SYNOPSIS

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

* Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; Janssen Infectious Diseases BVBA; Janssen R&D Ireland; or Janssen Research & Development, LLC. The term "sponsor" is used to represent these various legal entities as identified on the Sponsor List.

Status: Approved

Date: 12 September 2014

Prepared by: Janssen Research & Development, LLC

Protocol No.: DOXILNAP1002

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

EudraCT Number: 2013-000376-15

NCT No.: NCT01815294

Clinical Registry No.: CR100961

Coordinating/Principal Investigator(s): [redacted], MD - [redacted] Spain

Study Centers: The study was conducted in Belgium (2 sites), Spain (3 sites), the United Kingdom (UK) (2 sites), and the United States (US) (2 sites).

Publication (Reference): Not applicable.

Study Period: The first subject signed the informed consent form (ICF) on 30 May 2013 and the last subject signed the ICF on 26 February 2014. The clinical cutoff was on 28 April 2014. The database was locked on 6 June 2014.

Phase of Development: 1

Objectives: The primary objective was to demonstrate bioequivalence (BE) between DOXIL/CAELYX reference product and test product based on the encapsulated doxorubicin pharmacokinetic parameters of maximum plasma concentration (C_{max}), area under the plasma concentration-time curve from time 0 to time t (AUC_{0-t}), and area under the plasma concentration-time curve from time 0 to infinite time ($AUC_{0-\infty}$) in subjects with ovarian cancer.

The secondary objectives were:

- To demonstrate BE of free doxorubicin based on pharmacokinetic parameters of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ in subjects with solid malignancies
- Safety of DOXIL/CAELYX
- Investigator-determined response at the End-of-Treatment visit.

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, including subjects with ovarian cancer. 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-day cycles each), and an End-of-Treatment visit. Subjects could then enter the Optional Extension Phase.

On Cycle 1, Day 1 of the Open-Label Treatment Phase, subjects were randomized in a 1:1 ratio to 1 of 2 treatment sequence groups (AB or BA). Randomization was stratified by ovarian versus (vs.) non-ovarian cancer. A description of the treatments and treatment sequences is provided below.

- Treatment A: DOXIL/CAELYX, produced at the current manufacturing site ([redacted] US; reference product) administered by intravenous (IV) infusion over 90 minutes at a dose of 50 mg/m^2
- Treatment B: DOXIL/CAELYX, produced at a new manufacturing site ([redacted] Taiwan; test product) administered by IV infusion over 90 minutes at a dose of 50 mg/m

Treatment sequence

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 to be closely monitored for adverse events (AEs), laboratory abnormalities, and clinical response. Blood samples were to be obtained from all subjects at specified times over 29 days after starting each study agent administration in Cycles 1 and 2 for determination of plasma concentrations of encapsulated and free doxorubicin.

After completion of Cycle 2, subjects were to participate in the End-of-Treatment visit. Subjects who met the continuation criteria 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.

This study was planned as an adaptive 2-stage design. Stage 1 was to include at least 42 subjects with solid cancer who completed the required pharmacokinetic assessments, at least 24 of whom were to be subjects with ovarian cancer. Bioequivalence based on encapsulated doxorubicin was to be tested at the end of Stage 1 using data from at least 24 ovarian cancer subjects. This was to be the final and primary analysis for determination of BE of encapsulated doxorubicin. Bioequivalence based on free doxorubicin was to be evaluated using the adaptive 2-stage procedure. Per this procedure, an interim analysis of free doxorubicin was to be performed on data of all pharmacokinetic-evaluable (PK-evaluable) subjects from Stage 1, which would have led to 1 of 3 possible outcomes: (1) BE of free doxorubicin would have been established and the study was to be stopped; (2) BE based on free doxorubicin would have failed and the study was to be stopped; or (3) the study would have continued into Stage 2 with additional subjects (all solid cancer types) based on sample size re-estimation, and the final analysis of BE based on free doxorubicin was to be performed at the end of Stage 2.

As planned in the protocol, the key consideration for Stage 1 enrollment was to ensure that at least 42 PK-evaluable subjects (for the interim analysis of free doxorubicin), including at least 24 ovarian cancer subjects (for the final analysis of encapsulated doxorubicin), were recruited, considered PK evaluable, and completed the study. Recruitment for Stage 2 was to continue with subjects of all cancer types while these analyses were performed.

