CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-660

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	21,660
Brand Name:	Abraxane
Generic Name:	Paclitaxel protein-bound particles for injectable suspension (albumin bound)
Indication:	[redacted]
Dosage Form:	100 mg of paclitaxel and 900 mg of human albumin
Strength:	Each milliliter (ml) of reconstituted suspension contains 5 mg paclitaxel
Route of Administration:	IV Infusion
Dosage and administration:	260 mg/m^2 over 30 minutes every 3 weeks
Applicant:	American Bioscience, Inc. Santa Monica, CA 90403
OCPB Division:	Division of Pharmaceutical Evaluation I (HFD-860)
OND Division:	Division of Oncology Drug Products (HFD-150)
Submission Date:	19-MAR-2004; 21-JUN-2004; 7-JUL-2004; 22-JUL-2004; 11-OCT-2004
Primary Reviewer:	Angela Yuxin Men, M.D., Ph.D.
Acting Team Leader:	Brian Booth, Ph.D.
Pharmacometrics Team Leader:	Jogarao Gobburu, Ph.D.

TABLE OF CONTENTS

I Executive Summary

The applicant submitted the original NDA 21-660, Abraxane, seeking marketing approval for the use of Abraxane in patients with metastatic breast cancer through the 505(b)(2) approach using Taxol® as a reference drug.

Abraxane is a Cremophor–free formulation of paclitaxel. It is developed with the objective of eliminating Cremophor-EL and alcohol from Taxol to overcome some problems associated with these solvents, such as hypersensitivity. The clinical pharmacology section contains 4 study reports (CA005-0, DM97-123, CA012-0, and CA008-0) in patients with non-hematologic malignancies/solid tumor/metastatic breast cancer. In summary, pharmacokinetic (PK) studies were conducted in 65 cancer patients aged 33 to 83 years old. Patients were dosed from 80 to 375 mg/m^2. Exposure increased linearly with doses between 80 to 375 mg/m^2. Compared to Taxol, Abraxane showed higher total clearance (43%) and larger volume of distribution (53%). The terminal half-life, about 21 hours, was identical for Abraxane and Taxol. The applicant did not study the safety and pharmacokinetics of Abraxane in hepatic impaired patients. In the Phase 3 comparison study, 260 mg/m^2 Abraxane was more efficacious than 175 mg/m^2 Taxol. Abraxane demonstrated significantly higher reconciled target lesion response rate compared to Taxol. Abraxane did not require any pre-medication for hypersensitivity and there were no severe hypersensitivity reactions observed for Abraxane. This review evaluates the submitted data and provides recommendations on the labeling.

A. Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) finds the submitted data in NDA 21-660 for Abraxane acceptable, with some revisions to the applicant's proposed label (please refer to Section III on page 24).

B. Phase IV Commitment

The applicant should evaluate Abraxane safety and pharmacokinetics in subjects with hepatic impairment, to allow the determination of dosing adjustment for this population.

C. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Abraxane (paclitaxel protein-bound particles for injectable suspension) is an albumin bound paclitaxel, which is free of Cremophor-EL solvents. The active ingredient, paclitaxel, is the same as Taxol. Pharmacokinetic parameters of total paclitaxel were determined in Phase 1, 2 and 3 studies after intravenous infusion of Abraxane over 30- and 180- minutes in cancer patients at doses of 80-375 mg/m^2. The maximal tolerated dose (MTD) of Abraxane was determined to be 300 mg/m^2, which was about 50% higher than the MTD for Taxol. Linear pharmacokinetics (PK) of Abraxane were observed

between 80 to 375 mg/m^2. The total clearance of Abraxane was 15 L/hr/m^2 and the volume of distribution was 632 L/m^2. The total clearance and volume of distribution of paclitaxel were higher when administered as Abraxane compared to Taxol. The terminal half-life of 21-hour was the same as Taxol. Urinary excretion of Abraxane accounted for <6% of paclitaxel and the renal clearance was 0.16 to 1.08 L/hr/m^2 which indicates that extra-renal elimination was extensive. Fecal excretion accounted for 22% of total dose. Paclitaxel accounted for 3% and its metabolite, 6α-hydroxypaclitaxel, 18%.

In the Phase 3 study, Abraxane 260 mg/m^2 was more efficacious than Taxol 175 mg/m^2 in the treatment of patients with breast cancer. Patients with metastatic breast cancer who received Abraxane demonstrated significantly higher Reconciled Target Lesion Response Rate (22% vs 11%, P = 0.003). Unlike Taxol, without any pre-medication, there were no severe hypersensitivity reactions observed for Abraxane. In the Phase 3 comparison of Abraxane versus Taxol, patients treated with Abraxane experienced less neutropenia despite a 49% higher dose of paclitaxel. However, compared to Taxol, sensory neuropathy was more common in patients treated with Abraxane.

_____ Date: _____

Angela Yuxin Men, Ph.D.
Reviewer
Division of Pharmaceutical Evaluation I
Office of Clinical Pharmacology and Biopharmaceutics

_____ Date: _____

Brian Booth, Ph.D.
Acting Team Leader
Division of Pharmaceutical Evaluation I
Office of Clinical Pharmacology and Biopharmaceutics

II. Question-Based Review

A. General attributes of the drug

What are the highlights of the chemistry properties of the drug substance, and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Abraxane (paclitaxel protein-bound particles for injectable suspension) is an albumin bound form of paclitaxel (Figure 1), which has anti-tumor activity. Paclitaxel is obtained as a natural product from *Taxus media* and its structure is shown in Figure 2.

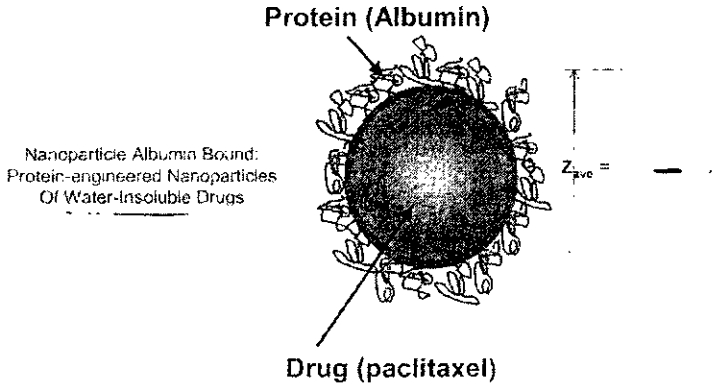


Figure 1 Structure of Abraxane (Nanoparticle Albumin-bound Paclitaxel)

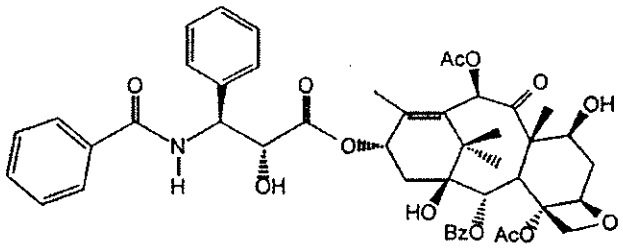


Figure 2 Chemical Structure of paclitaxel

Formulation

Abraxane is a cremophor-free formulation. Its negatively charged albumin prevents paclitaxel nanoparticle agglomeration. Abraxane is supplied as a white to yellow, sterile, lyophilized powder. Each single-use vial contains 100 mg of paclitaxel and

approximately 900 mg of human albumin. Each vial is reconstituted with 20 mL of Sodium Chloride Injection, USP, to produce a suspension containing 5 mg paclitaxel/mL.

