

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**20-449/s-029**

**CLINICAL PHARMACOLOGY AND**  
**BIOPHARMACEUTICS REVIEW(S)**

## CLINICAL PHARMACOLOGY/BIPHARMACEUTICS REVIEW

**NDA:** 20-449/SE1-029  
**BRAND NAME:** Taxotere®  
**GENERIC NAME:** Docetaxel Hydrochloride  
**DOSAGE FORM/STRENGTH:** 40 mg/ml Docetaxel Hydrochloride in Single-Dose Vials For Intravenous Injection  
**INDICATION:** —  
**SUBMISSION DATES:** 17-Mar-2004, 26-May-2004, 03-Jun-2004  
**SUBMISSION TYPE:** NDA-Supplement  
**APPLICANT:** Aventis Pharmaceuticals  
Bridgewater, NJ 08807  
**OND DIVISION:** Division of Oncology Drug Products (HFD-150)  
**OCPB DIVISION:** Division of Pharmaceutical Evaluation I (HFD-860)  
**OCPB REVIEWER:** Sophia Abraham, Ph.D.  
**OCPB ACTING TEAM LEADER:** Brian Booth, Ph.D.

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### 1 Executive Summary

The Applicant seeks approval for the use of Taxotere® (docetaxel hydrochloride) in combination with doxorubicin and cyclophosphamide for the adjuvant treatment of patients with operable node-positive breast cancer. In support of this new indication, Aventis conducted a pivotal Phase 3 study (Study TAX316) and used this study for their Supplemental New Drug Application (sNDA) registration. Study TAX316 was an open-label, multi-center, active-control, randomized, parallel-group, comparative, two-arm,

**Phase 3 study in 1491 operable breast cancer patients with positive axillary lymph nodes. Patients were randomized to receive either:**

- Taxotere® 75 mg/m<sup>2</sup> (as a 1-hour intravenous (IV) infusion) one hour after doxorubicin 50 mg/m<sup>2</sup> (as a 15-minute IV infusion) and cyclophosphamide 500 mg/m<sup>2</sup> (as a 1- to 5-minute IV infusion) on Day 1 every 3 weeks for 6 cycles in 745 patients (TAC) or
- Doxorubicin 50 mg/m<sup>2</sup> (as a 15-minute IV infusion) followed by 5-fluorouracil 500 mg/m<sup>2</sup> (as an IV infusion) and cyclophosphamide 500 mg/m<sup>2</sup> (as a 1- to 5-minute IV infusion) on Day 1 every 3 weeks for 6 cycles in 746 patients (FAC).

No dose-escalation studies were conducted for this triple combination, the doses selected for individual drugs were the usual standard doses used in the metastatic breast cancer settings.

The potential for drug-drug interactions between docetaxel, doxorubicin, and cyclophosphamide was assessed in a separate study (Study XRP6976D/1001) in 30 women with advanced breast cancer. The results of this study indicate that docetaxel has no effect on the pharmacokinetics of doxorubicin or cyclophosphamide when the three drugs are given in combination compared to coadministration of doxorubicin and cyclophosphamide only. In addition, doxorubicin and cyclophosphamide have no effect on docetaxel plasma clearance when the three drugs are given in combination compared to historical data for docetaxel monotherapy.

### **1.1            *Recommendations***

The Supplemental NDA 20-449 submitted for the use of Taxotere® (docetaxel) in combination with doxorubicin and cyclophosphamide for the adjuvant treatment of patients with operable node-positive breast cancer is acceptable from the perspectives of the Office of Clinical Pharmacology and Biopharmaceutics (OCPB). The Applicant should incorporate the OCPB Labeling Recommendations as outlined under Section 3 of this review (pp.20).

Please forward the above Recommendation and OCPB Labeling Recommendations (pp.20) to the Applicant.

### **1.2            *Phase 4 Commitments***

None

### 1.3 **Summary of Important Clinical Pharmacology and Biopharmaceutics Findings**

Aventis Pharmaceuticals developed an adjuvant therapy of Taxotere® (docetaxel) in combination with doxorubicin and cyclophosphamide for the adjuvant treatment of patients with operable node-positive breast cancer. The proposed dose is docetaxel 75 mg/m<sup>2</sup> administered as a 1-hour infusion every 3 weeks in combination with doxorubicin 50 mg/m<sup>2</sup> given as a 15-minute IV infusion and cyclophosphamide 500 mg/m<sup>2</sup> as a 1- to 5-minute IV infusion every 3 weeks.

In support of this new indication, Aventis conducted a pivotal Phase 3 study (Study TAX316). Study TAX316 was an open-label, multi-center, active-control, randomized, parallel-group, comparative, two-arm, Phase 3 study in 1491 operable breast cancer patients with positive axillary lymph nodes. Patients were randomized to receive either

- Taxotere® 75 mg/m<sup>2</sup> (as a 1-hour intravenous (IV) infusion) one hour after doxorubicin 50 mg/m<sup>2</sup> (as a 15-minute IV infusion) and cyclophosphamide 500 mg/m<sup>2</sup> (as a 1- to 5-minute IV infusion) on Day 1 every 3 weeks for 6 cycles in 745 patients (TAC) or
- Doxorubicin 50 mg/m<sup>2</sup> (as a 15-minute IV infusion) followed by 5-fluorouracil 500 mg/m<sup>2</sup> (as an IV infusion) and cyclophosphamide 500 mg/m<sup>2</sup> (as a 1- to 5-minute IV infusion) on Day 1 every 3 weeks for 6 cycles in 746 patients (FAC).

The primary efficacy endpoint was to compare the overall disease-free survival (DFS) for TAC versus FAC in the intent-to-treat (ITT) population. According to the Applicant, 84% of TAC-treated patients and 76% of FAC-treated patients were disease free at 3-year. The TAC regimen was associated with a 28% relapse risk reduction compared to FAC (Hazard Ratio=0.72, 95% Confidence Interval= 0.59-0.88, p=0.001). According to the Applicant, TAC was associated with greater hematological toxicity than FAC, including a higher overall incidence of infections during the treatment period. Other toxicities were consistent with those previously described for Taxotere® monotherapy.

The potential for drug-drug interactions between docetaxel, doxorubicin, and cyclophosphamide was assessed in a separate study (Study XRP6976D/1001) in 30 women with advanced breast cancer.

Study XRP6976D/1001 was an open-label, multi-center, randomized, cross-over study conducted to determine the impact of docetaxel on the pharmacokinetics (PK) of doxorubicin and cyclophosphamide and to determine the impact of doxorubicin and cyclophosphamide on the PK of docetaxel. Patients received doxorubicin and cyclophosphamide either with (TAC) or without (AC) docetaxel in cycle 1 and were crossed over to the alternate regimen in cycle 2 according to the following dosing schedules:

**AC:** Doxorubicin 50 mg/m<sup>2</sup> (as a 15-minute i.v. infusion) on Day 1, followed immediately by cyclophosphamide 500 mg/m<sup>2</sup> (as a 15-minute i.v. infusion) on Day 1 every 3 weeks.

**TAC:** Doxorubicin 50 mg/m<sup>2</sup> (as a 15-minute i.v. infusion) on Day 1, followed immediately by cyclophosphamide 500 mg/m<sup>2</sup> (as a 15-minute i.v. infusion) on Day 1, followed immediately by Taxotere® 75 mg/m<sup>2</sup> (as a 1-hour i.v. infusion) on Day 1 every 3 weeks.

It is noted that the infusion time for cyclophosphamide in Study XRP6976D/1001 (15-minutes infusion) differed from the one used in the pivotal Phase 3 Study TAX316 (1- to 5-minute IV infusion). Secondly, although the dosing sequence was similar in both studies, Taxotere® was given immediately after doxorubicin and cyclophosphamide in Study XRP6976D/1001 compared to a whole one hour in Study TAX316. The impact of these differences on the pharmacokinetics of the drug is not known.

Docetaxel plasma concentration/time data were analyzed using the previously developed population PK (NONMEM) model and individual docetaxel clearance values were determined using a Bayesian approach. According to this approach, the population PK parameters were fixed at the values reported in the published population PK model and only the individual PK parameters were estimated (MAXEVALS=0 in NONMEM).

Doxorubicin and cyclophosphamide plasma concentration/time data were analyzed using non-compartmental methods.

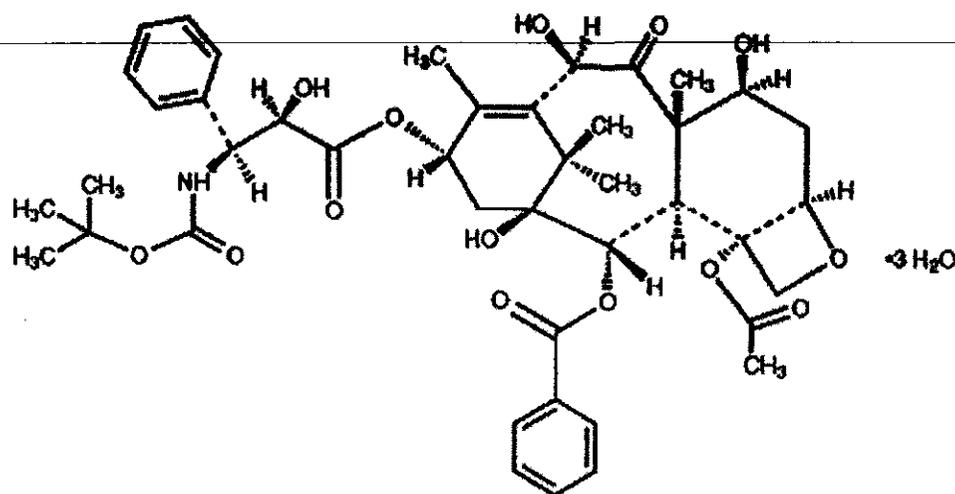
The results of the study indicate that the coadministration of docetaxel has no effect on the pharmacokinetics of each of doxorubicin and cyclophosphamide when the three drugs are given in combination compared to coadministration of doxorubicin and cyclophosphamide only. In addition, doxorubicin and cyclophosphamide have no effect on docetaxel plasma clearance when the three drugs are given in combination compared to historical data for docetaxel monotherapy.