Changes to the Planned Analysis:

In consultation with the US Food and Drug Administration (FDA) on 14 April 2014, changes were made to the planned analyses. Based on this agreement, the primary analysis for BE testing would be based on encapsulated doxorubicin using data from PK-evaluable subjects of all cancer types (not just ovarian) who completed both treatment cycles (1 with reference and 1 with test product). Free doxorubicin concentration in plasma and BE testing of free doxorubicin measured from plasma that was specified in the protocol would no longer be required. As an alternative, a mass balance approach would be used to estimate free doxorubicin concentration as the arithmetic difference between the total and encapsulated plasma concentrations. As an additional endpoint, total doxorubicin concentrations for subjects of all cancer types would be measured and tested for BE. Based on this agreement and the sufficient number of subjects already recruited for the revised study design, subject enrollment was permanently stopped and the 2-stage adaptive design planned in the protocol was not implemented. This report summarizes the results of this study as of the cutoff date of 28 April 2014.

Number of Subjects (planned and analyzed): Planned: At least 42 subjects with solid cancer including at least 24 subjects with ovarian cancer were planned to be enrolled in the study. Analyzed: A total of 52 subjects were randomized and analyzed in this report, 24 with ovarian cancer and 28 with other types of solid tumors. Forty (40) subjects were evaluable for the primary BE analysis (ie, PK evaluable), and 51 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 institutional normal 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 by IV infusion, manufactured at the new site [redacted] Taiwan). The test product is referred to throughout this report as Treatment B. Lot number DCXIA1201.

Reference Therapy, Dose and Mode of Administration, Batch No.: DOXIL/CAELYX 50 mg/m^2 by IV infusion, manufactured at the current site ([redacted] US). The test product is referred to throughout this report as Treatment A. Lot numbers CLZ0P00, DCZ0H00, DGZ0S00.

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 day cycles each) and an End-of-Treatment visit. 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 29 days after starting each study drug administration in Cycles 1 and 2 for determination of plasma concentrations of encapsulated and free doxorubicin. The following plasma pharmacokinetic parameters were determined for each dose as appropriate: 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 (λ_z).

Safety: Safety evaluations included AEs, electrocardiograms (ECG), vital signs, and laboratory tests. All AEs were to be recorded from the time the ICF was signed until completion of the last study procedure. Thereafter in the Optional Extension Phase only serious adverse events (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:

This section describes the planned analyses based on the agreement with FDA.

Sample size determination: For BE assessment of encapsulated doxorubicin, a sample size of 24 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) of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ falls 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. The total number of PK-evaluable subjects included in the analyses would be greater than 24 (approximately 40) because of the study design modification per agreement with the FDA.

Endpoints and Analyses:

The primary endpoint was the pharmacokinetic analysis of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ for encapsulated doxorubicin measured up to 29 days after dosing in Cycles 1 and 2. The secondary endpoints were 1) free doxorubicin plasma concentration, which was estimated by the arithmetic difference of total doxorubicin concentration minus encapsulated doxorubicin concentration measured up to 29 days after dosing in Cycles 1 and 2; 2) safety; and 3) investigator-determined response at the End-of-Treatment visit. As an additional endpoint, C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ for total doxorubicin were measured up to 29 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, treatment sequence, and cancer type (ovarian/non-ovarian) 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 was constructed. The limits of the CIs were retransformed using antilogarithms to obtain the specified CIs for the ratios of the 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: Fifty-four subjects were randomized into the study, and data from 52 subjects are included in this report. Data from 2 subjects who had not completed 2 cycles of treatment by the time of clinical cutoff were not included in this report and will be reported at a later time. Of the 52 subjects, 46 subjects (88.5%) completed the treatment phase, 5 subjects (9.6%) discontinued early, and 1 subject never received study drug. Reasons for early discontinuation included AE (bone marrow failure), withdrawal of consent, and progressive disease (1 subject each), and the reason was categorized as "other" for 2 subjects.

The study included 24 subjects with ovarian cancer and 28 subjects with other types of solid tumors. The most common diagnoses other than ovarian cancer were breast cancer (9 subjects) and colorectal cancer

(7 subjects). The median age was 61.5 years, and the study population comprised 38 women (73.1%) and 14 men (26.9%). Of the 52 randomized subjects, 48 subjects received both the Cycle 1 and Cycle 2 doses of study drug, 3 subjects received only the Cycle 1 dose of study drug, and 1 subject received no study drug. Twenty-nine subjects (55.8%) entered the Optional Extension Phase of the study.