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

Proposed Mechanisms of Action

Abraxane's antitumor activity is mediated through paclitaxel. Using proprietary nanoparticle technology, Abraxane combines the active drug paclitaxel with a natural protein called albumin into a nanoparticle 1/100th the size of a red blood cell, avoiding the need of a solvent for paclitaxel. Paclitaxel is an antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. In addition, paclitaxel induces abnormal arrays or "bundles" of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis. In animal studies, administration of Abraxane resulted in higher intra-tumor and lower normal tissue concentrations of paclitaxel than Cremophor (CrEL)-based paclitaxel.

Indication

Abraxane is indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.

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

For metastatic breast cancer patients, the recommended dose of Abraxane is 260 mg/m^2, administered intravenously over 30 minutes once every 3 weeks.

Hepatic Impairment: The appropriate dose of Abraxane for patients with bilirubin greater than 1.5 mg/dL is not known.

The incidence of severe neutropenia following Abraxane was about 9%. Patients who experience severe neutropenia (neutrophil <500 cells/mm^3 for a week or longer) or severe sensory neuropathy during Abraxane therapy should have the dosage reduced by 20% for subsequent courses of Abraxane.

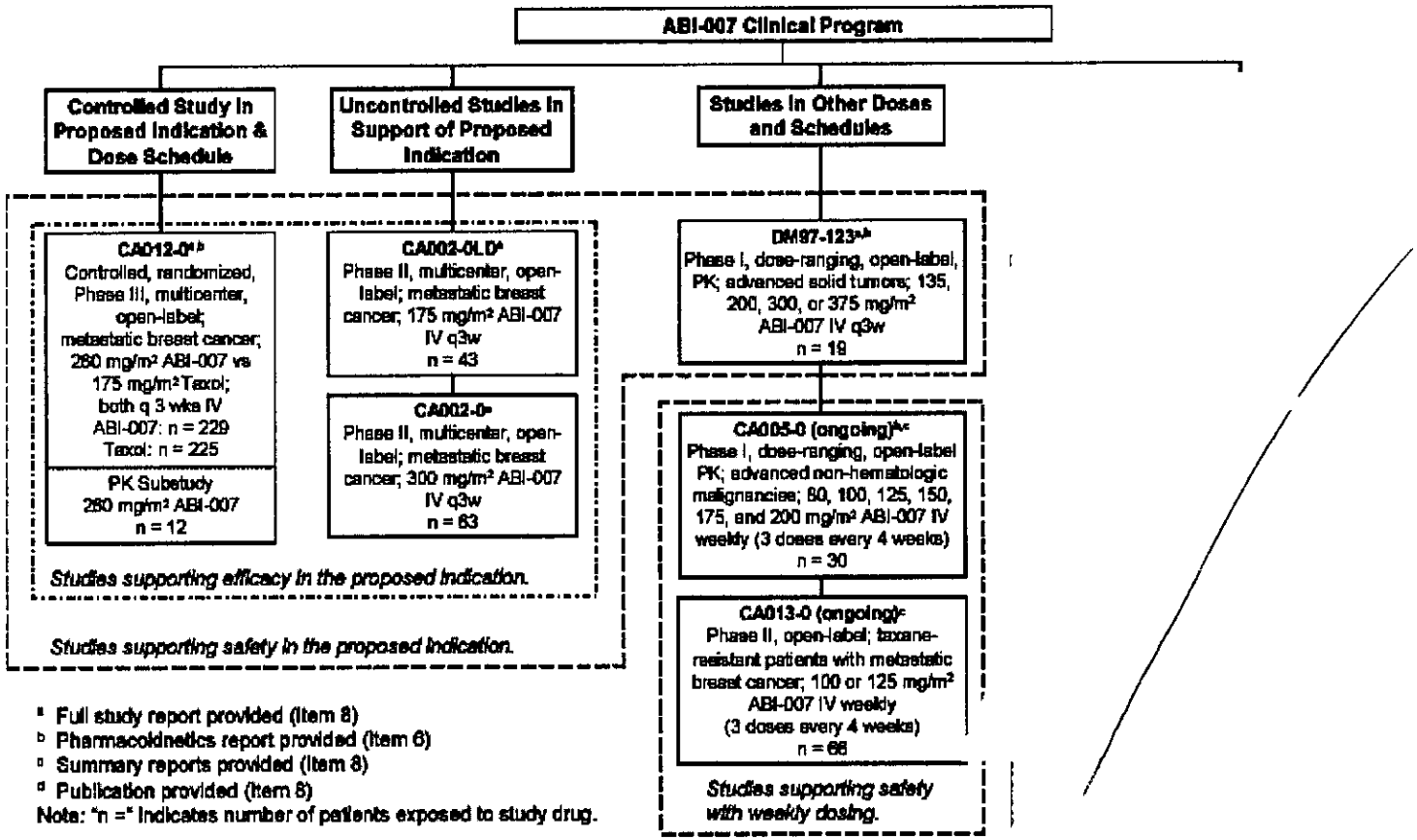
B. General Clinical Pharmacology

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

The overall schematic of Abraxane clinical studies is listed in Table 1. Per suggestion from FDA, the applicant conducted Study CA008-0 later to compare PK of Abraxane and Taxol. Each PK study design was described.

APPEARS THIS WAY
ON ORIGINAL

Table 1 Schematic of Abraxane Clinical Program



[a] Full study report provided (Item 8)
[b] Pharmacokinetics report provided (Item 6)
[c] Summary reports provided (Item 8)
[d] Publication provided (Item 8)
Note: "n =" indicates number of patients exposed to study drug.

Pivotal Study:

Study CA012-0

This was a phase 3, multi-center, open-label, controlled randomized study in patients with metastatic breast cancer. Two hundred and twenty-nine patients received 260 mg/m^2 Abraxane IV over 30 minutes and 225 patients received Taxol 175 mg/m^2 as a 3-hour infusion every three weeks. The primary objective of this clinical trial was to compare the efficacy and safety between Abraxane and Taxol.

A subgroup of twelve non-randomized patients, who received 260 mg/m^2 Abraxane, was enrolled for PK study during the first treatment cycle. Blood, urine, and feces samples were collected and analyzed by HPLC/MS for total paclitaxel and two metabolites, 6α-hydroxypaclitaxel and 3'-p-hydroxypaclitaxel. The biodisposition and elimination of total paclitaxel (Abraxane) were investigated in this study.

Supportive Studies:

1. Study CA005-0

This was a phase 1 study to evaluate the safety, tolerability, and efficacy of Abraxane administered IV over 30 minutes once weekly for three weeks, followed by a week of rest, in patients with advanced non-hematological malignancies.

The study was a single center, open-label, out-patient study, which consists of three phases: baseline, treatment, and 3-month follow up. A subgroup of twenty-three patients, who received Abraxane at doses of 80-200 mg/m^2, was selected for the PK study during the first dosing cycle. Total paclitaxel PK parameters were calculated.