## **2 Question Based Review**

### **2.1 General Attributes of the Drug**

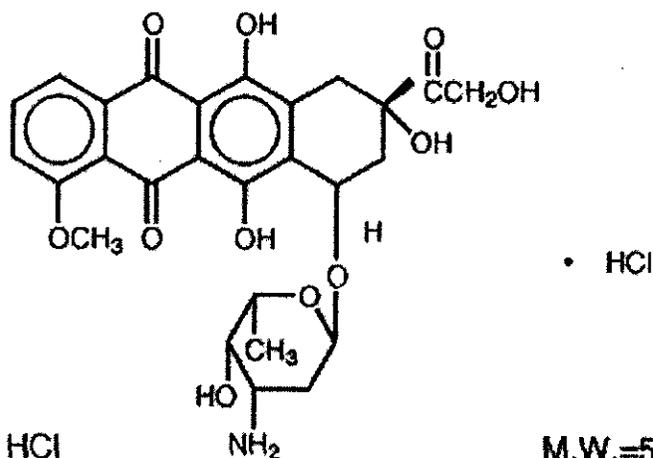
#### **2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?**

**Docetaxel** is a semisynthetic antineoplastic agent that is very similar to paclitaxel in structure, mechanism of action, and spectrum of antitumor activity. Docetaxel differs structurally from paclitaxel at the C-10 position where docetaxel has a hydroxy group instead of an acetyl group and contains an -OC(CH<sub>3</sub>)<sub>3</sub> moiety on the C-13 side chain as opposed to a benzamide phenyl group as in paclitaxel. Docetaxel is synthesized from 10-deacetyl baccatin III, a noncytotoxic substance extracted from the needles of the European yew tree (*Taxus baccata*). Docetaxel has the following structural formula:



Docetaxel is a white to almost-white powder with an empirical formula of  $C_{43}H_{53}NO_{14} \cdot 3H_2O$ , and a molecular weight of 861.9. It is highly lipophilic and practically insoluble in water. Docetaxel (Taxotere®) Injection Concentrate is a clear yellow to brownish-yellow viscous solution. Taxotere® is sterile, non-pyrogenic. Docetaxel is available in single-dose vials containing 20 mg (0.5 mL) or 80 mg (2.0 mL) docetaxel (anhydrous) for intravenous administration. Each mL contains 40 mg docetaxel (anhydrous) and 1040 mg polysorbate 80.

**Doxorubicin** is an anthracycline antineoplastic agent used to treat a wide variety of solid and hematogenous tumors. It is a natural product isolated from *Streptomyces peucetius var caesius*. Doxorubicin differs from daunorubicin by an additional hydroxyl group. Doxorubicin has the following structural formula:

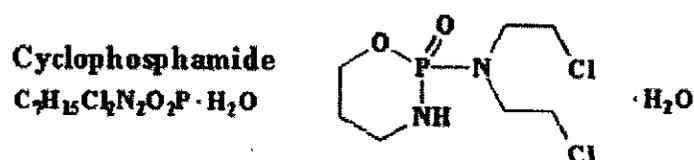


$C_{27}H_{29}NO_{11} \cdot HCl$

M.W.=579.99

Doxorubicin (Adriamycin) for Injection is supplied in the hydrochloride form as 10 mg, 20 mg, and 50 mg sterile red-orange lyophilized powder and as a sterile parenteral, isotonic solution with sodium chloride for intravenous use only.

**Cyclophosphamide** is a bifunctional alkylating agent related to mechlorethamine (nitrogen mustard). Cyclophosphamide has the following structural formula:



### 2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Docetaxel, similar to paclitaxel, promotes the assembly of microtubules and stabilizes their formation by inhibiting depolymerization.

Doxorubicin induces cytotoxicity by forming complexes with DNA by intercalating between DNA base pairs, causing the helix to change shape. This simple act of changing the conformation of DNA can interfere with strand elongation by inhibiting DNA polymerase and can inhibit protein synthesis due to affects on RNA polymerase.

Cyclophosphamide is a prodrug that requires hepatic activation in order to be cytotoxic. Phosphoramidate mustard and acrolein are formed following hepatic and cellular activation. Phosphoramidate mustard is the active alkylating moiety responsible for the cytotoxic effects. As with other bifunctional alkylating agents, phosphoramidate mustard forms intrastrand and interstrand DNA-DNA cross-links, which are responsible for the inactivation of the DNA.

### 2.1.3 What are the proposed dosage(s) and route(s) of administration?

The FDA approved docetaxel for Injection Concentrate on 15-May-1996 under trade name, **Taxotere®** (NDA 20-449) for the treatment of refractory, locally advanced or metastatic breast cancer. On 23-Dec-1999, FDA approved Taxotere® as a single agent for the treatment of advanced or metastatic non-small cell lung cancer after failure of platinum containing chemotherapy at the recommended dose of 60-100 mg/m<sup>2</sup> infused intravenously (IV) over one hour once every three weeks. As an adjuvant therapy, FDA approved Taxotere® on 19-May-2004 in combination with prednisone for the treatment for patients with androgen independent (hormone refractory) metastatic prostate cancer at a recommended dose of Taxotere® 75 mg/m<sup>2</sup> administered intravenously over one hour every three weeks in combination with prednisone 5 mg administered orally twice a day (BID).

The FDA approved doxorubicin in 1974 under trade name of **ADRIAMYCIN**. According to the Physician's Desk Reference (PDR®), the pharmacokinetic of doxorubicin were determined in patients with various types of tumors undergoing either single or multi-agent therapy. The most commonly used dose schedule when used as a single agent is 60-75 mg/m<sup>2</sup> as a single intravenous injection administered at 21-day intervals. Doxorubicin is a component of many combination chemotherapy regimens. It is part of standard regimens for breast, lung, gastric and ovarian cancers, Hodgkin's disease, non-Hodgkin's lymphoma, sarcoma, myeloma, and acute lymphocytic leukemia.

The FDA approved cyclophosphamide in 1959 under trade name of **Cytoxan®**. The dosage for cyclophosphamide is dependent on the disease state, performance status, and other chemotherapy agents or radiation therapy given in combination. For the treatment of breast cancer, intravenous doses of 500-1000 mg/m<sup>2</sup> could be given on Day 1 in combination with fluorouracil and methotrexate (CMF) or doxorubicin (CAF) or doxorubicin alone (AC).

## 2.2 General clinical pharmacology

### 2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

In support of the use of the combination of Taxotere®, doxorubicin, and cyclophosphamide for the adjuvant treatment of patients with operable node-positive breast cancer, Aventis Pharmaceuticals conducted a pivotal Phase 3 study (Study TAX316). Study TAX316 was an open-label, multi-center, active-control, randomized, parallel-group, comparative, two-arm, Phase 3 study in 1491 operable breast cancer patients with positive axillary lymph nodes. Patients were randomized to receive either:

- Taxotere® 75 mg/m<sup>2</sup> (as a 1-hour intravenous (IV) infusion) one hour after doxorubicin 50 mg/m<sup>2</sup> (as a 15-minute IV infusion) and cyclophosphamide 500 mg/m<sup>2</sup> (as a 1- to 5-minute IV infusion) on Day 1 every 3 weeks for 6 cycles in 745 patients (TAC) or
- Doxorubicin 50 mg/m<sup>2</sup> (as a 15-minute IV infusion) followed by 5-fluorouracil 500 mg/m<sup>2</sup> (as an IV infusion) and cyclophosphamide 500 mg/m<sup>2</sup> (as a 1- to 5-minute IV infusion) on Day 1 every 3 weeks for 6 cycles in 746 patients (FAC).

Patients were similar in the two treatment groups (TAC and FAC) for demographics and baseline characteristics. Patients had a median age of 49 years (range=23–70 years), with 6.0% elderly (65 years). Most patients (75.9%) had positive estrogen (ER) or progesterone (PgR) receptors. More than 90% of all patients were Caucasians.

The primary efficacy endpoint was the comparison of the disease-free survival (DFS) for TAC versus FAC in the intent-to-treat (ITT) population. The secondary efficacy endpoint of this study was overall survival (OS) in the ITT population. The results are shown in Tables 1 and 2 (According to the Applicant).

**Table 1. Disease-free survival in all randomized subjects – ITT Analysis**

Statistic	TAC	FAC
N	745	746
Events	172	227
3-year DFS	84%	76%
5-year DFS	75%	68%
Hazard Ratio	0.72	
95% CI	[0.59 - 0.88]	
p-value	0.001	

Table 1 shows that 84% of TAC-treated patients and 76% of FAC-treated patients were disease free at 3-year. Seventy-five (75%) TAC-treated patients and 68% of FAC-treated patients were disease free at 5-year. The TAC regimen was associated with a 28% relapse risk reduction compared to FAC (Hazard Ratio=0.72, 95% Confidence Interval= 0.59-0.88, p=0.001).

**Table 2. Overall survival in all randomized subjects – ITT Analysis**

Statistic	TAC	FAC
N	745	746
Events	91	130
3-year OS	92%	89%
5-year OS	87%	81%
Hazard Ratio	0.70	
95% CI	[0.53 - 0.91]	
p-value	0.008	

Table 2 shows that 92% of TAC-treated patients and 89% of FAC-treated patients survived at 3-year. Seventy-five (75%) TAC-treated patients and 68% of FAC-treated patients survived at 5-year. The TAC regimen was associated with a 30% relapse risk reduction compared to FAC (Hazard Ratio=0.70, 95% Confidence Interval= 0.53-0.91, p=0.008).

According to the Applicant, the most common adverse events observed among TAC-treated patients were: anemia (4.3%), asthenia (11.2%), nausea (5.1%), neutropenia (65.5%), stomatitis (7.1%), fever in the absence of infection (1.3%), vomiting (4.3%), pain (3.8%), and infection (3.9%). The most common adverse events observed among FAC-treated patients were: nausea (9.5%), neutropenia (49.3%), anemia (1.6%), asthenia (5.6%), vomiting (7.3%), stomatitis (2.0%), pain (1.8%), and infection (2.2%).

Based on the results of this study (Study TAX316), Aventis Pharmaceuticals provided an updated version for Taxotere® package insert (see Appendix 4.1).

**2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?**

The primary efficacy endpoint used in the pivotal Phase 3 Study TAX316 was the comparison of the disease-free survival (DFS) for TAC versus FAC in the intent-to-treat (ITT) population. The selection of this endpoint was based on the fact that the method to determine DFS endpoint is prospectively specified to ensure the integrity and reliability of the observed results which provides compelling evidence of the overall efficacy associated with adjuvant Taxotere® administration.

**2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?**

Plasma concentrations of each of docetaxel, doxorubicin, and cyclophosphamide were measured in Study XRP6976D/1001.

**2.2.4 Exposure-response**

**2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?**

None

**2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?**

None

**2.2.4.3 Does this drug prolong the QT or QTc interval?**

None

**2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?**

No, the dosing regimens selected to be used in the pivotal Phase 3 Study TAX316 are the usual standard doses used in the metastatic breast cancer settings. The dosing regimen selected for the combination is docetaxel 75 mg/m<sup>2</sup> administered as a 1-hour infusion on Day 1 every 3 weeks in combination with doxorubicin 50 mg/m<sup>2</sup> given as a 15-minute IV infusion and cyclophosphamide 500 mg/m<sup>2</sup> as a 1- to 5-minute IV infusion on Day 1 every 3 weeks.

**2.2.5 What are the PK characteristics of the drug and its major metabolite?**

According to the PDR®, docetaxel pharmacokinetics were evaluated in cancer patients after administration of 20-115 mg/m<sup>2</sup> in Phase 1 studies. The area under the curve (AUC) is dose proportional following doses of 70-115 mg/m<sup>2</sup> with infusion times of 1 to 2 hours. Docetaxel plasma levels decline triexponentially with half-lives for the alpha, beta and gamma elimination phases of 4 minutes, 36 minutes and 11.1 hours, respectively. Mean total body clearance and steady state volume of distribution are 21 L/h/m<sup>2</sup> and 65 L/m<sup>2</sup>, respectively.

According to the PDR®, the pharmacokinetic of doxorubicin were determined in patients with various types of tumors undergoing either single or multi-agent therapy. Doxorubicin pharmacokinetics follow a multiphasic disposition after intravenous injection with an initial distributive half-life of approximately 5 minutes and a terminal half-life of 20 to 48 hours. Steady-state distribution volumes exceed 20 to 30 L/kg and are indicative of extensive drug uptake into tissues. Plasma clearance is in the range of 8 to 20 ml/min/kg and is predominately by metabolism and biliary excretion.