Treatment cycle delays at Cycle 2 were reported for 6 subjects after receiving Treatment A ([redacted] in Cycle 1, and 7 subjects after receiving Treatment B ([redacted] in Cycle 1. The majority were due to AEs. Two subjects (1 in each treatment sequence) had dose reductions (to 38 mg/m^2) at Cycle 2 because of toxicity (stomatitis for 1 subject and neutropenia for the other).

PHARMACOKINETIC RESULTS:

Primary Endpoint, Encapsulated Doxorubicin: Arithmetic mean values for the key pharmacokinetic exposure parameters for encapsulated 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 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 DOXILNAP1002: Pharmacokinetic Statistical Analysis Set)

Parameter[a]	Geometric Mean DOXIL/CAELYX[b], 50 mg/m^2 Treatment B (Test) n=40	Geometric Mean DOXIL/CAELYX[b], 50 mg/m^2 Treatment A (Reference) n=40	Geometric Mean Ratio (90% CI)	Intra-Subject CV (%)
C_{max} (µg/mL)	32.51	33.21	97.89 (94.68 - 101.22)	8.9
$AUC_{0\text{-}last}$ (µg.h/mL)	3,424.31	3,516.74	97.37 (93.19 - 101.75)	11.7
$AUC_{0\text{-}\infty}$ (µg.h/mL)[c]	3,651.59	3,763.25	97.03 (93.31 - 100.90)	10.1

[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] A: DOXIL/CAELYX 50 mg/m^2 IV infusion manufactured at current site ([redacted] B: DOXIL/CAELYX 50 mg/m^2 IV infusion manufactured at new site[redacted] Treatment A was used as the reference group.
[c] n=38

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 included zero and negative values. 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, percent of 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 further confirm that only a small fraction (less than 3%) of free doxorubicin relative to total doxorubicin is present in circulation and the percent free doxorubicin values were similar for Treatments A and B.

Additional Endpoint, Total Doxorubicin: Arithmetic mean values for the key pharmacokinetic exposure parameters of 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. Treatment B and Treatment A met the predefined BE criteria stated in the statistical analysis plan (SAP) with respect to $AUC_{0\text{-}\infty}$, $AUC_{0\text{-last}}$, and C_{max} of total doxorubicin as the 90% CIs for the test-to-reference GMRs of these parameters were entirely 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 DOXILNAP1002: Pharmacokinetic Statistical Analysis Set)

	Geometric Mean			
Parameter[a]	**DOXIL/CAELYX[b], 50 mg/m^2 Treatment B (Test) n=40**	**DOXIL/CAELYX[b], 50 mg/m^2 Treatment A (Reference) n=40**	**Geometric Mean Ratio (90% CI)**	**Intra-Subject CV (%)**
C_{max} (µg/mL)	32.75	32.76	99.95 (97.65 - 102.29)	6.2
$AUC_{0\text{-last}}$ (µg.h/mL)	3,492.45	3,619.72	96.48 (92.01 - 101.17)	12.6
$AUC_{0\text{-}\infty}$ (µg.h/mL)[c]	3,718.50	3,874.53	95.97 (92.22 - 99.88)	10.3

[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] A: DOXIL/CAELYX 50 mg/m^2 IV infusion manufactured at current site ([redacted] B: DOXIL/CAELYX 50 mg/m^2 IV infusion manufactured at new site [redacted] Treatment A was used as the reference group.
[c] n=38

Ovarian vs. Non-Ovarian Encapsulated and Total Doxorubicin Pharmacokinetic Parameters: Mean plasma encapsulated and total doxorubicin concentration-time profiles for ovarian vs. non-ovarian cancer subjects were similar after administration of DOXIL/CAELYX, manufactured at the new site [redacted] [test product, Treatment B]), and DOXIL/CAELYX, manufactured at the current site ([redacted] (reference product, Treatment A). For both the test and reference formulations, arithmetic mean values for all pharmacokinetic parameters were similar in ovarian and non-ovarian cancer subjects, indicating similar disposition of DOXIL/CAELYX in these cancer groups. The 90% CIs of the GMRs for pharmacokinetic parameters of interest were all within 80% to 125%.