2. Study DM97-123

This was an open-label, dose-escalating study to determine the safety, tolerability, and PK of Abraxane in patients with solid tumors/breast cancer. Sixteen of the nineteen enrolled patients participated in this PK study. Three patients received 135 mg/m^2 over a 3-hour infusion and the other patients received Abraxane, at dosages that ranged from 135 to 375 mg/m^2, as a 30-minute infusion once every three weeks. The maximal tolerated dose (MTD) was defined as the dosage level below the dosage resulting in > Grade 2 nonmyelosuppressive toxicity or > Grade 3 myelotoxicity in at least 2 of 6 patients. Total paclitaxel PK for a 3-hour and 30-minute infusion were investigated.

3. Study CA008-0

This was a phase 1, multi-center, open-label, controlled randomized comparative PK study comparing Abraxane (260 mg/m^2 over 30 minutes) and Taxol (175 mg/m^2 over 3 hours) in patients with advanced solid tumors.

Twenty-six patients were randomly assigned to receive either Abraxane 260 mg/m^2 over 30 minutes (n=14) or Taxol 175 mg/m^2 over 3 hours (n=12). Whole blood samples were collected to measure the PK of total paclitaxel from the first dose cycle. The PK parameters of Abraxane and Taxol were obtained.

What are the effectiveness and safety endpoints?

Effectiveness Endpoints

Two types of responses were assessed according to RECIST guidelines: target lesion and overall responses (target and nontarget lesion), in which the confirmation of a complete response (CR) and a partial response (PR) required response duration $\geq$ 4 weeks.

The primary efficacy endpoint was the percentage of patients who achieved confirmed complete or partial target lesion response. The assessment of target lesion response (TLRR) by the Cycle 6 visit was based on the Reconciled Response Assessment Dataset (*rec*TLRR).

Secondary efficacy endpoints for this study included the following:

- percentage of patients who achieved complete or partial overall response;
- time to disease progression (TTP);
- patient survival;
- percentage of patients who achieved each target lesion response of complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD);
- percentage of patients who achieved each overall response of CR, PR, SD, or PD;
- time to first complete or partial target lesion response;
- time to first complete or partial overall response;
- duration of complete or partial target lesion response;
- duration of complete or partial overall response;
- number of cycles of therapy to maximum target lesion response;
- number of cycles of therapy to maximum overall response;
- duration of CR, PR, or SD for target lesion response;
- duration of CR, PR, or SD for overall response; and
- QOL evaluated by changes from baseline in scores on the Eastern Cooperative Oncology Group (ECOG) (Zubrod) performance status scale, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30, and weight.

In the labeling, *rec*TLRR is reported.

Safety Endpoints

The safety/tolerability endpoints for this study included the following:

- adverse events (AEs), serious adverse events (SAEs), and toxicities;
- hematology and clinical chemistry;
- maximal degree of myelosuppression (nadir white blood cell [WBC] count and absolute neutrophil count [ANC]);
- patients with Grade 4 neutropenia (defined as ANC $< 0.5 \times 10^9$/L);
- time to recovery from Grade 4 neutropenia (defined as ANC $\geq 1.5 \times 10^9$/L), with and without growth factor treatment;
- patient and physician assessments of peripheral neuropathy;
- vital signs (during dosing and follow-up);
- electrocardiogram (ECG).

Are the active moieties in the plasma appropriately identified and measured to assess pharmacokinetic parameters?

The plasma concentration of active moiety, free paclitaxel, was not measured. The concentrations of total paclitaxel of Abraxane and Taxol were measured in plasma/whole blood by LC/MS. The review of the assay can be found in Item II Section F.

What are the characteristics of the exposure-response relationships of Abraxane?

There is no relationship between the paclitaxel exposure and clinical responses available because the PK and effectiveness results were not obtained from the same clinical study.

Does this drug prolong the QT or QTc interval?

The effect of Abraxane on QT/QTc interval prolongation was not addressed in the submission. It is reported that mean heart rate, QT, corrected QT (QTc) did not change after infusion of 175-200 mg/m^2 paclitaxel over one hour with recommended antihistamine premedication in cancer patients.[1]

What are the pharmacokinetics (PK) characteristics of Abraxane and its major metabolite?

Pivotal Study:

Study CA012-0

The plasma concentrations of total paclitaxel and its two metabolites, 6α-hydroxypaclitaxel and 3'-p-hydroxypaclitaxel, were measured in this study. Their concentration vs. time profiles are demonstrated in Figure 3. The PK parameters of paclitaxel are listed in Table 2.

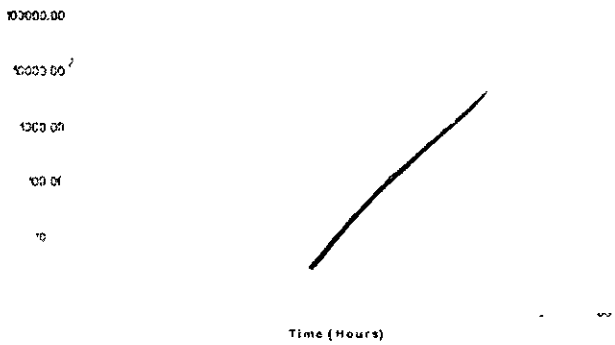


Figure 3 Paclitaxel, 6α-hydroxypaclitaxel and 3'-p-hydroxypaclitaxel Blood Concentration- Time Profiles (mean)

Table 2 Paclitaxel PK Parameters in Study CA012-0

Parameter	Mean	%CV	Range
C_{max} (ng/ml)	18741	27	
T_{max} (hr)	0.46	21	
AUC$_\infty$ (hr*ng/ml)	17940	23	
CL (L/hr/m^2)	15.2	24	
$T_{1/2}$ (hr)	27.4	33	
λ_z (hr^{-1})	0.027	21	
V_z (L/m^2)	632	63	
CL_0 (L/hr/m^2)	0.62	51	

Paclitaxel displayed a multi-phasic disposition with total CL of 15L/h/m^2, $t_{1/2}$ of 27 hours and V_z of 632 L/m^2. Urinary elimination of paclitaxel only accounts for 4% of the CL_{tot}.

The metabolite profiles follow a similar pattern to the parent drug except that the metabolite concentrations are substantially lower. The T_{max} was delayed relative to that for parent drug due to the formation of metabolites.

Total paclitaxel (Abraxane) had greater exposure than 6α-hydroxypaclitaxel (22-fold) and 3'-p-hydroxypaclitaxel (59-fold). Urinary excretion of Abraxane only accounted for <6% of paclitaxel and the renal clearance was 0.16 to 1.08 L/hr/m^2 which indicates that extra-renal elimination was extensive. Fecal excretion accounted for 22% of total dose. Paclitaxel accounted for 3% and its metabolite, 6α-hydroxypaclitaxel 18%.

Study CA005-0

In this study, only the plasma concentration of total paclitaxel was measured. The mean paclitaxel concentration obtained from all patients vs. time profile is shown in Figure 4. The PK parameters of paclitaxel are shown in Table 3. Patient #7, who received 100 mg/m^2 Abraxane over 30-minute, appears to be an outlier, which showed much higher concentrations at all time points. The disposition of paclitaxel showed a multi-phasic concentration-time profile. The PK of paclitaxel (Patient #7 excluded) over the dose range of 80-200 mg/m^2 appears linear when administered as a 30-minute infusion (Figure 5).

