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# Pharmacokinetic Bioequivalence of ATI-0918 and DOXIL®/CAELYX® in Patients with Ovarian Cancer

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## PURPOSE

### Objective

To assess the pharmacokinetic (PK) bioequivalence of ATI-0918 (test product) and DOXIL®/CAELYX® (reference product).

### Introduction:

Doxorubicin is an anticancer chemotherapy drug. It is an anthracycline topoisomerase inhibitor which prevents DNA replication and inhibits protein synthesis. Doxorubicin is used to treat hematological and solid cancers such as breast and ovarian carcinoma, sarcoma and many other solid tumors[1,2]. Liposomal formulations of doxorubicin are effective in reducing doxorubicin cardiotoxicity and improving its delivery to tumor sites [3,4]. DOXIL is a doxorubicin hydrochloride pegylated liposome injection which is marketed in the United States, Israel and Japan as DOXIL and elsewhere as CAELYX. DOXIL is approved by the FDA for treatment of ovarian cancer, AIDS-related Kaposi's sarcoma, and in combination therapy for multiple myeloma[5]. ATI-0918 is being developed by Azaya Inc. as a generic formulation of DOXIL/CAELYX, a liposomal formulation of doxorubicin hydrochloride.

## MATERIALS

### Study

This is a Single-blind, Randomized, Two-way, Crossover Bioequivalence study. Subjects with ovarian cancer were randomized in a 1:1 ratio and received one of two treatment sequences. The study enrolled 60 subjects from which 55 were evaluable for BE assessment (Five subjects were dropped out due to under-dosing).

### Dose

In Sequence A, patients received a single dose of 50 mg/m$^2$ DOXIL/CAELYX on Day 1 of Cycle 1 and a single dose of 50 mg/m$^2$ ATI-0918 on Day 1 of Cycle 2. In Sequence B, patients received a single dose of 50 mg/m$^2$ ATI-0918 on Day 1 of Cycle 1 and a single dose of 50 mg/m$^2$ DOXIL/CAELYX on Day 1 of Cycle 2. There was a 3-week wash-out period between Cycle 1 and Cycle 2. Blood samples were obtained over 216 hours postdose during Cycle 1 and Cycle 2.

## METHOD

### Analytical Method

The plasma was analyzed for liposomal encapsulated doxorubicin, free (i.e., released) doxorubicin and doxorubicinol metabolite by a validated HPLC-MS/MS assay (Below Quantification Limit; BQL < 10.0 ng/mL for free (i.e., released) doxorubicin, 50.0 ng/mL for encapsulated doxorubicin and 0.200 ng/mL for doxorubicinol).

## METHOD(CONT.)

### Pharmacokinetic Analysis

The bioequivalence was performed by standard non-compartmental methods [6] based on the concentration-time data of each subject using a validated WinNonlin Professional 6.3 (Pharsight Corp., Mountain View, CA, USA). The bioequivalence of ATI-0918 (test product) to DOXIL/CAELYX (reference product) was assessed using the ln-transformed $AUC_{0-t}$, $AUC_{0-inf}$, and $C_{max}$ of the liposomal encapsulated doxorubicin, free doxorubicin, and doxorubicinol. The Least Squares Geometric Means (LSGM), %Ratio of LSGM and the lower and upper limits of the 90% Confidence Intervals (CI) of the %Ratio were calculated. Pharmacokinetic equivalence was concluded if the 90% CI for the ratio of ATI-0918 to DOXIL/CAELYX for $AUC_{0-t}$, $AUC_{0-inf}$, and $C_{max}$ of the liposomal encapsulated doxorubicin, free doxorubicin, and doxorubicinol fall within 80.00% -125.00%.

## RESULTS

Following a 50 mg/m$^2$ intravenous dose of ATI-0918 (test product) or DOXIL/CAELYX (reference product), the LSGM for the encapsulated doxorubicin $C_{max}$ values were 41,900 and 46,900 ng/mL, $AUC_{0-t}$ were 3,650,000 and 4,220,000 ng·h/mL, and $AUC_{0-inf}$ were 4,330,000 and 4,980,000 ng·h/mL, respectively. The %Ratios of LSGM of the $C_{max}$, $AUC_{0-t}$ and $AUC_{0-inf}$ (ATI-0918-to-CAELYX) were 89.39%, 86.48 and 86.93%, respectively. The corresponding 90% CI for those ratios were 85.60% to 93.34%, 83.56% to 89.49% and 82.24% to 91.89%, respectively.

The LSGM for the free doxorubicin Cmax values were 3,040 and 2,970 ng/mL, $AUC_{0-t}$ were 172,000 and 179,000 ng·h/mL, and $AUC_{0-inf}$ were 220,000 and 230,000 ng·h/mL following ATI-0918 and DOXIL/CAELYX, respectively. The %Ratios of LSGM of the $C_{max}$, $AUC_{0-t}$ and $AUC_{0-inf}$ (ATI-0918 -to-CAELYX) were 102.48%, 95.99 and 95.66%, respectively. The corresponding 90% CI for those ratios were 90.27% to 116.34%, 90.72% to 101.57% and 88.03% to 103.95%, respectively.