EFFICACY RESULTS: Fifty subjects had a response assessment at the end of treatment. At the end of 2 cycles of treatment, the investigator-determined response was complete response (CR) for 1 subject, partial response (PR) for 1 subject, stable disease for 28 subjects, and progressive disease for 20 subjects. The CR was reported for a subject with ovarian cancer and the PR for a subject with colorectal cancer.

SAFETY RESULTS: Fifty-one subjects received at least 1 dose of study medication and were included in the safety population. Fifty subjects had at least one treatment-emergent adverse event (TEAE). Drug-related TEAEs were reported for 80.4% of total subjects. Serious adverse events were reported for 23.5% of subjects, with 1 subject reported to have drug-related SAEs of stomatitis and palmar-plantar erythrodysaesthesia syndrome (hereafter referred to as hand-foot syndrome [HFS]) following Treatment B. Only 1 subject had a TEAE leading to treatment discontinuation; the subject discontinued early due to bone marrow failure after receiving Treatment A in Cycle 1. One subject who received both cycles of study drug later died from progressive disease more than 30 days after the last dose of study drug. The most commonly reported TEAEs (ie, reported for >10% of subjects) were fatigue (43.1%), nausea (35.3%), neutropenia (33.3%), stomatitis (31.4%), vomiting (23.5%), anemia (21.6%), asthenia (19.6%), constipation (19.6%), HFS (17.6%), decreased appetite (17.6%), hepatic function abnormal (13.7%), and diarrhea (11.8%). As shown in the table below, no clinically meaningful differences were seen between Treatments A and B with respect to TEAEs.

Summary of Adverse Events; Safety Analysis Set (Study DOXILNAP1002)

	All Cancer Types		
	Trt B[a]	Trt A[a]	Total
Analysis set: safety subjects	49	50	51
Treatment-emergent adverse events (TEAEs)	43 (87.8%)	46 (92.0%)	50 (98.0%)
Toxicity grade 1	13 (26.5%)	14 (28.0%)	10 (19.6%)
Toxicity grade 2	13 (26.5%)	13 (26.0%)	13 (25.5%)
Toxicity grade 3	16 (32.7%)	17 (34.0%)	25 (49.0%)
Toxicity grade 4	1 (2.0%)	2 (4.0%)	2 (3.9%)
Drug-related[b]	32 (65.3%)	34 (68.0%)	41 (80.4%)
Serious TEAEs	5 (10.2%)	8 (16.0%)	12 (23.5%)
Drug-related[b]	1 (2.0%)	0	1 (2.0%)
TEAE leading to treatment discontinuation	0	1 (2.0%)	1 (2.0%)
Drug-related[b]	0	1 (2.0%)	1 (2.0%)
All deaths[c]	0	1 (2.0%)	1 (2.0%)
All deaths within 30 days of last dose	0	0	0

[a] A: DOXIL/CAELYX 50 mg/m^2 IV infusion manufactured at current site ([redacted] B: DOXIL/CAELYX 50 mg/m^2 IV infusion manufactured at new site [redacted]

[b]Drug-related adverse events are adverse events with causality reported as possible, probable or very likely.

[c]The one subject died more than 30 days after the last dose.

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 as follows for Treatment A and Treatment B, respectively: neutropenia was reported for 28.0% and 24.5% of subjects, stomatitis for 18.0% and 24.5%, HFS for 10.0% and 10.2%, and thrombocytopenia for 2.0% and 2.0%. Infusion-related reactions were reported for 2 subjects with Treatment A and no subjects with Treatment B. Both subjects recovered and continued in the study.

Few subjects had shifts in laboratory values from normal at baseline to Grade 4 during treatment. These included shifts in neutrophils for 2 subjects following Treatment A and 1 subject following Treatment B, and a decrease in sodium for 1 subject following Treatment A. No other Grade 4 abnormalities were reported. Shifts from normal to Grade 3 were most common for neutrophils, and were reported for 8 subjects following Treatment A and 7 subjects following Treatment B. Median changes in vital sign parameters from baseline to end of treatment were small. One subject had a clinically significant ECG finding of sinus bradycardia at end of treatment; the investigator considered the event to be unrelated to study drug.

STUDY LIMITATIONS: The results from this study adequately addressed the objectives of the protocol as agreed upon with the FDA. No notable study limitations were identified by the sponsor.

Disclaimer

Information in this posting shall not be considered to be a claim for any marketed product. Some information in this posting may differ from, or not be included in, the approved labeling for the product. Please refer to the full prescribing information for indications and proper use of the product.