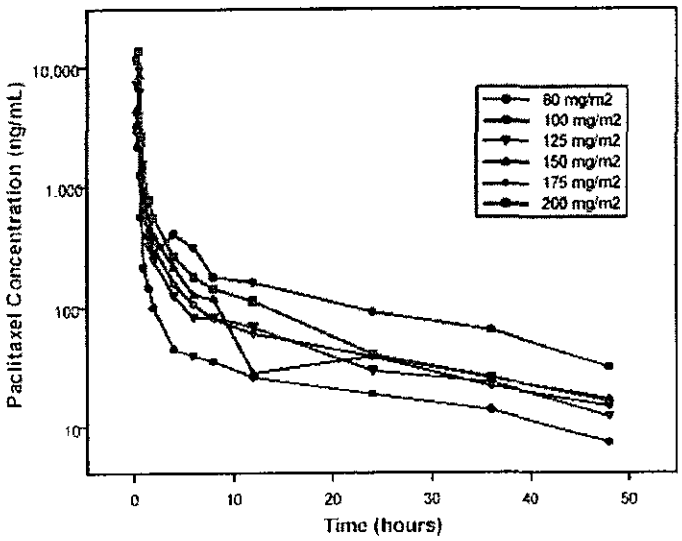


Figure 4 Total Paclitaxel (Abraxane) Concentration -Time Profiles for Patients Receiving 80 mg/m^2 through 200 mg/m^2 in Study CA005-0

Table 3 Summary of Total Paclitaxel (Abraxane) PK Parameters (Mean, SD) in Study CA005-0

Dose (mg/m^2)	T_{max} (hr)	C_{max} (ng/ml)	AUC_∞ (ng hr/ml)	$T_{1/2}$ (hr)	Cl (L/hr/m^2)	V_s (L/m^2)	Cl (L/hr/kg)	V_z (L/kg)
80	0.25	3017	2653	17.63	30.6	772	0.81	20.2
N=3	(0.025)	(487)	(394)	(5.35)	(4.8)	(217)	(0.20)	(5.7)
100	0.39	5197	8320	17.74	22.4	581	0.54	13.9
N=7	(0.135)	(2572)	(10703)	(3.08)	(11.4)	(297)	(0.30)	(7.2)
125	0.35	7916	6102	16.77	22.0	549	0.52	12.9
N=5	(0.132)	(3426)	(1809)	(5.41)	(6.3)	(259)	(0.15)	(6.0)
150	0.52	8433	7107	14.83	27.4	617	0.79	17.8
N=3	(0.091)	(4816)	(4231)	(2.74)	(16.9)	(432)	(0.48)	(12.3)
175	0.51	9827	6869	18.47	27.4	750	0.65	17.8
N=3	(0.010)	(6232)	(2053)	(1.94)	(9.9)	(356)	(0.24)	(8.6)
200	0.50	13400	11363	18.62	17.9	483	0.42	11.4
N=2	(0.000)	(990)	(4867)	(1.73)	(2.9)	(123)	(0.07)	(2.8)

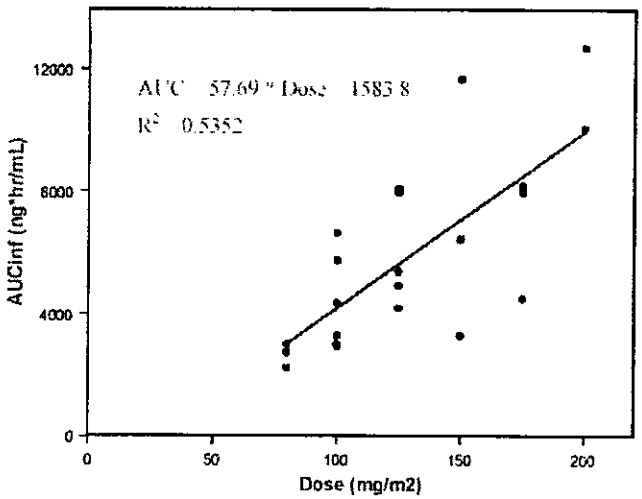


Figure 5 Linear Regression Plot of AUC_∞ versus Dose in Study CA005-0 (Patient #7 excluded)

Study DM97-123

The plasma concentration of total paclitaxel was measured in this study. The paclitaxel concentration vs. time profile is shown in Figure 6. The PK parameters of paclitaxel are listed in Table 4.

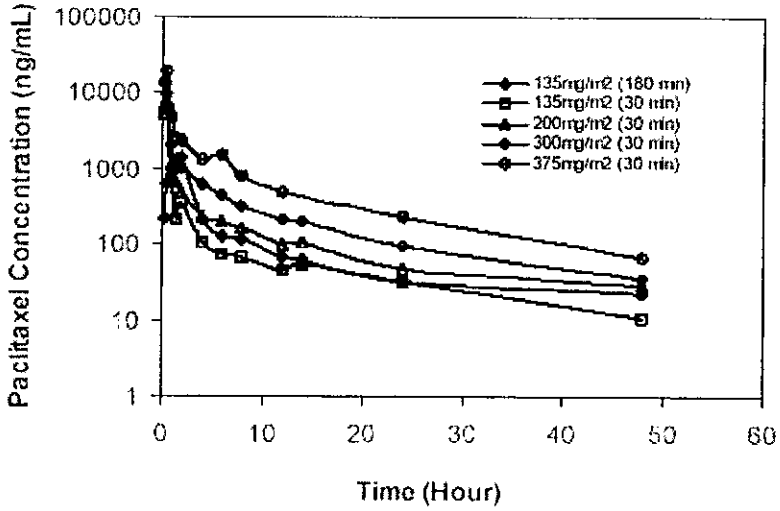


Figure 6 Mean Total Paclitaxel (Abraxane) Plasma/Whole Blood Concentration-Time Profiles in Study DM97-123

Note: The Pharmacokinetic parameters for the 135 mg/m^2 dose were generated from plasma samples (n = 3 for 180 minute infusion; n = 1 for 30 minute infusion); for the 200 mg/m^2 dose were generated from plasma (n = 1) and whole blood (n = 2); and for the 300 (n = 5) and 375 mg/m^2 dose (n = 4) were generated from whole blood samples.

Table 4 Summary of Paclitaxel (Abraxane) PK Parameters (mean, %CV) in Study DM97-123

Dose (mg/m^2)	Infusion Duration (min)	N	C_{max} (ng/mL)	AUC_∞ (ng.h/mL)	$t_{1/2}$ (hr)	CL ($L/h/m^2$)	V_z (L/m^2)
135*	180	3	1392 (30)	5427 (35)	15.7 (27)	27.2 (34)	598 (33)
135*	30	1	6100	5844	14.5	23.2	485
200#	25 - 30	3	7757 (35)	8998 (20)	13.2 (63)	22.9 (21)	407 (58)
300+	27 - 30	5	13520 (7)	16736 (22)	14.4 (15)	18.7 (24)	387 (26)
375+	30 - 45	4	19350 (15)	32525 (36)	11.7 (29)	12.9 (41)	235 (64)

*PK parameters were generated from plasma samples; #PK parameters were generated from plasma(n=1) and whole blood (n=2); +PK parameters were generated from whole blood samples.

