Publication (Reference): Not applicable.

Study Period: The first subject signed the informed consent form (ICF) on 11 August 2014 and the last subject signed the ICF on 16 December 2014. The last subject completed or discontinued from the Open-Label Treatment Phase on 23 April 2015. The database was locked on 28 April 2015.

Phase of Development: 1

Objectives: The primary objective of this study was to demonstrate bioequivalence (BE) between DOXIL/CAELYX reference product and test product based on the encapsulated doxorubicin pharmacokinetic parameters of C_{max}, $AUC_{0-t,}$ and $AUC_{0-\infty}$ in subjects with solid malignancies.

The secondary objectives of this study were:

- To evaluate free doxorubicin based on arithmetic difference of total doxorubicin plasma concentrations minus encapsulated doxorubicin plasma concentrations
- Safety of DOXIL/CAELYX
- Investigator determined response at End-of-Treatment visit.

The additional objective of this study was to demonstrate BE between DOXIL/CAELYX reference product and test product based on the total doxorubicin pharmacokinetic parameters of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ in subjects with solid malignancies.

Methodology: This was a randomized, open-label, single dose, 2-cycle, crossover BE study of DOXIL/CAELYX. The study was open to enrollment of subjects with advanced or refractory solid malignancies. The study included a Screening Phase (within 28 days before the first DOXIL/CAELYX administration) followed by an Open-Label Treatment Phase consisting of 2 DOXIL/CAELYX treatment cycles (28 days each) and an End-of-Treatment visit. Subjects could then enter the Optional Extension Phase.

On Day 1 of Cycle 1 of the Open-Label Treatment Phase, before administration of study drug, subjects were to be randomized to 1 of 2 treatment sequence groups (AB or BA) in a 1:1 ratio as follows:

- Treatment A: DOXIL/CAELYX, produced at the current manufacturing site (Ben Venue Laboratories [BVL]; reference product) administered by IV infusion over 90 minutes at a dose of 50 mg/m^2
- Treatment B: DOXIL/CAELYX, produced at a new manufacturing site (GlaxoSmithKline [GSK]; test product) administered by IV infusion over 90 minutes at a dose of 50 mg/m^2

A description of the treatment sequence is provided below.

Treatment Sequence	Cycle 1	Cycle 2
AB	Treatment A (Reference)	Treatment B (Test)
BA	Treatment B (Test)	Treatment A (Reference)

During the Open-Label Treatment Phase, subjects were closely monitored for adverse events (AEs), laboratory abnormalities, and clinical response. Blood samples were to be obtained from all subjects at specified times over 26 days after starting each study drug administration in Cycles 1 and 2 for determination of plasma concentrations of encapsulated and total doxorubicin.

After completion of Cycle 2, subjects were to participate in the End-of-Treatment visit and could enter the Optional Extension Phase of the study at the discretion of the Investigator. Treatment with DOXIL/CAELYX reference product could be continued for up to 1 year after first dose in the absence of disease progression or unacceptable toxicity. During the Extension Phase, subjects were monitored for safety and followed for efficacy as per institutional guidelines, and in accordance with standard of care and accepted medical practices at the discretion of the Investigator. In the Optional Extension Phase, only serious adverse events (SAEs) within 30 days of last dose were to be collected.

Number of Subjects (planned and analyzed): Planned: Approximately 32 subjects were planned to be enrolled in the study in order to ensure there were at least 24 pharmacokinetic evaluable subjects for assessment of bioequivalence. Analyzed: A total of 35 subjects were randomized and analyzed in this report. Twenty-nine subjects were evaluable for the primary BE analysis (ie, PK evaluable), and all 35 subjects were evaluable for safety.

Diagnosis and Main Criteria for Inclusion: The main criteria for inclusion were men or women of age 18 years or older with histologically or cytologically confirmed solid malignancies, who had Eastern Cooperative Oncology Group (ECOG) performance status score of 0 to 2, prior cumulative doxorubicin (or other anthracyclines) exposure of ≤360 mg/m^2 or prior cumulative epirubicin exposure of ≤720 mg/m^2, left ventricular ejection fraction (LVEF) within normal institutional limits, adequate liver and renal function, and adequate bone marrow reserve.

Test Product, Dose and Mode of Administration, Batch No.: DOXIL/CAELYX 50 mg/m^2 as a 90-minute IV infusion, manufactured at the new site (GSK). The test product is referred to throughout this report as Treatment B. The lot number was 4002.

Reference Therapy, Dose and Mode of Administration, Batch No.: DOXIL/CAELYX 50 mg/m^2 as a 90-minute IV infusion, manufactured at the current site (BVL). The reference product is referred to throughout this report as Treatment A. The lot numbers were DJBS300 and EDBS000.