The LSGM for doxorubicinol $C_{max}$ values were 2.97 and 3.24 ng/mL and $AUC_{0-t}$ were 440 and 474 ng·h/mL following ATI-0918 and DOXIL/CAELYX, respectively. The %Ratios of LSGM of $C_{max}$ and $AUC_{0-t}$ (ATI-0918-to- CAELYX) were 91.59 and 92.89%, respectively. The corresponding 90% CI for those ratios were 84.80% to 98.92 and 85.94% to 100.41 %, respectively. The $AUC_{0-inf}$ was incalculable due to the absence of an elimination phase.

These results indicated that the PK of free doxorubicin, encapsulated doxorubicin and the metabolite doxorubicinol following ATI-0918 was equivalent to that following DOXIL/CAELYX.

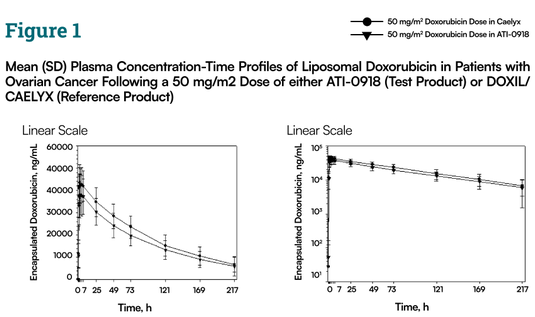
## Table 1

**Summary of the PK Bioequivalence for Liposomal Doxorubicin, Free Doxorubicin and Doxorubicinol in Patients with Ovarian Cancer Following a 50 mg/m2 Dose of either ATI-0918 (Test Product) or DOXIL/CAELYX (Reference Product)**

| PK Parameter | DOXIL/ CAELYX LSGM | ATI-0918 LSGM | %Ratio | CI 90% Lower | CI 90% Upper |
|---|---|---|---|---|---|
| **Encapsulated Doxorubicin** | | | | | |
| $C_{max}$ | 46,900 | 41,900 | 89.39 | 85.60 | 93.34 |
| $AUC_{(0-T)}$ | 4,220,000 | 3,650,000 | 86.48 | 83.56 | 89.49 |
| $AUC_{(0-inf)}$ | 4,980,000 | 4,330,000 | 86.93 | 82.24 | 91.89 |
| **Non-Encapsulated Doxorubicin** | | | | | |
| $C_{max}$ | 2,970 | 3,040 | 102.48 | 90.27 | 116.34 |
| $AUC_{(0-T)}$ | 179,000 | 172,000 | 95.99 | 90.72 | 101.57 |
| $AUC_{(0-inf)}$ | 230,000 | 220,000 | 95.66 | 88.03 | 103.95 |
| **Doxorubicinol** | | | | | |
| $C_{max}$ | 2,970 | 3,040 | 102.48 | 90.27 | 116.34 |
| $AUC_{(0-T)}$ | 179,000 | 172,000 | 95.99 | 90.72 | 101.57 |

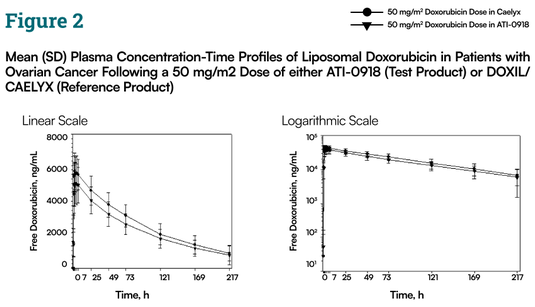
## Figure 1

**Mean (SD) Plasma Concentration-Time Profiles of Liposomal Doxorubicin in Patients with Ovarian Cancer Following a 50 mg/m2 Dose of either ATI-0918 (Test Product) or DOXIL/CAELYX (Reference Product)**



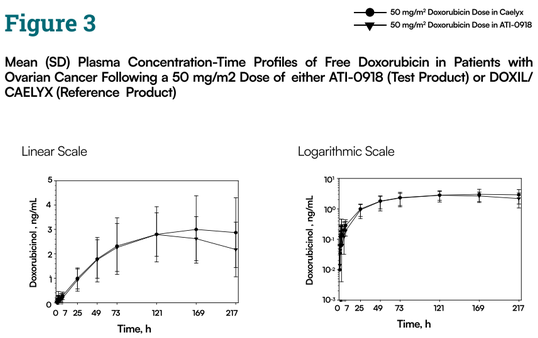

## Figure 2

**Mean (SD) Plasma Concentration-Time Profiles of Liposomal Doxorubicin in Patients with Ovarian Cancer Following a 50 mg/m2 Dose of either ATI-0918 (Test Product) or DOXIL/CAELYX (Reference Product)**




## Figure 3

**Mean (SD) Plasma Concentration-Time Profiles of Free Doxorubicin in Patients with Ovarian Cancer Following a 50 mg/m2 Dose of either ATI-0918 (Test Product) or DOXIL/CAELYX (Reference Product)**




## CONCLUSION

ATI-0918 (test product) is equivalent to DOXIL/CAELYX (reference product). The lower and higher 90% CI ratios for ln-$C_{max}$, ln-$AUC_{0-t}$ and ln-AUC of free doxorubicin, encapsulated doxorubicin and the metabolite doxorubicinol following ATI-0918 were within 80.00% to 125.00% of those ratios following DOXIL/CAELYX.

## FUNDING / GRANTS / ENCORE / REFERENCE or other use

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