The biphasic disposition of Abraxane was similar for both a 3-hr and 30-min infusion. There was a linear PK between 135 and 375 mg/m^2 (Figure 7). CL and V_z decrease slightly with increasing dose, and the resulting half-life remains constant across different dose levels. At the dose of 375 mg/m^2, CL and V_z decrease significantly, which makes Abraxane half-life much shorter than the values at other dose levels.

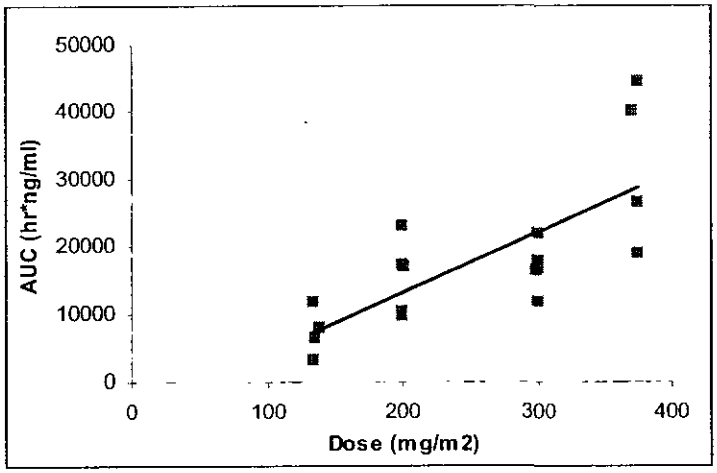


Figure 7 Total Paclitaxel AUC_∞ across Different groups

In summary, there is a linear PK of Abraxane between 80-375 mg/m^2 (Figure 8) after pooling data from all four clinical studies.

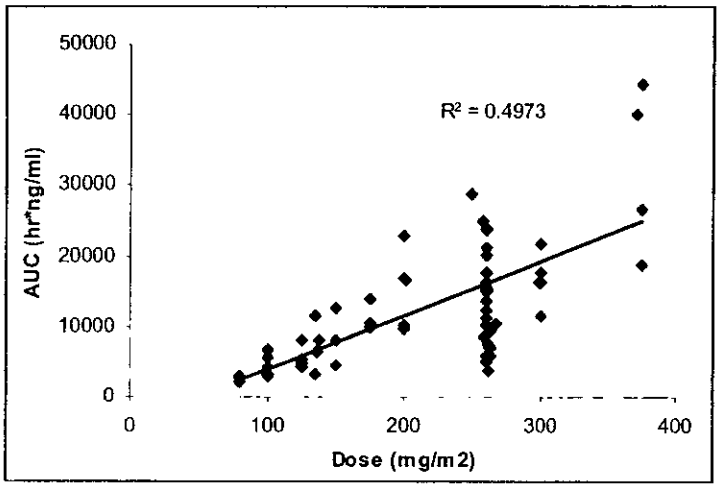


Figure 8 Total Paclitaxel AUC_{∞} vs. Dose (Data from four clinical studies)

Study C008-0

In this study, the patients in the two treatment arms (Abraxane or Taxol) had no statistically significant differences with respect to age, weight, BSA or height.

The plot of the mean total paclitaxel concentration vs. time is presented in Figure 9. A summary of the estimated PK parameters for paclitaxel administered as both Abraxane and Taxol is listed in Table 5.

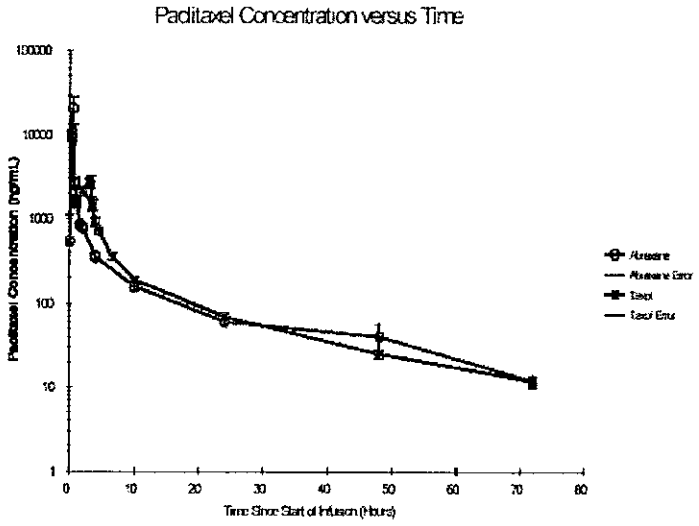


Figure 9 Plot of Mean Total Paclitaxel Concentration versus Time with Standard Error Bars for both Abraxane and Taxol

Table 5 Summary of Paclitaxel PK Parameters for Abraxane and Taxol

Parameter	ABI-007			Taxol			
	Mean	%CV	Range	Mean	%CV	Range	p-value
CL (L/hr/m^2)	21.13	43.8	8.72 - 43.41	14.76	31.8		0.018
Vdss (L/m^2)	230.7	51.3	53.2 - 492.9	156.3	13.2		0.211
Vz (L/m^2)	663.8	48.1	296.3 - 1317.3	433.4	31.1		0.040
AUC inf (ng-hr/mL)	11788.6	45.3	5981.7 - 28680.2	12602.7	21.0		0.524
AUC inf dose corrected (ng-hr/mL)	56.81	46.3	23.01 - 111.7	71.90	21.1		0.049
Cmax (ng/mL)	22968.6	112.5	1060 - 86700	3513.3	57.2		< 0.001
Cmax/dose corrected (ng/mL)	88.69	111.2	15.61 - 346.8	20.11	55.8		< 0.001
Tmax (hr)	0.36	15.2	0 - 0.5	2.65	27.6		< 0.001
λz (hr^{-1})	0.033	16.9	0.023 - 0.042	0.031	13.0		0.177
T1/2 (hr)	21.6	17.2	16.5 - 29.6	20.5	11.6		0.479
AUC %extrap (%)	2.8	11.3	1.0 - 5.0	2.8	52.6		0.983

The paclitaxel AUC_{inf} for Abraxane 260 mg/m^2 and Taxol 175 mg/m^2 are not significantly different. The terminal elimination rate constants (λ_z) are nearly identical. Compared to Taxol, Abraxane showed higher total clearance (43%) and larger volume of distribution (53%).

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

The PK of Abraxane has not been studied in healthy adults, therefore comparison between the PK in healthy volunteers and patients is not known.

C. Intrinsic Factors

What intrinsic factors influence exposure (PK usually) and/or response and what is the impact of any differences in exposure on efficacy or safety responses?

C1. Influence on Drug Exposure

The applicant reported that age had no effect on paclitaxel PK parameters.

In Study DM97-123, five out of sixteen patients were aged 65 years or older. None of these patients had abnormal hepatic or renal function. The PK parameters of the elderly patient populations are listed in Table 6.

Table 6 PK Parameters of Abraxane in Elderly Patient Populations in Study DM97-123

Patient Type	Patient Number & Dose		Pharmacokinetic Parameters				
			C_{max} (ng/ml)	AUC (hr*ng/ml)	CL (L/hr/m^2)	$t_{1/2}$ (hr)	V_z (L/ m^2)
65 years and older	3*	135/3					
	5	200					
	6	200					
	8	300					
	11	300					

- Patient #3: 3-hour infusion

The PK parameters from the elderly patients were similar to those of young patients.