Duration of Treatment: The study included a Screening Phase (within 28 days before the first DOXIL/CAELYX administration) followed by an Open-Label Treatment Phase consisting of 2 DOXIL/CAELYX treatment cycles (28 days each) and an End-of-Treatment visit on Cycle 3, Day 1. Subjects could then enter the Optional Extension Phase and receive treatment for up to 1 year after their first dose.

Criteria for Evaluation:

Pharmacokinetics:

Blood samples were to be obtained from all subjects at specified times over 26 days after starting each study drug administration in Cycles 1 and 2 for determination of plasma concentrations of encapsulated and total doxorubicin. The following plasma pharmacokinetic parameters were determined for each dose as appropriate: maximum observed plasma concentration (C_{max}), time to reach the maximum observed plasma concentration (t_{max}), AUC_{0-t} (interchangeable with AUC_{0-last}), $AUC_{0-\infty}$, elimination half-life associated with the terminal slope (λ_z) of the semilogarithmic drug concentration-time curve, calculated as $0.693/\lambda_z$ ($t_{1/2,\lambda}$) and first-order rate constant associated with the terminal portion of the curve, determined as the negative slope of the terminal log-linear phase of the drug concentration-time curve. In addition, CL and Vd were also determined.

Safety: Safety evaluations included AEs, electrocardiograms (ECG), vital signs, and laboratory tests. All AEs were to be collected from the time the ICF was signed until completion of the last study procedure. Thereafter in the Optional Extension Phase only SAEs were to be collected until 30 days after the last dose of DOXIL/CAELYX. The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03, were used to grade the severity of AEs.

Statistical Methods:

Sample Size Determination: For BE assessment of encapsulated doxorubicin, a sample size of 24 pharmacokinetic-evaluable (PK-evaluable) subjects provides an 80% power to ensure that the 2-sided 90% confidence interval (CI) for the geometric mean ratio (GMR; reference product vs. test product) of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ fall completely within (0.80, 1.25). This calculation assumes an intra-subject variability (coefficient of variation, CV) of 20% and an underlying GMR of 0.95. Thirty-two subjects were to be enrolled to ensure that at least 24 subjects would be evaluable for pharmacokinetic assessments.

Endpoints and Analyses: The primary endpoint was the pharmacokinetic analysis of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ for encapsulated doxorubicin collected up to 26 days after dosing in Cycles 1 and 2. The secondary endpoint was to evaluate the arithmetic difference of total doxorubicin concentration minus encapsulated doxorubicin concentration collected up to 26 days after dosing in Cycles 1 and 2. An additional endpoint was C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ for total doxorubicin measured up to 26 days after dosing in Cycles 1 and 2.

Statistical analyses to determine BE were based on C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$. The analyses were performed on the log-transformed pharmacokinetic parameters for encapsulated and total doxorubicin for

all PK-evaluable subjects. A mixed-effect model that included treatment, cycle, and treatment sequence as fixed effects, and subject as a random effect, was used to estimate the least squares means and intra-subject variance.

Using these estimated least squares means and intra-subject variance, the point estimate and 90% CIs for the difference in means on a log scale between Treatment A and Treatment B were constructed. The limits of the CIs were retransformed using antilogarithms to obtain the specified CIs for the ratios of geometric mean C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ of the test to reference formulation (Treatment B/Treatment A). Bioequivalence of Treatment B vs. Treatment A was to be concluded if the specified CIs for the ratios fell within 0.80 to 1.25 for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$. The primary objective of the study would be achieved if BE was concluded for encapsulated doxorubicin on subjects of all cancer types.

RESULTS:

STUDY POPULATION: Thirty-five subjects were randomized into the study. Of the 35 subjects, 31 subjects (88.6%) completed the treatment phase and 4 subjects (11.4%) discontinued early. Reasons for early discontinuation included death, AE, withdrawal of consent, and progressive disease (PD) or relapse (1 subject each).

The most common diagnoses were breast cancer (9 subjects) and ovarian cancer (6 subjects). The median age was 57.0 years, and the study population comprised 26 women (74.3%) and 9 men (25.7%). Of the 35 randomized subjects, 33 subjects received both the Cycle 1 and Cycle 2 doses of study drug, and 2 subjects received only the Cycle 1 dose of study drug. Nineteen subjects (54.3%) entered the Optional Extension Phase of the study.

Treatment cycle delays at Cycle 2 were reported for 4 subjects after receiving Treatment B (GSK) in Cycle 1, and 2 subjects after receiving Treatment A (BVL) in Cycle 1. The majority were due to AEs. Two subjects (1 in each treatment sequence) were reported to have dose adjustments. One subject (treatment sequence AB) had a dose reduction in Cycle 2 because of toxicity (Grade 3 stomatitis) and the other subject (treatment sequence BA) had their calculated weight-based dose rounded up from 78.5 mg to 79.0 mg in both Cycles 1 and 2 at the discretion of the hospital pharmacist.