According to the Clinical Pharmacology Monographs, the half-life of **cyclophosphamide** is about 8 hours (range 3-10 hours) and the half-life of the active metabolite (4HC/aldophosphamide) is about 1-5 hours.

#### **2.2.5.1 What are the single dose and multiple dose PK parameters?**

Docetaxel, doxorubicin, and cyclophosphamide are administered every three weeks and no accumulation of either drug is expected.

#### **2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?**

Docetaxel, doxorubicin, and cyclophosphamide are cytotoxic agents and were never tested in healthy volunteers.

#### **2.2.5.3 What are the characteristics of drug absorption?**

NOT APPLICABLE

#### **2.2.5.4 What are the characteristics of drug distribution?**

*In vitro* studies showed that **docetaxel** is about 94% protein bound, mainly to  $\alpha_1$ -acid glycoprotein, albumin, and lipoproteins.

The binding of **doxorubicin** and its major metabolite, doxorubicinol to plasma proteins is about 74 to 76% and is independent of plasma concentration of doxorubicin up to 2  $\mu$ M.

The protein binding of **cyclophosphamide** is not known.

#### **2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?**

**Docetaxel:** According to PDR®, a [ $^{14}$ C] study in three cancer patients indicated that docetaxel is eliminated in both the urine and feces following oxidative metabolism of the *tert*-butyl ester group, but fecal excretion is being the main elimination route. Within 7 days, urinary and fecal excretion accounted for approximately 6% and 75% of the administered radioactivity, respectively. About 80% of the radioactivity recovered in feces is excreted during the first 48 hours as 1 major and 3 minor metabolites with very small amounts (less than 8%) of unchanged drug.

**Doxorubicin:** According to PDR®, approximately 40% of the dose appears in the bile in 5 days, while only 5-12% of the drug and its metabolites appear in the urine during the same time period. In urine, <3% of the dose was recovered as doxorubicinol (DOX-OL) over 7 days.

**Cyclophosphamide:** According to the Clinical Pharmacology Monographs, about 15-20% of the total dose is eliminated in the urine as unchanged cyclophosphamide. Although the kidney excretes cyclophosphamide, it is actively reabsorbed, thus hepatic metabolism is the major route of elimination of cyclophosphamide.

### **2.2.5.6 What are the characteristics of drug metabolism?**

According to PDR®, **docetaxel** is metabolized by cytochrome P450 (CYP) 3A4 and 3A5 enzymes to one major metabolite and three minor metabolites. All four metabolites are oxidation products of the tert-butyl group attached to the C13-side chain. The metabolites are markedly less cytotoxic and less myelotoxic than the parent drug.

According to PDR®, **doxorubicin** is extensively metabolized in the liver by CYP3A4 and eliminated primarily as glucuronide or hydroxylated conjugates. Doxorubicinol is the primary metabolite and has 1/20th cytotoxic properties of doxorubicin. The disposition of doxorubicinol (DOX-OL) in patients is formation rate limited. The terminal half-life of DOX-OL is similar to doxorubicin. The relative exposure of DOX-OL, compared to doxorubicin ranges between 0.4-0.6.

According to the Clinical Pharmacology Monographs, **cyclophosphamide** undergoes activation and metabolism principally in the liver via CYP2B6 and to a lesser extent by CYP2C9, CYP2C18, CYP2C19, and CYP3A4/5. The contribution of CYP3A4 to the activation of cyclophosphamide is variable, from a low level of 5-10% to 35% of total enzyme activity. CYP3A5 and CYP2C9 might be important in extrahepatic activation of cyclophosphamide. The extensive P-450 catalyzed metabolism of cyclophosphamide yields both therapeutically active (N-hydroxylated) and therapeutically inactive but neurotoxic (N-dechloroethylated) metabolites.

### **2.2.5.7 What are the characteristics of drug excretion?**

Hepatic metabolism is the major route of elimination of each of docetaxel, doxorubicin, and cyclophosphamide.

### **2.2.5.8 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?**

Docetaxel, doxorubicin, and cyclophosphamide exhibit linear kinetics.

### **2.2.5.9 How do the PK parameters change with time following chronic dosing?**

None

### **2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?**

None

## **2.3 Intrinsic Factors**

**2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?**

None

**2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations (examples shown below), what dosage regimen adjustments, if any, are recommended for each of these groups?**

None

**2.3.2.1 Elderly**

None

**2.3.2.2 Pediatric patients. Also, what is the status of pediatric studies and/or any pediatric plan for study?**

**2.3.2.3 Gender**

None

**2.3.2.4 Race**

None

**2.3.2.5 Renal impairment**

None

**2.3.2.6 Hepatic impairment**

None

**2.3.2.7 What pharmacogenetics information is there in the application and is it important or not?**

None

**2.3.2.7 What pregnancy and lactation use information is there in the application?**

None

## **2.4 Extrinsic Factors**

**2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?**

None

## 2.4.2 Drug-drug interactions

### 2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

None

### 2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

**Docetaxel** is metabolized by CYP 3A4 and 3A5 enzymes.

**Doxorubicin** is extensively metabolized in the liver by CYP3A4.

**Cyclophosphamide** undergoes metabolism principally in the liver via CYP2B6 and to a lesser extent by CYP2C9, CYP2C18, CYP2C19, and CYP3A4/5.

### 2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

None

### 2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

None

### 2.4.2.5 Are there other metabolic/transporter pathways that may be important?

None

### 2.4.2.6 Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

The potential for drug-drug interactions between docetaxel, doxorubicin, and cyclophosphamide was evaluated when given in combination to women with advanced breast cancer in Study XRP6976D/1001. **Study XRP6976D/1001** was an open-label, multi-center, randomized, two-period, crossover study in 30 women with advanced breast cancer. Patients were treated with the double combination, doxorubicin + cyclophosphamide (**AC**) in Cycle 1 followed by the triple combination, Taxotere® + doxorubicin + cyclophosphamide (**TAC**) in Cycle 2. Patients were then crossed over to the alternate regimen in each cycle. Doses given were as follows:

**AC:** Doxorubicin 50 mg/m<sup>2</sup> (as a 15-minute i.v. infusion) on Day 1, followed immediately by cyclophosphamide 500 mg/m<sup>2</sup> (as a 15-minute i.v. infusion) on Day 1 every 3 weeks.

**TAC:** Doxorubicin 50 mg/m<sup>2</sup> (as a 15-minute i.v. infusion) on Day 1, followed immediately by cyclophosphamide 500 mg/m<sup>2</sup> (as a 15-minute i.v. infusion) on Day 1,

followed immediately by Taxotere® 75 mg/m<sup>2</sup> (as a 1-hour i.v. infusion) on Day 1 every 3 weeks.

**Docetaxel** plasma concentration/time data were analyzed using the previously developed population PK model [Launay-Iliadis, MC et al. Population pharmacokinetics of docetaxel during Phase 1 studies using nonlinear mixed-effect modeling and nonparametric maximum-likelihood estimation. Cancer Chemother Pharmacol 1995, 37:47-54]. A Bayesian approach (POSTHOC analysis) was used to calculate the individual plasma clearance (CL) and area under plasma curve (AUC<sub>inf</sub>) values for docetaxel. According to this approach, the population PK parameters were fixed at the values reported in the published population PK model, and only the individual PK parameters were estimated (MAXEVALS=0 in NONMEM).

**Table 1 - Arithmetic Mean ± SD (CV%) Bayesian Clearance and AUC<sub>inf</sub> Estimates for Docetaxel**

Parameter	Study XRP6976D/1001 (TAC)	*Historical Data (Monotherapy)
N	**29	231
CL (L/h/m <sup>2</sup> )	24.3±9.2 (38%)	22.3±6.9 (31%)
AUC <sub>inf</sub> (µg·h/ml)	4.25±3.9 (93%)	4.9±1.6 (32%)

\* Historical data consisted of 231 breast cancer patients who were administered docetaxel 75 or 100 mg/m<sup>2</sup> as a 1-hour i.v. infusion as a monotherapy (population pharmacokinetic dataset)

\*\*Subject 6 (Arm A) was excluded from docetaxel pharmacokinetic analysis because she had only one recorded plasma sample

**Table 2 - Docetaxel Treatment Comparison to Historical Monotherapy data**

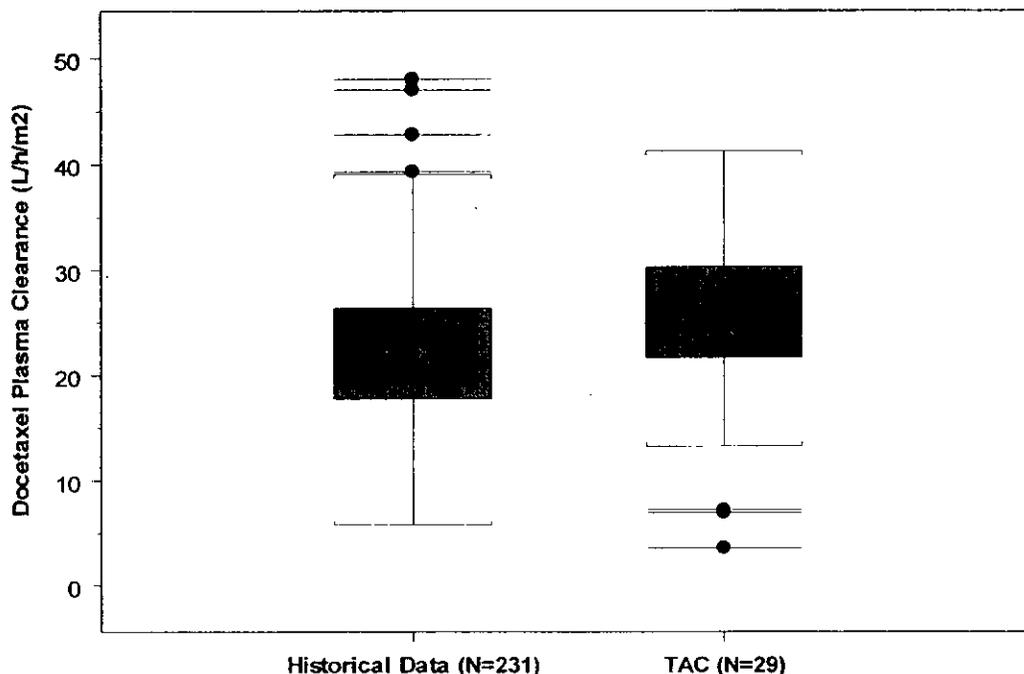
Parameter	Treatment	N	Geometric Mean	TAC/Monotherapy Ratio (%)*	90% Confidence Interval
CL (L/h/m <sup>2</sup> )	TAC	29	21.8	103%	92-116%
	Monotherapy	231	21.1		

There was no statistically significant difference in docetaxel plasma clearance (CL) when given in combination with doxorubicin and cyclophosphamide (TAC) and when compared to historical population pharmacokinetic dataset from Phase 2 studies in breast cancer patients who received docetaxel (75 or 100 mg/m<sup>2</sup> as a 1-hour infusion every 3 weeks) as monotherapy [Bruno R, et al., Population pharmacokinetics/pharmacodynamics of docetaxel in phase II studies in patients with cancer. J Clin Oncol 1998;16:187-196]. A comparison of AUC<sub>inf</sub> values could not be made since individual dosing information was not available for the historical population data to estimate dose-normalized AUC<sub>inf</sub> values. An arbitrary 95% confidence interval for AUC<sub>inf</sub> values was calculated to compare between the combination TAC data (Study XRP6976D/1001) and historical monotherapy data:

Parameter	Treatment	N	Arithmetic Mean	p-value	95% Confidence Interval
AUC <sub>inf</sub> (µg·h/ml)	TAC	29	4.25	0.05	2.8-5.7%
	Monotherapy	231	4.97	0.05	4.8-5.2%

Much less variability and a tighter confidence interval were noted with the historical monotherapy data; this is because of the larger sample size (n=231) compared to the sample size of 29 in the combination study (Study XRP6976D/1001).