C2. Influence on Age and Race on Efficacy Responses

Of the 233 patients in a Phase 3 pivotal study (Study CA012-0) using the recommended dose and schedule of Abraxane, 14% were older than 65 years. Efficacy appeared similar in elderly and younger patients (Table 7). No toxicities occurred notably more frequently among elderly patients who received Abraxane. No overall differences in safety or effectiveness were observed between these patients and younger patients.

Most of the patients (96.6%) were Caucasian. Data was too sparse for a meaningful exploratory subgroup analysis by race.

Table 7 Subgroup Analysis by Age: Exploratory Results of FDA-Confirmed *rec*TLRR (All Randomized Patients)

Category	Abraxane [N = 233]
Age < 65:	
No. of Patients	201
No. of FDA-Confirmed Responders	41
Response Rate (95% Binomial Confidence Interval)	20.4% (14.83% – 25.97%)
Age ≥ 65:	
No. of Patients	32
No. of FDA-Confirmed Responders	9
Response Rate (95% Binomial Confidence Interval)	28.1% (15.55% – 43.70%)

D. Extrinsic Factors

Were any formal drug interaction studies performed and are they necessary?

Because of the same active entity (paclitaxel) of Abraxane (260 mg/m^2) and Taxol (260 mg/m^2), the information obtained from Taxol drug-drug interaction can be applied to Abraxane. No formal CYP-based drug-drug interaction studies are necessary.

In vitro studies with human liver microsomes and tissue slices showed that paclitaxel was metabolized primarily to 6α-hydroxypaclitaxel by the cytochrome P450 (CYP) isozyme CYP2C8; and to two minor metabolites, 3'-p-hydroxypaclitaxel and 6α, 3'-p-dihydroxypaclitaxel, by CYP3A4. The PK of paclitaxel may be altered *in-vivo* as a result of interactions with compounds that are substrates. In Study DM97-123, two out of sixteen patients had Quinine and Ritalin, which are metabolized by the CYP enzymes involving paclitaxel metabolism. The PK parameters of these special populations are listed in Table 8.

Co-administration of Quinine and Ritalin did not change the PK of paclitaxel. However, the result was obtained from only 1 patient each.

Table 8 PK Parameters of Patients with co-administration of Quinine and Ritalin in Study DM97-123

Patient Type	Patient Number & Dose		Pharmacokinetic Parameters				
			C_{max} (ng/ml)	AUC (hr*ng/ml)	CL (L/hr/m^2)	$t_{1/2}$ (hr)	V_z (L/ m^2)
Concomitant medications	6 *Quinine*	200					
	9 Ritalin	300					

E. General Biopharmaceutics

Were the different Abraxane batches/formulations used in the Clinical Studies?

Yes. In the Abraxane PK studies, the different Abraxane clinical investigational formulations were used (Table 9). Product codes used in the PK clinical trials are listed in Table 10. Abraxane with product code 103450, which was used in the comparative PK study (CA008-0), is the formulation that will be marketed.

There are no formal bioequivalence studies conducted to compare these formulations. In order to compare them, PK data were pooled from clinical studies CA005-0, CA012-0 and CA008-0. The mean dose-corrected AUC_∞ for these formulations versus product codes is shown in Figure 10. There is no apparent difference among these formulations.

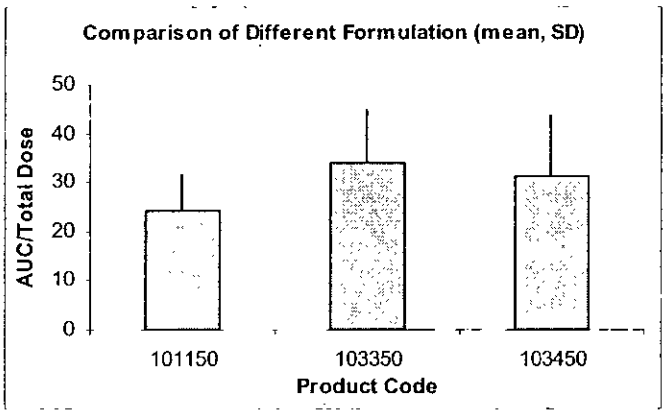


Figure 10 Dose Corrected AUC_∞ vs. Product Codes

Table 9 Comparison of Abraxane Clinical Investigational Formulations [a]

Component	Product Code		
	101150	103350	103450
Paclitaxel (mg/50 mL Vial)	30	100	100
Human Albumin (mg/50 mL Vial)	[redacted]		
Concentration of Reconstituted Suspension (mg Paclitaxel mL)	2	5	5
pH of Reconstituted Suspension	[redacted]		

a. The formulation of individual batches of development lots (in terms of paclitaxel and human albumin content) which were not assigned formal product code numbers is provided in the test results, in Table 8 for each lot of ABI-007.

b. The concentration of human albumin was not adjusted prior to [redacted] formulation, therefore the concentration may vary within the stated range.

c. Theoretical content is based on the concentration of human albumin in the final formulated suspension prior to [redacted] n [redacted] 0). The actual value in the finished product is approximately 900 mg vial

Table 10 Product Code Used in Clinical Trials

Product Code		
101150	103350	103450
Study Protocol Number		
DM97-123 CA005-0	DM97-123 CA005-0 CA012-0	CA005-0 CA008-0

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

There is no such information available for Abraxane in the submission. The applicant only reported that when the concentration of paclitaxel was within the solubility range (paclitaxel concentration of 20μg/mL), the release was immediate (Figure 11). The release of paclitaxel from Abraxane was influenced by the solubility of paclitaxel and was not altered by storage conditions for up to —

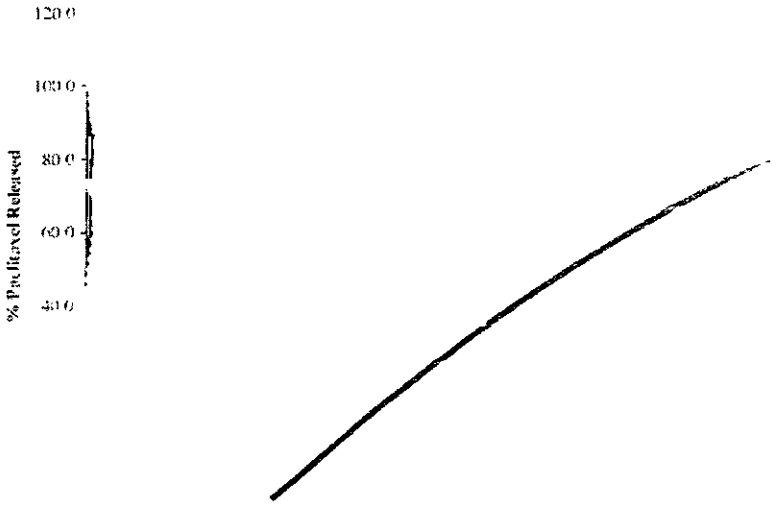


Figure 11 Percent of Paclitaxel Released in Phosphate Buffered Saline (pH 7.4), Abraxane (Lot # 0102073B) at Various Storage Conditions for 9 Months

F. Analytical Section

F1. How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

For initial studies of Abraxane, plasma samples were assayed using a validated, sensitive, specific, high performance liquid chromatographic mass spectrometry (HPLC-MS) method. Subsequently, — — method was developed for assay of Abraxane for the PK studies.