PHARMACOKINETIC RESULTS:

Primary Endpoint, Encapsulated Doxorubicin: Arithmetic mean values for the key pharmacokinetic exposure parameters for encapsulated doxorubicin, C_{max}, AUC_{0-last}, and $AUC_{0-\infty}$, were similar for both treatments. Median t_{max} values, mean $t_{1/2}$ values, and mean values for systemic clearance and volume of distribution were also similar for both treatments. The table below shows the 90% CIs for the test-to-reference GMRs of $AUC_{0-\infty}$, AUC_{0-last}, and C_{max} of encapsulated doxorubicin, which were fully contained within the prespecified BE limits of 80% to 125%, indicating BE of the 2 treatments with respect to encapsulated doxorubicin.

Statistical Analyses Results: Geometric Means and the Ratio of Geometric Means With Corresponding 90% Confidence Intervals for Encapsulated Doxorubicin Pharmacokinetic Parameters in Cancer Subjects

(Study DOXILNAP1004: Pharmacokinetic Statistical Analysis Set)

Parameter[a]	Geometric Mean DOXIL/CAELYX[b], 50 mg/m^2 Treatment B (Test) n=29	DOXIL/CAELYX[b], 50 mg/m^2 Treatment A (Reference) n=29	Geometric Mean Ratio (90% CI)	Intra-Subject CV (%)
C_{max} (µg/mL)	32.94	33.06	99.66 (97.05 – 102.33)	5.9
$AUC_{0\text{-last}}$ (µg.h/mL)	2,816.51	2,838.64	99.22 (90.29 – 109.03)	21.3
$AUC_{0\text{-}\infty}$ (µg.h/mL)[c]	3,114.13[c]	3,099.17[c]	100.48 (91.14 – 110.78)	21.2

[a] A mixed-effect model with treatment, cycle, sequence and cancer type as fixed effects, and subject within sequence as random effect was used for analysis on a log scale, and the results were presented at the original scale after anti-log transformation.
[b] Treatment A: DOXIL/CAELYX 50 mg/m^2 IV infusion manufactured at current site (BVL); Treatment B: DOXIL/CAELYX 50 mg/m^2 IV infusion manufactured at new site (GSK). Treatment A was used as the reference group.
[c] n=27

Secondary Endpoint, Free Doxorubicin: An attempt was made to estimate free doxorubicin concentrations as the arithmetic difference between the total and encapsulated doxorubicin plasma concentrations (a mass balance approach), for all subjects and all time points. Because of similarity in the concentrations of total and encapsulated doxorubicin, the differences across the individual time points were small and sometimes negative. These data were not considered suitable for pharmacokinetic analysis or interpretation, other than to note that the low estimated values indicate that only a small fraction of the administered dose is present in plasma as the free (unencapsulated) form.

In addition to the mass balance approach, the percent free doxorubicin exposure was estimated based on the ratio of observed geometric mean parameters of encapsulated to total doxorubicin. Due to the small difference between total and encapsulated forms of doxorubicin, the ratio for the pharmacokinetic parameters was close to 1 for both Treatment A and Treatment B. These data suggest that approximately 10% of the circulating doxorubicin was present in the free form and the percent free doxorubicin values were similar for all 3 pharmacokinetic parameters for Treatments A and B.

Other Endpoint, Total Doxorubicin: Arithmetic mean values for the key pharmacokinetic exposure parameters for total doxorubicin, C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-}\infty}$, were similar for both treatments. Median t_{max} values, mean $t_{1/2}$ values, and mean values for systemic clearance and volume of distribution were also similar for both treatments. The table below shows the 90% CIs for the test-to-reference GMRs of $AUC_{0\text{-}\infty}$, $AUC_{0\text{-last}}$, and C_{max} of total doxorubicin, which were fully contained within the prespecified BE limits of 80% to 125%, indicating BE of the 2 treatments with respect to total doxorubicin.