A box plot of docetaxel CL values following the TAC combination and historical monotherapy data is shown below. The median (range) CL values were 23.6 (13.2-41.25) L/h/m<sup>2</sup> for Study XRP6976D/1001 (TAC combination) and 22.1 (7.5-34.9) L/h/m<sup>2</sup> for historical data (docetaxel monotherapy). There were three outliers CL values in the data from Study XRP6976D/1001 (3.6, 6.95, and 7.2 L/h/m<sup>2</sup> and four outliers CL values in the historical data (39.3, 42.8, 47.0, and 48.0 L/h/m<sup>2</sup>).



The pharmacokinetic parameters for **doxorubicin** and **cyclophosphamide** ( $C_{max}$ ,  $AUC_{inf}$ ,  $t_{1/2}$ , CL, and  $V_{ss}$ ) were calculated using non-compartmental methods. A summary of the non-compartmental PK parameters for doxorubicin and cyclophosphamide is shown in the tables below:

**Table 3 - Arithmetic Mean  $\pm$  SD (CV%) Non-Compartmental PK Parameters for Doxorubicin**

	TAC	AC
<b>N</b>	30	30
$C_{max}$ (ng/ml)	2251 $\pm$ 743 (33%)	2067 $\pm$ 763 (37%)
$AUC_{inf}$ (ng·h/ml)	1594 $\pm$ 359 (22%)	1536 $\pm$ 440 (28%)
CL (L/h/m <sup>2</sup> )	33.7 $\pm$ 10.6 (31%)	35.2 $\pm$ 9.7 (27%)
$t_{1/2}$ (h)	18.5 $\pm$ 2.9 (16%)	19.2 $\pm$ 2.5 (13%)
$V_{ss}$ (L)	910 $\pm$ 331 (36%)	984 $\pm$ 443 (45%)

**Table 4 – Doxorubicin Treatment Comparison**

Parameter	Treatment	N	Geometric Mean	TAC/AC Ratio (%)	90% Confidence Interval
AUC <sub>inf</sub> (ng•h/ml)	AC	30	1481.7	105%	98 – 112%
	TAC	30	1549.5		
C <sub>max</sub> (ng/ml)	AC	30	1877.9	111.5%	94 – 133%
	TAC	30	2094.7		

**Table 5 - Arithmetic Mean ± SD (CV%) Non-Compartmental PK Parameters for Cyclophosphamide**

	TAC	AC
N	30	30
C <sub>max</sub> (µg/ml)	34.2±10.0 (29%)	32.3±8.2 (25%)
AUC <sub>inf</sub> (µg•h/ml)	222±54 (24%)	225±58 (26%)
CL (L/h/m <sup>2</sup> )	2.4±0.74 (30%)	2.4±0.69 (29%)
t <sub>1/2</sub> (h)	5.6±0.94 (17%)	5.7±1.2 (20%)
V <sub>ss</sub> (L)	28.3±6.7 (23%)	28.6±6.3 (22%)

**Table 6 – Cyclophosphamide Treatment Comparison**

Parameter	Treatment	N	Geometric Mean	TAC/AC Ratio (%)	90% Confidence Interval
AUC <sub>inf</sub> (µg•h/ml)	AC	30	217.9	99%	93 – 104%
	TAC	30	215.1		
C <sub>max</sub> (µg/ml)	AC	30	31.3	105%	96 – 116%
	TAC	30	32.9		

Except for doxorubicin C<sub>max</sub> which increased by 11.5% when the triple combination was administered, the PK parameters for each of doxorubicin and cyclophosphamide were similar when administered either as a double combination (AC) or as a triple combination with docetaxel (TAC). The 11.5% increase in C<sub>max</sub> of doxorubicin in the presence of docetaxel and cyclophosphamide is not clinically significant since the dose used in this study (50 mg/m<sup>2</sup>) is less than the recommended dosing range for doxorubicin monotherapy are is 60-75 mg/m<sup>2</sup>. The cardiotoxicity induced by doxorubicin (i.e., a decline in left ventricular ejection fraction) is estimated to be 1-2% at a total cumulative dose of 300 mg/m<sup>2</sup> of doxorubicin, 3-5% at a dose of 400 mg/m<sup>2</sup>, 5-8% at a dose of 450 mg/m<sup>2</sup> and 6-20% at a dose of 500 mg/m<sup>2</sup> given in a schedule of a bolus injection once every 3 weeks (PDR®).

In conclusion, the results of this study demonstrate that the coadministration of docetaxel has no effect on the pharmacokinetics of each of doxorubicin and cyclophosphamide when the three drugs given in combination compared to coadministration of doxorubicin and cyclophosphamide only. In addition, doxorubicin and cyclophosphamide have no effect on docetaxel plasma clearance when the three drugs given in combination compared to historical data for docetaxel monotherapy.

**2.4.2.7 What other co-medications are likely to be administered to the target patient population?**

Dexamethasone (8 mg) is to be administered on Days 1 and 2 of each treatment cycle to reduce the risk of allergic reactions and fluid retention. In case of febrile neutropenia or neutropenia lasting > 5 days in Cycle 1, granulocyte colony-stimulating factor (G-CSF) support is to be administered. Prophylactic antiemetics (e.g., granisetron, ondansetron), antiallergics, antibiotics are to be administered.

**2.4.2.8 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?**

None

**2.4.2.9 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?**

None

**2.4.2.10 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?**

None

**2.4.3 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?**

None

**2.5 General Biopharmaceutics (NOT APPLICABLE)**

2.5.1 Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

2.5.2.1.1 What data support or do not support a waiver of in vivo BE data?

- BCS classification system
- Formulation ingredient information
- Dissolution profiles
- Others

2.5.2.2 What are the safety or efficacy issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?

**2.5.2.3 If the formulations do not meet the standard criteria for bioequivalence, what clinical pharmacology and/or clinical safety and efficacy data support the approval of the to-be-marketed product?**

**2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?**

**2.5.4 When would a fed BE study be appropriate and was one conducted?**

**2.5.5 How do the dissolution conditions and specifications ensure in vivo performance and quality of the product?**

**2.5.6 If different strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of the various strengths of the to-be-marketed product?**

**2.5.7 If the NDA is for a modified release formulation of an approved immediate product without supportive safety and efficacy studies, what dosing regimen changes are necessary, if any, in the presence or absence of PK-PD relationship?**

**2.5.8 If unapproved products or altered approved products were used as active controls, how is BE to the approved product demonstrated? What is the basis for using either in vitro or in vivo data to evaluate BE?**

**2.5.9 What other significant, unresolved issues related to in vitro dissolution or in vivo BA and BE need to be addressed?**

## **2.6 Analytical section**

**2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?**

Docetaxel, doxorubicin, and cyclophosphamide were the active moieties measured in plasma samples.

**2.6.2 Which metabolites have been selected for analysis and why?**

No metabolites were measured in plasma samples.

**2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?**

Total drug concentrations of docetaxel, doxorubicin, and cyclophosphamide were measured in plasma samples.

## 2.6.4 What bioanalytical methods are used to assess concentrations?

Published bioanalytical methods were used to assess plasma concentrations of docetaxel, doxorubicin, and cyclophosphamide.

**Docetaxel** plasma concentrations were measured using a validated liquid chromatography-mass spectrometry (LC/MS/MS) assay method [Wang LZ, et al., A rapid and sensitive liquid chromatography/tandem mass spectrometry method for determination of docetaxel in human plasma. *Rapid Commun Mass Spectrom.* 2003;17:1548-1552].

**Doxorubicin** plasma concentrations were measured using a validated high-performance liquid chromatography (HPLC) assay method with fluorescence detection [Andersen A, et al., A sensitive and simple high-performance liquid chromatographic method for the determination of doxorubicin and its metabolites in plasma. *Ther Drug Monit.* 1993, 15:455-61].

**Cyclophosphamide** plasma concentrations were measured using a validated HPLC assay method with UV Detection [Huitema AD, et al., Simple and selective determination of the cyclophosphamide metabolite phosphoramidate mustard in human plasma using high-performance liquid chromatography. *J Chromatogr B Biomed Sci Appl.* 2000, 18;745:345-355].

### 2.6.4.1 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

Docetaxel calibration curves were linear over the concentration range of  $0.1 - 100$  ng/ml (the coefficient of determination ( $r^2$ ) for the standard curve was  $> 0.997$ ). The calibration range was extended up to  $1000$  ng/ml with 20-fold dilution to accommodate plasma samples with concentrations higher than  $50$  ng/ml.

Doxorubicin calibration curves were linear over the concentration range of  $0.1 - 100$  ng/ml ( $r^2=0.999$ ).

Cyclophosphamide calibration curves were linear over the concentration range of  $0.1 - 100$   $\mu$ g/ml ( $r^2 > 0.990$ ).

### 2.6.4.2 What are the lower and upper limits of quantification (LLOQ/ULOQ)?

Docetaxel calibration curve has an LLOQ of  $0.1$  ng/ml.

Doxorubicin calibration curve has an LLOQ  $0.1$  ng/ml.

Cyclophosphamide calibration curve has an LLOQ of  $0.1$   $\mu$ g/ml.

### 2.6.4.3 What are the accuracy, precision, and selectivity at these limits?

For docetaxel: the within and between run precision (%CV) of quality control samples ranged from  $1 - 5$ . The within and between run accuracy of quality control samples were within  $1 - 5$ .

~~For doxorubicin: the within and between run precision (%CV) of quality control samples ranged from — . The within and between run accuracy of quality control samples were within —~~

For cyclophosphamide: the within and between run precision (%CV) of quality control samples ranged from — . The within and between run accuracy of quality control samples were within —

### **3 OCPB Labeling Recommendations**

We recommend that you add the following labeling statement under the **CLINICAL PHARMACOLOGY/ HUMAN PHARMACOKINETICS** section of the current package insert for Taxotere®:

“A study was conducted in 30 patients with advanced breast cancer to determine the potential for drug-drug-interactions between docetaxel (75 mg/m<sup>2</sup>), doxorubicin (50 mg/m<sup>2</sup>), and cyclophosphamide (500 mg/m<sup>2</sup>) when administered in combination. The coadministration of docetaxel has no effect on the pharmacokinetics of each of doxorubicin and cyclophosphamide when the three drugs are given in combination compared to coadministration of doxorubicin and cyclophosphamide only. In addition, doxorubicin and cyclophosphamide have no effect on docetaxel plasma clearance when the three drugs are given in combination compared to historical data for docetaxel monotherapy”.