F2. Which metabolites have been selected for analysis and why?

The concentrations of total paclitaxel and its two metabolites, 6α-hydroxypaclitaxel (primary metabolite) and 3'-p-hydroxypaclitaxel, were measured in whole blood, plasma, urine and feces to assess the elimination pathway of Abraxane.

F3. For all moieties measured, is free, bound or total measured? What is the basis for that decision, if any, and is it appropriate?

For all moieties, the total form is measured.

F4. What is the bioanalytical method that is used to assess concentrations of Abraxane?

Paclitaxel is the active ingredient of Abraxane and Taxol. Several Liquid Chromatography Mass Spectrometric methods, with Deuterated d_5- paclitaxel as internal standard (IS), were developed by The concentrations of total paclitaxel and its two metabolites, 6α-hydroxypaclitaxel and 3'-p-hydroxypaclitaxel were measured in whole blood, plasma, urine and feces. The different assays are listed in Table 11. These assays were validated with the intra-day and inter-day accuracy and precision within ±15% and are acceptable.

Table 11 Analytical Methods used in Abraxane PK Studies

Study #	Sample	Assay	LOQ (ng/ml)	Linear Range (ng/ml)	Measure
CA005-0	0.2 mL plasma	HPLC-			Paclitaxel
DM97-123	whole blood				Paclitaxel
	plasma				
CA012-0	whole blood				paclitaxel and two metabolites, 6α-hydroxypaclitaxel and 3'-p-hydroxypaclitaxel
	urine				
	feces				
CA008-0	Whole blood				Paclitaxel

Reference

1. Irfan Barutcu, Alpay Turan Sezgin, Hakan Gullu, Ergun Topal, Nurzen Sezgin, Ramazan Ozdemir Effect of Paclitaxel Administration on Electrocardiographic Parameters Reflecting Ventricular Heterogenity. The Medical Journal of Kocatepe 2003;1: 42-46

35 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

Appendices B: Individual Study Review

1. Study CA005-0

A Phase I Trial of ABI-007 Administered Weekly for Three Doses Every 4 Weeks In Patients with Advanced Non-Hematologic malignancies

Study: Phase I, single-center, open-label, out-patient study

Objectives: To evaluate the safety, tolerability, efficacy and PK of ABI-007

Subjects: patients with advanced non-hematologic malignancies

Dosing Regimen: IV over 30 minutes weekly for three doses every 4 weeks

Patients (n)	Dose (mg/m^2)
3	80
7	100
5	125
3	150
3	175
2	200

PK: During the first dosing cycle, blood samples were collected at pre-dose, 15, 30, 45, 60 min and 1.5, 2, 4, 6, 8, 12, 24, 36, 48 hr. Samples, plasma concentrations of paclitaxel, were measured by [redacted]. The data were used for plasma paclitaxel concentration NCA analysis – multi-phasic disposition.

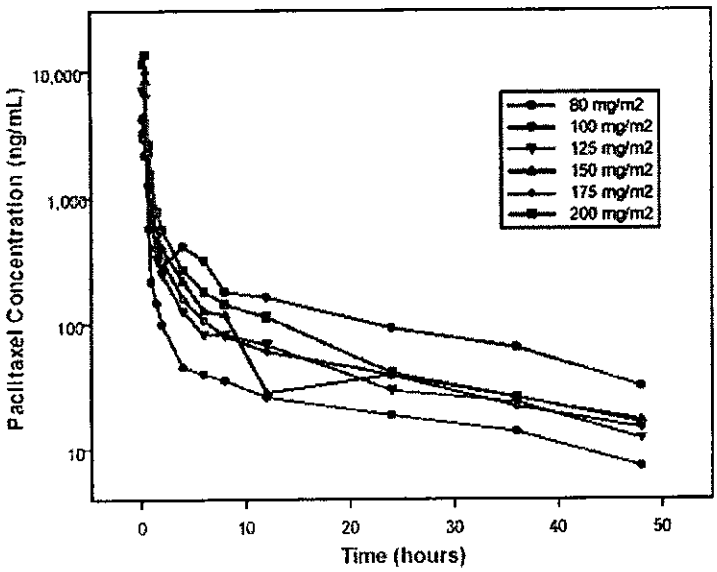


Figure 1.1. Mean paclitaxel Plasma Concentration – Time Profiles (All Patients)

? Why Pt #7 has high and Pt#12 has low concentrations at all time points?

Table 1.1 Paclitaxel PK Summary (mean, SD)

Dose (mg/m^2)	T_{max} (hr)	C_{max} (ng/ml)	AUC_∞ (nghr/ml)	$T_{1/2}$ (hr)	Cl ($L/hr/m^2$)	V_s (L/m^2)	Cl (L/hr/kg)	V_z (L/kg)
80 N=3	0.25 (0.025)	3017 (487)	2653 (394)	17.63 (5.35)	30.6 (4.8)	772 (217)	0.81 (0.20)	20.2 (5.7)
100 N=7	0.39 (0.135)	5197 (2572)	8320 (10701)	17.74 (3.08)	22.4 (11.4)	581 (297)	0.54 (0.30)	13.9 (7.2)
125 N=5	0.35 (0.132)	7916 (3426)	6102 (1809)	16.77 (5.41)	22.0 (6.3)	549 (259)	0.52 (0.15)	12.9 (6.0)
150 N=3	0.52 (0.091)	8433 (4816)	7107 (4231)	14.83 (2.74)	27.4 (16.9)	617 (432)	0.79 (0.48)	17.8 (12.3)
175 N=3	0.51 (0.010)	9827 (6232)	6869 (2053)	18.47 (1.94)	27.4 (9.9)	750 (356)	0.65 (0.24)	17.8 (8.6)
200 N=2	0.50 (0.000)	13400 (990)	11363 (1867)	18.62 (1.73)	17.9 (2.9)	483 (123)	0.42 (0.07)	11.4 (2.8)

The volume of distribution exceeds the body fluid, indicating that ABI-007 is extensively distributed and bound to tissue and extravascular proteins.

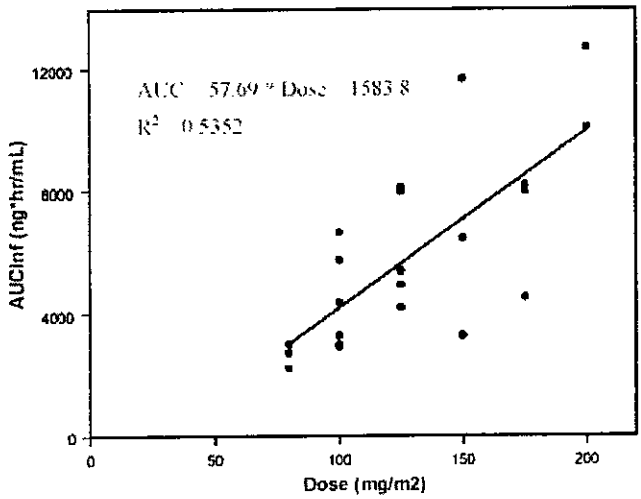


Figure 1.2. Linear Regression Plot of AUC_{oo} vs. Dose (Patient #7 excluded)

Linear PK of ABI-007 for paclitaxel over the range 80-150 mg/m^2.