Statistical Analyses Results: Geometric Means and the Ratio of Geometric Means With Corresponding 90% Confidence Intervals for Total Doxorubicin Pharmacokinetic Parameters in Cancer Subjects

(Study DOXILNAP1004: Pharmacokinetic Statistical Analysis Set)

Parameter[a]	Geometric Mean DOXIL/CAELYX[b], 50 mg/m^2 Treatment B (Test) n=29	DOXIL/CAELYX[b], 50 mg/m^2 Treatment A (Reference) n=29	Geometric Mean Ratio (90% CI)	Intra-Subject CV (%)
C_{max} (µg/mL)	32.50	31.45	103.33 (100.34 – 106.42)	6.6
$AUC_{0\text{-last}}$ (µg.h/mL)	3,119.06	3,071.36	101.55 (95.29 – 108.23)	14.3
$AUC_{0\text{-}\infty}$ (µg.h/mL)[c]	3,420.24[c]	3,448.42[c]	99.18 (92.96 – 105.83)	13.7

[a] A mixed-effect model with treatment, cycle, sequence and cancer type as fixed effects, and subject within sequence as random effect was used for analysis on a log scale, and the results were presented at the original scale after anti-log transformation.
[b] Treatment A: DOXIL/CAELYX 50 mg/m^2 IV infusion manufactured at current site (BVL); Treatment B: DOXIL/CAELYX 50 mg/m^2 IV infusion manufactured at new site (GSK). Treatment A was used as the reference group.
[c] n=26

EFFICACY RESULTS: Thirty-one subjects had a response assessment at the end of treatment. At the end of 2 cycles of treatment, the investigator-determined response was partial response (PR) for 2 subjects, stable disease for 19 subjects, and PD for 10 subjects. The PRs were reported for 1 subject with breast cancer and 1 subject with endometrial cancer.

SAFETY RESULTS: All 35 subjects received at least 1 dose of study medication and were included in the safety population. Thirty-three subjects had at least one treatment-emergent adverse event (TEAE). Drug-related TEAEs were reported for 85.7% of total subjects. Serious adverse events were reported for 42.9% of subjects, with 2 subjects reported to have drug-related SAEs (stomatitis and febrile neutropenia). Three subjects died within 30 days of their last dose; all 3 had fatal TEAEs of general physical health deterioration that were considered by investigators to be unrelated to study treatment and 2 of 3 happened in the context of disease progression. One subject had a TEAE leading to treatment discontinuation of general deterioration of health due to PD; this was one of the subjects who died within 30 days. The most commonly reported TEAEs (ie, reported for ≥20% of subjects) were nausea (40.0%), stomatitis (40.0%), decreased appetite (37.1%), fatigue (31.4%), anemia (28.6%), constipation (28.6%), vomiting (22.9%), pyrexia (20.0%), dyspnea (20.0%), and neutropenia (20.0%). A summary of adverse events is displayed in the table below.

Summary of Adverse Events; Safety Analysis Set (Study DOXILNAP1004)

	All Cancer Types		
	Trt B[a]	Trt A[a]	Total
Analysis set: safety subjects	34	34	35
Treatment-emergent adverse events(TEAEs)	30 (88.2%)	30 (88.2%)	33 (94.3%)
Toxicity grade 1	6 (17.6%)	9 (26.5%)	3 (8.6%)
Toxicity grade 2	10 (29.4%)	11 (32.4%)	12 (34.3%)
Toxicity grade 3	11 (32.4%)	6 (17.6%)	12 (34.3%)
Toxicity grade 4	2 (5.9%)	3 (8.8%)	4 (11.4%)
Drug-related[b]	22 (64.7%)	24 (70.6%)	30 (85.7%)
Serious TEAEs	11 (32.4%)	6 (17.6%)	15 (42.9%)
Drug-related[b]	1 (2.9%)	1 (2.9%)	2 (5.7%)
TEAE leading to treatment discontinuation	1 (2.9%)	0	1 (2.9%)
Drug-related[b]	0	0	0
All deaths	1 (2.9%)	2 (5.9%)	3 (8.6%)
All deaths within 30 days of last dose	1 (2.9%)	2 (5.9%)	3 (8.6%)

[a] A: DOXIL/CAELYX 50 mg/m^2 IV infusion manufactured at current site (BVL); B: DOXIL/CAELYX 50 mg/m^2 IV infusion manufactured at new site (GSK).
[b] Drug-related adverse events are adverse events with causality reported as possible, probable or very likely.
Note: Grade 5 toxicity events are excluded from toxicity frequency counts.
Note: A subject was counted once within each adverse event category and treatment. For toxicity grade a subject was counted once for the worst grade.

The incidence of TEAEs of clinical interest was comparable for Treatment B and Treatment A, respectively: neutropenia was reported for 11.8% and 11.8% of subjects, stomatitis for 26.5% and 26.5%, palmar-plantar erythrodysaesthesia syndrome (ie, hand-foot syndrome [HFS]) for 8.8% and 5.9%, and thrombocytopenia for 8.8% and 5.9%.

STUDY LIMITATIONS: No notable study limitations were identified by the Sponsor.

CONCLUSION(S): DOXIL/CAELYX produced at a proposed new manufacturing site (GSK) was shown to be bioequivalent to DOXIL/CAELYX produced at BVL. The safety profile observed in this study was consistent with the known safety profile of DOXIL/CAELYX. No new safety concerns were identified.

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