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37 Page(s) Withheld

\_\_\_\_\_ § 552(b)(4) Trade Secret / Confidential

\_\_\_\_\_ § 552(b)(5) Deliberative Process

\_\_\_\_\_ § 552(b)(5) Draft Labeling

**4.2 Individual Study Report**

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**Sponsor**

Aventis Pharmaceuticals, Inc.  
Route 202-206, PO Box 6800  
Bridgewater, NJ 08807-0800, USA

**CLINICAL STUDY REPORT**

**A PHARMACOKINETIC INTERACTION STUDY OF DOCETAXEL (RP56976, TAXOTERE®) 75 mg/m<sup>2</sup> i.v. ON THE COMBINATION THERAPY DOXORUBICIN (50 mg/m<sup>2</sup> i.v.) AND CYCLOPHOSPHAMIDE (500 mg/m<sup>2</sup> i.v.) IN THE TREATMENT OF ADVANCED BREAST CANCER.**

**XRP6976D-1001 Docetaxel**

---

Clinical development phase:	I
Investigators:	Multicenter Study
Date first patient was enrolled:	03 April 2003
Date last patient completed the study:	30 December 2003

Study managers:

Clinical Pharmacokineticist:

Medical Officer:

Report type: Clinical study report

**This study was conducted in accordance with good clinical practice and Aventis standard operating procedures for clinical investigation and documentation**

*See Ethics and Administration*

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**Date of issue:** 11 May 2004

**Document number:** CLN-B-2004-0072

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## 2 STUDY OBJECTIVES

### 2.1 PRIMARY OBJECTIVE

The primary objective was to determine in a randomized, cross-over setting (each patient being her own control) how the pharmacokinetic profiles of doxorubicin ( $50 \text{ mg/m}^2$ ) and cyclophosphamide ( $500 \text{ mg/m}^2$ ) are impacted by the presence of docetaxel ( $75 \text{ mg/m}^2$ ).

### 2.2 SECONDARY OBJECTIVE

The secondary objective was to assess from a historical comparison how the pharmacokinetic profile of docetaxel ( $75 \text{ mg/m}^2$ ) is impacted by doxorubicin ( $50 \text{ mg/m}^2$ ) and cyclophosphamide ( $500 \text{ mg/m}^2$ ).

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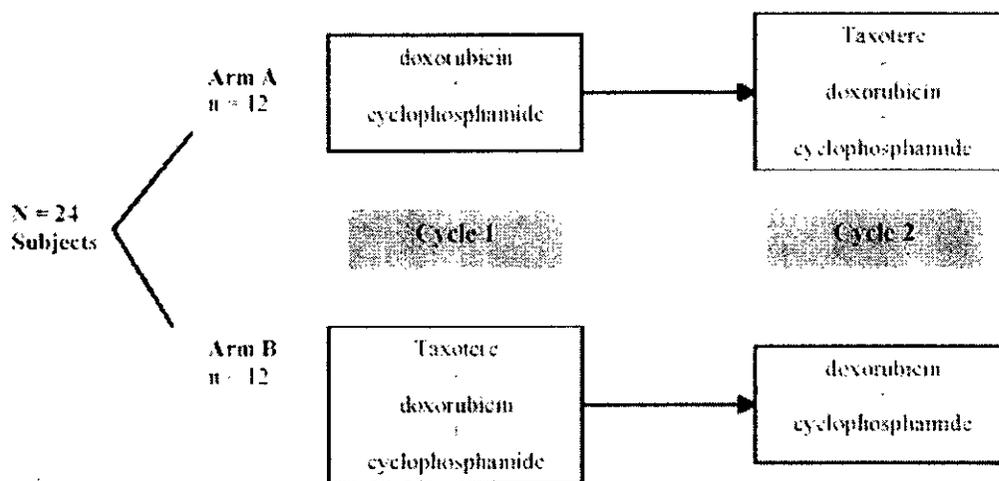
### 3 INVESTIGATIONAL PLAN

For full details of the investigational plan, see the relevant sections of the clinical study protocol in Appendix A.1.1. Clinical Study Protocol.

#### 3.1 STUDY DESIGN

This was a multicenter, open label, 2-cycle, cross-over, randomized pharmacokinetic study of doxorubicin in combination with cyclophosphamide, with or without docetaxel, in the treatment of advanced breast cancer patients. No single-agent control for pharmacokinetics was studied because of ethical considerations. Figure 1 graphically illustrates the study design. The duration of the study (enrollment period + study treatment period + follow-up period) was planned to be 9 months.

Figure 1 – Study design



#### 3.2 SELECTION OF PATIENTS

##### 3.2.1 Number of patients

At least 24 patients (12 per arm) were to be enrolled and treated in this study. Enrollment was to be stopped when the anticipated or actual numbers of patients had been achieved. A patient may have been replaced if an adequate number of pharmacokinetic samples was not collected.

Any waiver of these inclusion and exclusion criteria was to be approved by the investigator and the Sponsor on a case-by-case basis prior to enrolling the patient. This was to be documented by both the Sponsor and the investigator.

No patient was allowed to enroll in this study more than once.

Sample size justification is provided in Section 4.3.

### 3.2.2 Inclusion criteria

Patients meeting all of the following criteria were to be considered for enrollment into the study

1. Written informed consent.
2. Females of childbearing potential were to be nonpregnant, nonlactating, and using adequate contraception.
3. Age  $\geq 18$  years and  $< 70$  years. The upper age limit was not meant to be exclusionary but rather was based on limited safety data for the TAC regimen in women  $> 70$  years of age.
4. Histologically or cytologically confirmed advanced breast cancer (including adjuvant setting for high-risk patients).
5. WHO Performance Status  $\leq 2$  or Karnofsky Performance status index  $\geq 60\%$ .
6. No symptomatic evidence or history of brain metastases.
7. No peripheral neuropathy  $\geq$  grade 2, unless related to a mechanical etiology.
8. Normal cardiac function confirmed by LVEF or shortening fraction (MUGA scan or echocardiography). The result was to be above the lower limit of normal for the institution.
9. Laboratory requirements (within 14 days prior to registration).
  - Hematology
    - Neutrophils  $\geq 2.0 \times 10^9/L$ ,
    - Platelets  $\geq 100 \times 10^9/L$ , and
    - Hemoglobin  $> 10$  g/dL.
  - Hepatic function.
    - Total bilirubin  $\leq 1$  x ULN,
    - AST (SGOT) and ALT (SGPT)  $\leq 2.5$  x UNL, and
    - Alkaline phosphatase  $\leq 5$  x UNL.
    - Patients with AST and/or ALT  $\geq 1.5$  x UNL associated with alkaline phosphatase  $> 2.5$  x UNL were not eligible for the study.
  - Renal function
    - Serum creatinine within upper normal limits

– For borderline values, the calculated creatinine clearance was to be  $\geq 60$  mL/min.

10. Patients were to be amenable to compliance with testing.

### 3.2.3 Exclusion criteria

Patients meeting any of the following criteria were not to be included in the study.

1. Less than 6 months since last infusion of prior anthracycline or taxoid (i.e. paclitaxel or docetaxel) therapy.
2. Prior cumulative anthracycline dose  $> 240$  mg/m<sup>2</sup>.
3. Pregnant or lactating patients. Patients of childbearing potential were to implement adequate non-hormonal contraceptive measures during study treatment.
4. Brain or leptomeningeal metastases.
5. Major surgical therapy within 2 weeks prior to study entry.
6. Pre-existing motor or sensory neurotoxicity of  $\geq$  Grade 2 severity by NCI criteria.
7. Other serious illness or medical condition including but not limited to
  - Congestive heart failure or unstable angina pectoris, previous history of myocardial infarction within 1 year of study entry, uncontrolled hypertension or high-risk, uncontrolled arrhythmias.
  - History of significant neurologic or psychiatric disorders, including psychotic disorders, dementia or seizures that would prohibit the understanding and giving of informed consent.
  - Active, uncontrolled infection
  - Active peptic ulcer.
  - Unstable diabetes mellitus.
8. Past or current history of neoplasm other than breast carcinoma, except for
  - Curatively treated, non-melanoma skin cancer.
  - *In situ* carcinoma of the cervix.
  - Other cancer, curatively treated and with no evidence of disease for at least 10 years.
  - Ipsilateral ductal carcinoma in situ of the breast, and
  - Lobular carcinoma in situ of the breast.
9. Chronic treatment with corticosteroids unless initiated  $> 6$  months prior to study entry and at low dose ( $\leq 20$  mg methylprednisolone or equivalent).
10. Concurrent treatment with ovarian hormone-replacement therapy. Prior treatment should be stopped before study entry.
11. Definite contraindications for the use of corticosteroids.

12. Concurrent treatment with other experimental drugs. Participation in another clinical trial with any investigational not marketed drug within 30 days prior to study entry.
13. Concurrent treatment with any other anticancer therapy.
14. Male patients.
15. Patients who cannot be regularly followed up for psychological, social, familial or geographic reasons.

### 3.3 STUDY TREATMENTS

#### 3.3.1 Details of study drugs

Table 1 – Study treatments

Drug code:	RP-56976	NDC-0015-3352-22	NDC-0015-0547-41
INN:	Docetaxel	Doxorubicin	Cyclophosphamide
Formulation:	Sterile clear viscous, yellow to brown-yellow solution containing 40 mg/mL docetaxel (anhydrous) in polysorbate 80. The solvent for Taxotere <sup>®</sup> is a 13% w/w solution of ethanol in water for injection.	Sterile, red-orange lyophilized powder containing 50 mg of doxorubicin for administration by intravenous infusion	Lyophilized Cytoxan <sup>®</sup> containing 500 mg of drug in 20–25-mL glass vial.
Manufacturer:	Aventis Pharma	Upon pharmacy hospital availability	Upon pharmacy hospital availability
Batch number:	see Appendix A.3.3. Batch numbers of investigational product(s)		

Full batch details (ie, batch number, date of expiry and number of vials used) for all study medications are provided in Appendix A.3.3. Batch numbers of investigational product(s).

#### 3.3.2 Dosage schedule

Treatments were administered in 3-week cycles. Dexamethasone was to be administered to all patients on Day –1, Day 1 and Day 2 of each treatment cycle in order to reduce the risk of allergic reactions and fluid retention. This is discussed further in Section 3.4.2.

In arm A, patients were treated with the double combination (doxorubicin + cyclophosphamide) in Cycle 1 followed by the triple combination (Taxotere + doxorubicin + cyclophosphamide) in Cycle 2.

In arm B, patients were treated with the triple combination in Cycle 1 followed by the double combination in Cycle 2.

**3.3.2.1 Double combination: doxorubicin + cyclophosphamide (AC)**

Doxorubicin administered first.

Dose: 50 mg/m<sup>2</sup>

Route: 15-minute i.v. infusion

Schedule: Day 1 of each treatment cycle

Followed immediately by cyclophosphamide

Dose: 500 mg/m<sup>2</sup>

Route: 15-minute i.v. infusion

Schedule: Day 1 of each treatment cycle

**3.3.2.2 Triple combination: docetaxel + doxorubicin + cyclophosphamide (TAC)**

Doxorubicin administered first

Dose: 50 mg/m<sup>2</sup>

Route: 15-minute i.v. infusion

Schedule: Day 1 of each treatment cycle

Followed immediately by cyclophosphamide

Dose: 500 mg/m<sup>2</sup>

Route: 15-minute i.v. infusion

Schedule: Day 1 of each treatment cycle

Followed immediately by Taxotere

Dose: 75 mg/m<sup>2</sup>

Route: 1-hour i.v. infusion

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Schedule: Day 1 of each treatment cycle

It should be noted that the TAC regimen used in the pivotal TAX 316 study employed a 1-hour interval between the end of the doxorubicin infusion and the start of the Taxotere infusion. There was no such interval in the present study. Otherwise, the doses and sequence of the drug administrations were the same as in study TAX 316.

**3.3.3 Treatment assignment**

The investigational products (doxorubicin and cyclophosphamide  $\pm$  Taxotere) were to be administered only to patients included in this study following the procedures set out in the clinical study protocol (CSP).

All patients included in the study were to receive a patient number. This patient number was to be used to identify the patient throughout the study.

Patients who permanently discontinued from the study were to retain their patient number. New patients were always to be allotted a new patient number.

All eligible patients were to be registered with Aventis via fax prior to the start of treatment. Randomization was to be performed at Aventis; treatment assignment and patient numbers were to be communicated to the investigator *via* fax through a randomization form and returned to the investigative site within 24 hours during working days.

The date for start of treatment was not to be scheduled more than 5 days after registration.

A patient who was not registered before the first treatment administration was not to be accepted for the study at a later date.

**3.3.4 Blinding, packaging and labeling**

**3.3.4.1 Taxotere**

Taxotere was packaged in cardboard boxes of 1 Taxotere vial and 1 solvent vial, provided by Aventis Pharmaceuticals Inc., Bridgewater, NJ, USA.

Affixed to each box was an investigational label containing the Sponsor's name and address, the product's name and concentration, the protocol number, the condition for use, packaging reference number and a use-by date. Additional statements were printed on the label(s) as required by local regulations.

The dose of study medication required for a patient to complete 1 cycle of TAC was to be taken from as many vials as required. Vials were intended for single administration only.

The label affixed to each vial of Taxotere contained at least the following information:

- Sponsor's name and address.

- Product name.
- Concentration and volume.
- Batch number.
- Packaging reference number.
- Storage condition, and
- Use-by date.

#### **3.3.4.2 Doxorubicin**

Doxorubicin available at the hospital pharmacy was used; the package insert was consulted for all relevant information (e.g., handling, reconstitution administrations and storage).

#### **3.3.4.3 Cyclophosphamide**

Cyclophosphamide available at the hospital pharmacy was used; the package insert was consulted for all relevant information (e.g., handling, reconstitution administrations and storage).

#### **3.3.5 Study drug accountability**

The investigator or pharmacist was to inventory and acknowledge receipt of all shipments of the investigational products. The investigational products were to be kept in a locked area with restricted access. The investigational products were to be stored and handled in accordance with the manufacturer instructions. The investigator or pharmacist was also to keep accurate records for each patient of the quantities of the investigational products dispensed, used and returned. The study monitor was to periodically check the supplies of investigational products held by the investigator or pharmacist to ensure accountability of all investigational products used. At the conclusion of the study, all unused investigational products and all medication containers were to be returned to the Sponsor unless other arrangements have been approved by the Sponsor. The Sponsor was to assure that a final report of drug accountability to the unit dose level is prepared and maintained in the investigator study file.

#### **3.3.6 Compliance**

The compliance of patients was under direct supervision of the investigator and was checked by the study monitor. Any delegation of this responsibility was to follow *Appendix A.1.1 Protocol Section 12.2 DELEGATION OF INVESTIGATOR DUTIES*.

All deaths considered related to drug treatment or occurring within 30 days after the last dose of study medication were to be reported as serious adverse events on study. Deaths occurring more than 30 days after the last treatment and not related to drug treatment were not to be considered serious adverse events.

### 3.5.2 Methods

#### 3.5.2.1 Pharmacokinetic data

##### *Blood collection*

Blood samples for pharmacokinetics were to be collected from each patient at both Cycle 1 and at Cycle 2. Since the test drug was administered intravenously, blood samples were not to be collected from the same arm in which the drug was infused. The protocol defined sampling schedules for doxorubicin, cyclophosphamide, and docetaxel as shown in the figures below. Blood samples for pharmacokinetic analysis were to be collected *via* an indwelling peripheral catheter or via peripheral venipuncture into heparinized coated tubes at the following times (see *Appendix A.1.1 Protocol* APPENDIX G: PHARMACOKINETIC SAMPLE HANDLING)

- Doxorubicin: Ten 3-ml, blood samples were drawn at the following times: start of the infusion, at the end of the infusion, 15min, 1h, 1h15min, 2h, 3h15min, 7h45min, 24h15min, 48h15min after the end of the doxorubicin infusion each cycle.
- Cyclophosphamide: Eight 2-ml, blood samples were drawn at the following times: start of the infusion, at the end of the infusion, 45min, 1h45min, 6h, 7h30min, 24h, and 48h after the end of the cyclophosphamide infusion each cycle.
- Taxotere: Seven 3-ml, blood samples were drawn at the following times: start of infusion, 15min before the end of the docetaxel infusion, and 15min, 45min, 2h, 5h, and 23h after the end of the docetaxel infusion each cycle.

The sampling schedules are displayed graphically in Figure 2 and Figure 3.

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Figure 2 – Sampling schedule – TAC

**BLOOD SAMPLING SCHEDULE - TAC**

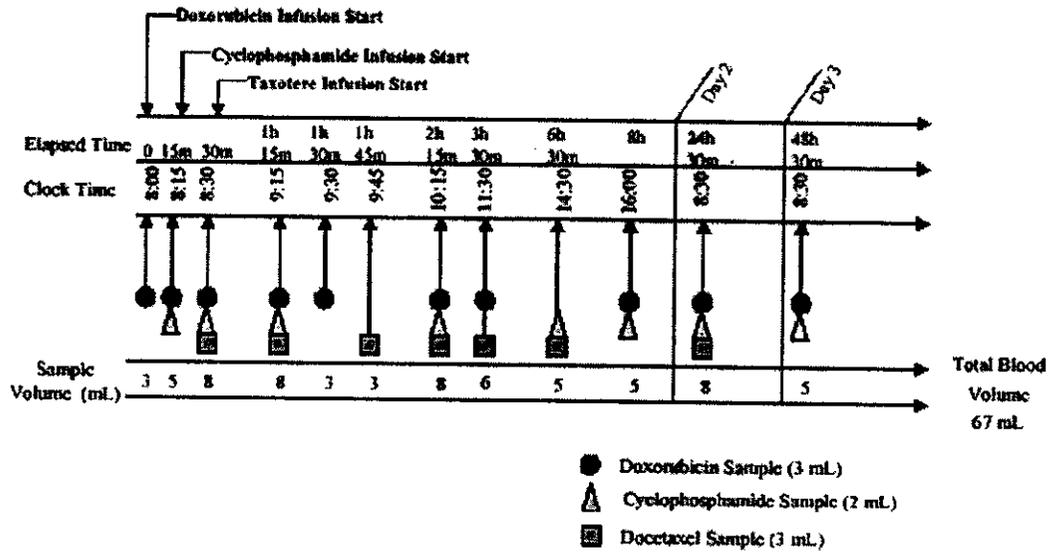
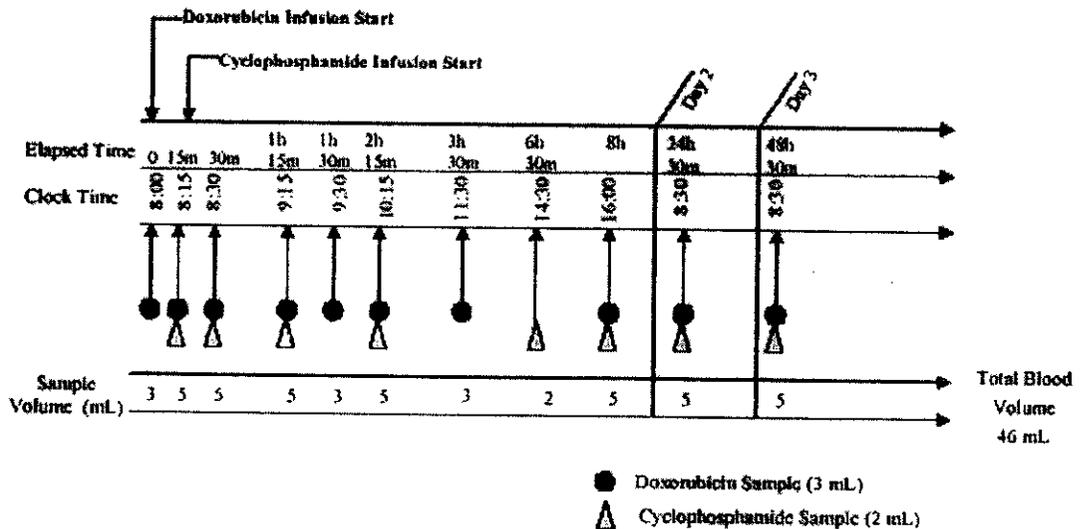


Figure 3 – Sampling schedule, AC regimen

**BLOOD SAMPLING SCHEDULE - AC**



For patients whose samples were collected through a catheter, 1 mL of blood was withdrawn at each sampling time and discarded to assure that the solution used to maintain catheter patency did not dilute the sample. Since the test drug was administered intravenously, blood samples were not collected from the arm through which the drug was infused.

A maximum total of 67 mL of whole blood was collected over each cycle for pharmacokinetic evaluation in the patients enrolled in this study.

For all collected samples, it was extremely important to collect samples at the specified times. Samples missed or lost for any reason were recorded. Both the scheduled and actual times of blood collection appeared on the blood collection record used at the clinics and on the CRF page. The times of drug administrations (doxorubicin + cyclophosphamide = Taxotere) were also to be recorded precisely (see *Appendix A.1.1 Protocol* APPENDIX G: PHARMACOKINETIC SAMPLE HANDLING).

#### *Bioanalysis*

- Docetaxel plasma concentration analysis was performed using liquid chromatography-mass spectrometry (LC/MS/MS).
- The assay method for doxorubicin and cyclophosphamide concentration determination in plasma high-performance liquid chromatography (HPLC).

These methods of drug concentration analysis are described in section 7.1 of this report.

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## 4 STATISTICAL AND ANALYTICAL PROCEDURES

The statistical analyses performed in this study were initially specified in the clinical study protocol (see Appendix A.1.1. Clinical Study Protocol). The primary analysis variables, described below, were pharmacokinetic parameters calculated from plasma concentrations of each drug (docetaxel, doxorubicin, and cyclophosphamide) in each cycle

### 4.1 ANALYSIS VARIABLES

#### 4.1.1 Pharmacokinetic analysis methods

Pharmacokinetic parameters were calculated from plasma concentrations of docetaxel, doxorubicin and cyclophosphamide at Cycle 1 and at Cycle 2. Docetaxel pharmacokinetics were estimated by nonlinear mixed effects modeling, and doxorubicin and cyclophosphamide pharmacokinetics were estimated via non-compartmental analysis.

##### 4.1.1.1 Docetaxel

The analysis of docetaxel pharmacokinetics focused on docetaxel CL and AUC, which are good predictors of clinical outcome[30]. Clearance was calculated by Bayesian estimation using individual concentration-time data for each patient as posterior information, and the previously defined population model as prior information [31]. A 3-compartmental structural model with first-order elimination was used, and individual pharmacokinetic analysis was performed with the NONMEM program (double precision, version V, level 1.0) with the NMTRAN pre-processor (Version III, level 1.0) and PREDDP routines (Version IV, level 1.0) implemented on an IBM Intellistation with Fortran 77 running under a Linux operating system [32]. Area under the concentration-time curve was calculated as dose/CL. The NONMEM dataset is listed in Appendix C.2.2.7.1 - Docetaxel NONMEM dataset. The NONMEM code, including the prior estimates, are listed in Appendix C.2.2.7.2 - Docetaxel analysis.

A number of graphical representations were produced from NONMEM generated data using Microsoft Excel 2000. In these figures, appended in Appendix C.2.2.7.2 - Docetaxel analysis, IPRED denotes NONMEM individual predictions, IWRES the individual weighted residuals, and DV denotes dependent variable (in this analysis, the concentration). Formulae used to simulate concentrations during and after the infusion for the individual model predicted plasma concentrations vs time profiles are presented in Appendix C.2.2.7.2 - Docetaxel analysis.

##### 4.1.1.2 Doxorubicin

For the characterization of doxorubicin pharmacokinetics, non-compartmental analysis was conducted using a validated WinNonlin® Version 3.3 (Pharsight Corporation). The maximum doxorubicin concentration in plasma after drug administration was determined directly from the observed concentration-time data. The following pharmacokinetic parameters were calculated, area under the concentration-time curve to the last measured concentration point (AUC<sub>last</sub>) was

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calculated via a linear trapezoidal method and then extrapolated to infinity to generate  $AUC_{0-\infty}$ . The  $k$  term is defined as the slope of the log-linear regression of the declining terminal portion of the concentration-time profile, and the terminal half-life ( $t_{1/2}$ ) is calculated as  $0.693/k$ . Total body clearance (CL) was calculated as  $dose/AUC_{0-\infty}$  and volume of distribution at steady-state ( $V_{ss}$ ) was calculated as  $CL * MRT$  (mean residence time).

#### 4.1.1.3 Cyclophosphamide

Cyclophosphamide pharmacokinetics were also determined using non-compartmental analysis conducted with validated WinNonlin® software Version 3.3 (Pharsight Corporation). The maximum cyclophosphamide concentration in plasma after drug administration was determined directly from the observed concentration-time data. The following pharmacokinetic parameters were calculated: area under the concentration-time curve to the last measured concentration point ( $AUC_{last}$ ) was calculated via a linear trapezoidal method and then extrapolated to infinity to generate  $AUC_{0-\infty}$ . The  $k$  term is defined as the slope of the log-linear regression of the declining terminal portion of the concentration-time profile, and the terminal half-life ( $t_{1/2}$ ) is calculated as  $0.693/k$ . Total body clearance (CL) was calculated as  $dose/AUC_{0-\infty}$  and volume of distribution at steady-state ( $V_{ss}$ ) was calculated as  $CL * MRT$  (mean residence time).

#### 4.1.2 Safety variables

Safety variables evaluated over the course of this study included the incidence of adverse events (including SAEs) recorded during the study, changes from baseline in vital signs (e.g., blood pressure, heart rate), ECG, weight and laboratory parameters (e.g., serum chemistry, hematology).

Treatment-emergent adverse events (TEAEs) were to be summarized as the primary assessment of safety and were determined programmatically. A TEAE was considered as any event not present prior to the initiation of treatment that developed during the on-study period or any event already present that worsened in intensity during the treatment period.

The investigator observed patients for adverse events (local or systemic) and instructed patients to report any events that occurred during the study. For the purposes of the study, the period of observation for each individual patient extended from the time the patient gave informed consent until thirty days after the last infusion of study chemotherapy or until the next therapy (whichever was shorter).

## 4.2 STATISTICAL METHODS

Descriptive statistics (number of patients, mean, standard deviation, standard error, coefficient of variation, geometric mean, scatter factor, median, minimum, and maximum) were generated on pharmacokinetic parameters for all three drugs.

For doxorubicin and cyclophosphamide, which were administered in both the double and triple combinations, comparisons of pharmacokinetic parameters across treatments were performed. Analysis of variance (ANOVA), with fixed effects for sequence, period and treatment and random

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effect for patient nested within sequence were performed on the natural logarithms of  $AUC_{0-\infty}$ ,  $AUC_{last}$ ,  $C_{max}$ . Within the framework of the ANOVA, the 90% confidence intervals (CI) for the ratio of the test treatment (TAC) least squares mean relative to the reference treatment (AC) least squares mean were provided. The 90% CIs were obtained by taking the antilog of the 90% CI for the difference between the least squares means on the natural logarithmic scale. The least squares means of  $AUC_{0-\infty}$ ,  $AUC_{last}$ , and  $C_{max}$  were transformed back into the original scale by taking the antilog.

For docetaxel, the clearance (CL) from this study was compared to the docetaxel CL from Aventis historical monotherapy PK data in the breast cancer population [34]. An ANOVA with fixed effects for sequence, period, treatment, and random effect for patient nested within sequence was performed on the natural logarithm of CL for docetaxel compared to the historical data.

The analysis of pharmacokinetic parameters and concentrations were calculated using SAS Version 8.02 (SAS Institute, Inc., Cary, NC, USA).

The safety analysis in this study was descriptive only.

#### 4.3 SAMPLE SIZE JUSTIFICATION

A total of at least 24 eligible and evaluable patients (see Section 3.6), 12 per arm, was necessary for pharmacokinetic analysis. Patients were enrolled until acceptable samples were confirmed from 24 patients. The sample size was based on historical docetaxel monotherapy population PK data, where the docetaxel AUC variability in the breast cancer population was 33%. N-Query 4.0 was used to calculate the sample size and a two-sided test was performed using an alpha risk of 5% and equivalence margins of 80% - 125%. At a power of 80%, this test yielded a sample size of 24.

```

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;RUN WITH final data
$INPUT C ID DATE=DROP TIME DV MDV TRT CYCL AMT RATE EVID
$DATA nmtaxotereD1001dataset.dat IGNORE=C
$SUBROUTINES ADVAN5 TRANS1
$MODEL
    NCOMPARTMENTS=3 NPARAMETERS=6
    COMP=(CENTRAL DEFDOSE DEFOBS NOOFF) COMP=('PERIPH.'
NOOFF)
    COMP=('PERIPH.'NOOFF)
$PK
    TVCL=THETA(1)
    CL=TVCL*EXP(ETA(1))
    TVV=THETA(2)
    V=TVV*EXP(ETA(2))
    TVK12=THETA(3)
    K12=TVK12*EXP(ETA(3))
    TVK21=THETA(4)
    K21=TVK21*EXP(ETA(4))
    TVK13=THETA(5)
    K13=TVK13*EXP(ETA(5))
    TVK31=THETA(6)
    K31=TVK31*EXP(ETA(6))
    K14=CL/V
    S1=V/1000
$ERROR
    DEL=0
    IF (F.EQ.0) DEL=1
    IPRED=F
    W=F+DEL
    IRES=DV-IPRED
    IWRES=IRES/W
    Y=F+W*ERR(1)
$THETA (36.8) (7.83) (1.19) (1.75) (1.22) (0.0879)
$OMEGA 0.226 0.307 0.599 1.28 0.13 0.123
$SIGMA 0.0421
$ESTIMATION MAXEVALS=0 POSTHOC METHOD=0 NSIG=3 PRINT=5
$TABLE ID TIME AMT RATE TRT CYCL CL K12 K21 K13 K31 V EVID MDV
    IPRED IWRES NOPRINT FILE=taxotereD1001.tab

```

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Listing 02 Subject Demographics

Investigator ID/ Subject Number	Age	Race [a]	Height (cm)	Weight (kg)	CRP BSA [b]	CBP [c]	Practicing Contraception Or Reason For No CBP	Pregnancy Test		
								Date	Type	Result
679/0007	41	3	150.0	73.5	1.8	Yes	None	19JUN2003	Serum	Negative
679/0011	44	3	157.0	56.0	1.5	Yes	Condom/diaphragm	15AUG2003	Serum	Negative
679/0012	66	3	160.0	51.0	1.5	No	Post-menopausal			
679/0013	49	1	170.0	113.0	2.3	Yes	Other: NOT SEXUALLY ACTIVE	22AUG2003	Serum	Negative
679/0014	54	1	157.0	51.0	1.5	No	Post-menopausal			
679/0015	64	3	162.0	80.5	1.9	No	Post-menopausal			
679/0016	46	1	160.0	55.5	1.6	No	Post-menopausal			
679/0017	58	1	175.2	72.0	1.9	No	Post-menopausal			
679/0019	53	1	163.0	79.5	1.8	Yes	Other: NOT SEXUALLY ACTIVE	26SEP2003	Serum	Negative
679/0020	51	1	170.0	73.0	1.9	Yes	Other: HUSBAND HAD VASECTOMY	29SEP2003	Serum	Negative
679/0021	42	1	162.0	68.4	1.7	Yes	Other: NOT SEXUALLY ACTIVE	01OCT2003	Serum	Negative
679/0024	50	3	156.0	57.5	1.5	Yes	Condom/diaphragm	24OCT2003	Serum	Negative
679/0028	54	1	157.0	59.0	1.6	No	Post-menopausal			
679/0029	66	1	158.0	81.5	1.8	No	Post-menopausal			
679/0030	40	3	149.0	53.0	1.5	Yes	Other: NOT SEXUALLY ACTIVE			

[a] 1=White, 2=Black, 3=Asian/Oriental, 4=Multiracial, 999=Other.

[b] Body Surface Area in square meters as per CRFs.

[c] Child Bearing Potential.

Listing 02 Subject Demographics

Investigator ID/ Subject Number	Age	Race [a]	Height (cm)	Weight (kg)	CRF BSA [b]	CBP [c]	Practicing Contraception Or Reason For No CBP	Pregnancy Test		
								Date	Type	Result
4664/0010	56	1	166.0	65.0	1.7	No	Post-menopausal			
4664/0027	32	1	173.0	48.5	1.5	No	Other: UTERUS EXTIRPATION			
9917/0001	64	1	164.0	64.0	1.7	No	Post-menopausal			
9917/0002	57	1	158.0	62.0	1.6	No	Post-menopausal			
9917/0003	48	1	167.0	76.0	1.8	Yes	Other: ABSTINENCE			
9917/0004	40	1	173.0	69.0	1.8	No	Other: CHEMICAL CASTRATION			
9917/0005	44	1	158.0	54.0	1.5	Yes	Other: ABSTINENCE			
9917/0008	50	1	163.0	68.0	1.7	No	Surgical sterilization			
9917/0018	46	1	165.0	58.0	1.6	Yes	Other: ABSTINENCE			
9917/0025	46	1		68.0	1.8	Yes	Other: ABSTINENCE			
9917/0026	50	1	169.0	80.0	1.9	No	Post-menopausal	05NOV2003	Serum	Negative
53523/0023	54	1	160.0	143.6	2.3	No	Surgical sterilization			
57686/0006	60	1	158.0	94.3	1.9	No	Post-menopausal			
59080/0009	58	1	154.9	59.4	1.6	No	Surgical sterilization			
59080/0022	40	1	170.2	57.2	1.6	No	Surgical sterilization			

[a] 1=White, 2=Black, 3=Asian/Oriental, 4=Multiracial, 999=Other.

[b] Body Surface Area in square meters as per CRFs.

[c] Child Bearing Potential.

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**Listing of Pharmacokinetic Parameters for Docetaxel**

Investigator ID/ Subject Number	Arm/ Cycle/ Trt [a]	Dose (mg)	Inf Duration (h)	CRF BSA [b]	AUCinf (ug <sup>2</sup> h/mL)	CL (L/h)	CL (L/h/m <sup>2</sup> )
679/0007	A/2/TAC	130.0	1.00	1.80			
679/0011	A/2/TAC	116.0	1.00	1.55			
679/0012	B/1/TAC	113.0	1.00	1.50			
679/0013	A/2/TAC	170.0	1.00	2.20			
679/0014	B/1/TAC	112.0	1.00	1.40			
679/0015	A/2/TAC	140.0	1.05	1.86			
679/0016	B/1/TAC	118.0	1.00	1.50			
679/0017	B/1/TAC	140.0	1.03	1.80			
679/0019	B/1/TAC	138.0	1.07	1.80			
679/0020	A/2/TAC	140.0	1.00	1.86			
679/0021	B/1/TAC	130.0	1.00	1.68			
679/0024	A/2/TAC	114.0	1.00	1.52			

[a] Arm A: the double combination doxorubicin + cyclophosphamide (AC) at cycle 1 and the triple combination docetaxel + doxorubicin + cyclophosphamide (TAC) at cycle 2.  
 Arm B: the triple combination docetaxel + doxorubicin + cyclophosphamide (TAC) at cycle 1 and the double combination doxorubicin + cyclophosphamide (AC) at cycle 2. Cycle: 1=Cycle 1, 2=Cycle 2. Trt=Treatment: AC: doxorubicin + cyclophosphamide, TAC: docetaxel + doxorubicin + cyclophosphamide.  
 [b] Body Surface Area in square meters as per CRFs.

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Listing of Pharmacokinetic Parameters for Docetaxel

Investigator ID/ Subject Number	Arm/ Cycle/ Trt [a]	Dose (mg)	Inf Duration (h)	CRP BSA [b]	AUCinf (ug*h/mL)	CL (L/h)	CL (L/h/m <sup>2</sup> )
679/0028	A/2/TAC	120.0	1.00	1.60			
679/0029	B/1/TAC	136.0	1.03	1.68			
679/0030	A/2/TAC	110.0	1.00	1.48			
4664/0010	B/1/TAC	130.0	1.00	1.70			
4664/0027	B/1/TAC	115.0	1.07	1.50			
9917/0001	B/1/TAC	127.0	0.90	1.70			
9917/0002	A/2/TAC	123.0	1.03	1.60			
9917/0003	B/1/TAC	139.0	1.07	1.80			
9917/0004	A/2/TAC	137.0	1.60	1.80			
9917/0005	B/1/TAC	115.0	1.02	1.50			
9917/0008	B/1/TAC	127.0	1.03	1.70			
9917/0018	A/2/TAC	121.0	1.05	1.60			

- [a] Arm A: the double combination doxorubicin + cyclophosphamide (AC) at cycle 1 and the triple combination docetaxel + doxorubicin + cyclophosphamide (TAC) at cycle 2.  
 Arm B: the triple combination docetaxel + doxorubicin + cyclophosphamide (TAC) at cycle 1 and the double combination doxorubicin + cyclophosphamide (AC) at cycle 2. Cycle: 1=Cycle 1, 2=Cycle 2. Trt=Treatment: AC: doxorubicin + cyclophosphamide, TAC: docetaxel + doxorubicin + cyclophosphamide.
- [b] Body Surface Area in square meters as per CRFs.

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Listing of Pharmacokinetic Parameters for Docetaxel

Investigator ID/ Subject Number	Arm/ Cycle/ Trt [a]	Dose (mg)	Inf Duration (h)	CRF BSA [b]	AUCinf (ug·h/mL)	CL (L/h)	CL (L/h/m <sup>2</sup> )
9917/0025	B/1/TAC	136.0	1.05	1.80			
9917/0026	A/2/TAC	143.0	1.03	1.90			
53523/0023	A/2/TAC	165.0	1.00	2.30			
59080/0009	A/2/TAC	120.0	1.25	1.60			
59080/0022	B/1/TAC	123.0	1.58	1.60			

[a] Arm A: the double combination doxorubicin + cyclophosphamide (AC) at cycle 1 and the triple combination docetaxel + doxorubicin + cyclophosphamide (TAC) at cycle 2.  
Arm B: the triple combination docetaxel + doxorubicin + cyclophosphamide (TAC) at cycle 1 and the double combination doxorubicin + cyclophosphamide (AC) at cycle 2. Cycle: 1=Cycle 1, 2=Cycle 2. Trt=Treatment: AC: doxorubicin + cyclophosphamide, TAC: docetaxel + doxorubicin + cyclophosphamide.  
[b] Body Surface Area in square meters as per CRFs.

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Listing of Pharmacokinetic Parameters for Doxorubicin

Investigator ID/ Subject Number	Arm/ Cycle/ Trt [a]	Dose (mg)	Inf Duration (h)	CRF BSA [b]	C <sub>max</sub> (ng/mL)	t <sub>1/2</sub> (h)	T <sub>max</sub> (h)	AUC <sub>inf</sub> (ng*h/mL)	AUC <sub>last</sub> (ng*h/mL)	CL (L/h)	CL (L/h/m <sup>2</sup> )	V <sub>ss</sub> (L)
679/0007	A/1/AC	88	0.25	1.80	1							
	A/2/TAC	88	0.28	1.80								
679/0011	A/1/AC	78	0.25	1.55								
	A/2/TAC	78	0.27	1.55								
679/0012	B/1/TAC	75	0.27	1.50								
	B/2/AC	75	0.25	1.50								
679/0013	A/1/AC	115	0.25	2.31								
	A/2/TAC	113	0.25	2.25								
679/0014	B/1/TAC	75	0.25	1.40								
	B/2/AC	75	0.25	1.49								
679/0015	A/1/AC	93	0.27	1.86								
	A/2/TAC	93	0.25	1.86								
679/0016	B/1/TAC	80	0.25	1.50								
	B/2/AC	80	0.28	1.57								
679/0017	B/1/TAC	94	0.25	1.87								
	B/2/AC	94	0.25	1.87								

[a] Arm A: the double combination doxorubicin + cyclophosphamide (AC) at cycle 1 and the triple combination docetaxel + doxorubicin + cyclophosphamide (TAC) at cycle 2.  
 Arm B: the triple combination docetaxel + doxorubicin + cyclophosphamide (TAC) at cycle 1 and the double combination doxorubicin + cyclophosphamide (AC) at cycle 2. Cycle: 1=Cycle 1, 2=Cycle 2. Trt=Treatment: AC: doxorubicin + cyclophosphamide, TAC: docetaxel + doxorubicin + cyclophosphamide.  
 [b] Body Surface Area in square meters as per CRFs.

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Listing of Pharmacokinetic Parameters for Doxorubicin

Investigator ID/ Subject Number	Arm/ Cycle/ Trt [a]	Dose (mg)	Inf Duration (h)	CRF BSA [b]	C <sub>max</sub> (ng/mL)	t <sub>1/2</sub> (h)	T <sub>max</sub> (h)	AUC <sub>inf</sub> (ng*h/mL)	AUC <sub>last</sub> (ng*h/mL)	CL (L/h)	CL (L/h/m <sup>2</sup> )	Yes (L)
679/0019	B/1/TAC	92	0.23	1.84								
	B/2/AC	92	0.25	1.84								
679/0020	A/1/AC	93	0.23	1.86								
	A/2/TAC	93	0.25	1.86								
679/0021	B/1/TAC	87	0.25	1.68								
	B/2/AC	84	0.27	1.68								
679/0024	A/1/AC	76	0.23	1.52								
	A/2/TAC	76	0.23	1.52								
679/0028	A/1/AC	80	0.23	1.60								
	A/2/TAC	80	0.25	1.60								
679/0029	B/1/TAC	90	0.28	1.81								
	B/2/AC	90	0.23	1.76								
679/0030	A/1/AC	75	0.25	1.48								
	A/2/TAC	75	0.25	1.48								
4664/0010	B/1/TAC	85	0.27	1.70								
	B/2/AC	85	0.27	1.70								

[a] Arm A: the double combination doxorubicin + cyclophosphamide (AC) at cycle 1 and the triple combination docetaxel + doxorubicin + cyclophosphamide (TAC) at cycle 2.  
 Arm B: the triple combination docetaxel + doxorubicin + cyclophosphamide (TAC) at cycle 1 and the double combination doxorubicin + cyclophosphamide (AC) at cycle 2. Cycle: 1=Cycle 1, 2=Cycle 2. Trt=Treatment: AC: doxorubicin + cyclophosphamide, TAC: docetaxel + doxorubicin + cyclophosphamide.  
 [b] Body Surface Area in square meters as per CRFs.

LDOXP.SAS

Listing of Pharmacokinetic Parameters for Doxorubicin

Investigator ID/ Subject Number	Arm/ Cycle/ Trt (a)	Dose (mg)	Inf Duration (h)	CRP BSA (b)	Cmax (ng/mL)	t1/2 (h)	Tmax (h)	AUCinf (ng*h/mL)	AUClast (ng*h/mL)	CL (L/h)	CL (L/h/m <sup>2</sup> )	Vss (L)
4664/0027	B/1/TAC	75	0.28	1.50								
	B/2/AC	75	0.25	1.50								
9917/0001	B/1/TAC	85	0.20	1.70								
	B/2/AC	84	0.28	1.70								
9917/0002	A/1/AC	81	0.30	1.60								
	A/2/TAC	82	0.30	1.60								
9917/0003	B/1/TAC	93	0.27	1.80								
	B/2/AC	93	0.17	1.80								
9917/0004	A/1/AC	92	0.40	1.80								
	A/2/TAC	92	0.25	1.80								
9917/0005	B/1/TAC	77	0.27	1.50								
	B/2/AC	77	0.23	1.50								
9917/0008	B/1/TAC	85	0.25	1.70								
	B/2/AC	85	0.28	1.70								
9917/0018	A/1/AC	82	0.28	1.60								
	A/2/TAC	81	0.20	1.60								

(a) Arm A: the double combination doxorubicin + cyclophosphamide (AC) at cycle 1 and the triple combination docetaxel + doxorubicin + cyclophosphamide (TAC) at cycle 2.

Arm B: the triple combination docetaxel + doxorubicin + cyclophosphamide (TAC) at cycle 1 and the double combination doxorubicin + cyclophosphamide (AC) at cycle 2. Cycle: 1-Cycle 1, 2-Cycle 2. Trt=Treatment: AC: doxorubicin + cyclophosphamide, TAC: docetaxel + doxorubicin + cyclophosphamide.

(b) Body Surface Area in square meters as per CRFs.

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/s/

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Sophia Abraham  
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Brian Booth  
8/10/04 01:55:30 PM  
BIOPHARMACEUTICS