Bilirubin level increased from 1.1 to 2.8 after ABI-007 dosing. The finding indicated that there was rapid progression of malignant disease in the liver and hepatic dysfunction in patients.

*

2. **Study DM97-123**

Phase I/II Study of Capxol™ (ABI-007): A Cremophor™ Free Formulation of Paclitaxel in Patients with Solid Tumors/Breast Cancer Study

Study: Phase I/II, single-center, open-label, dose-ranging study

Subjects: Nineteen patients with advanced solid tumors/breast cancer

Objectives: To determine the safety, tolerability and PK of ABI-007.

Dosing Regimen: 135-375 mg/m^2 IV inf 30 min to 3 hr

Table 2.1 Doses and Infusion Durations

Dose (mg/m^2)	Patient Numbers	Infusion Duration (min)
135	01	180
135	02	175
135	03	180
135	04	30
200	05	30
200	06	25
200	07	27
300	08	30
300	09	27
300	11	30
300	12	30
300	13	30
375	15	30
375	16	40
375	17	45
375	19	30

PK: 16 out of 19 patients participate this PK substudy.

Plasma samples collected from the first five patients and whole blood samples from the remaining 11 patients. The samples (5 mL) were collected at predose and at 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 14, 24 and 48 hours.

The MTD was defined as the study drug dose below the dose that elicited grade 3 or 4 toxic effects for $\geq$ 2 patients.

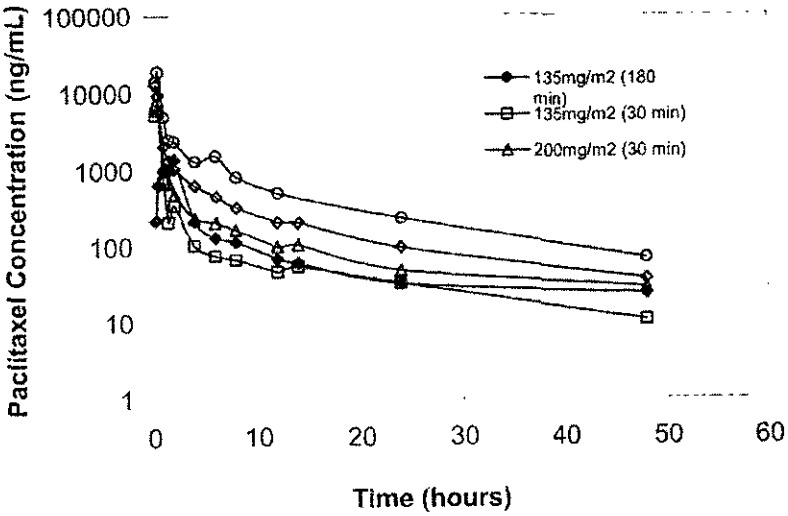


Figure 2.1 Mean Paclitaxel Plasma/Whole Blood Concentration –Time Profiles

Biphasic disposition profiles were similar for both a 3-hr and 30-min infusion. Dose normalized AUC were similar up to 300 mg/m^2 indicating linear PK between 135 and 300 mg/m^2. CL and V_z decrease slightly with increasing dose, and the resulting half-life remains constant across different dose levels.

Table 1.2 Summary of NCA PK Parameters (mean, %CV)

Dose (mg/m^2)	Infusion Duration (min)	N	C_{max} (ng/mL)	AUC_∞ (ng.h/mL)	$t_{1/2}$ (hr)	CL (L/h/m^2)	V_z (L/m^2)
135*	180	3	1392 (30)	5427 (35)	15.7 (27)	27.2 (34)	598 (33)
135*	30	1	6100	5844	14.5	23.2	485
200#	25 - 30	3	7757 (35)	8998 (20)	13.2 (63)	22.9 (21)	407 (58)
300+	27 - 30	5	13520 (7)	16736 (22)	14.4 (15)	18.7 (24)	387 (26)
375+	30 - 45	4	19350 (15)	32525 (36)	11.7 (29)	12.9 (41)	235 (64)

*PK parameters were generated from plasma samples; #PK parameters were generated from plasma(n 1) and whole blood (n-2); +PK parameters were generated from whole blood samples.

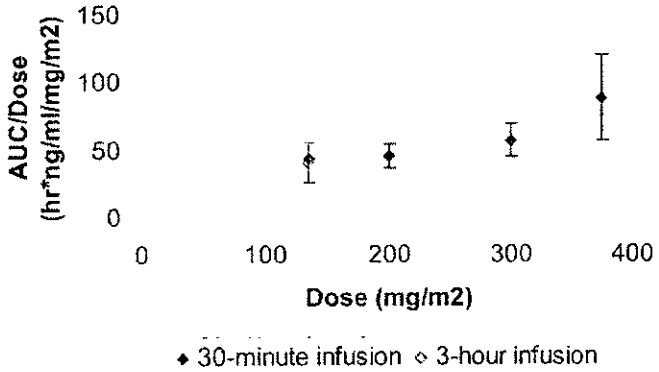


Figure 2.2 Paclitaxel Dose-normalized AUCoo across Different Groups (mean, SD)

Table 2.3 PK Parameters of Special Patient Populations

Patient Type	Patient Number & Dose		Pharmacokinetic Parameters				
			C_{max} (ng/ml)	AUC (hr*ng/ml)	CL (L/hr/m^2)	$t_{1/2}$ (hr)	V_z (L/ m^2)
65 years and older	3*	135/3					
	5	200					
	6	200					
	8	300					
	11	300					
Concomitant medications	6 *Quinine*	200					
	9 Ritalin	300					

*Patient #3: 3-hour infusion.

PK parameters from the elder patients were similar to those of young patients.

Co-administration of Quinine and Ritalin did not change the PK of paclitaxel. (but result was from only 1 pt)

*

Synopsis DM97-123

Sponsor Company Name: American BioScience, Inc. **Name of Finished Product:** ABI-007 **Name of Active Ingredient:** Paclitaxel	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(For National Authority Use Only)
Title of the Study: Phase I/II Study of CAPXOL (ABI-007) A Cremophor-Free Formulation of Paclitaxel in Patients with Solid Tumors/Breast Cancer		
Investigator and Study Center: Nuhad K Ibrahim, MD. Department of Melanoma/Sarcoma and Breast Medical Oncology, Division of Medicine, University of Texas, MD Anderson Cancer Center, Houston, Texas, USA		
Publication (reference): Ibrahim NK, Desai N, Legha S, et al. Phase I and pharmacokinetic study of ABI-007, a Cremophor-free, protein-stabilized, nanoparticle formulation of paclitaxel. *Clin Can Res* 2002;8:1038-1044.		
Study Dates: From 13 July 1998 (first patient assessment) To 16 March 2000 (last patient assessment)		**Phase of Development:** Phase I/II
Objectives: The objectives of this study were to determine the maximum tolerated dose (MTD) of ABI-007; evaluate the pharmacokinetic (PK) profile of ABI-007, and evaluate the antitumor activity of ABI-007 in patients with advanced solid tumors/breast cancer.		
Methodology: This was a Phase I, single-center, open-label, dose ranging, PK study. Four patients were initially recruited into the Phase II portion of this study; however, the protocol was amended, renumbered, and continued as a separate study (Protocol CA002-0). All Phase II patient's results are reported in a separate report, ie, Protocol CA002-0 Clinical Study Report. Patients in the PK study were hospitalized for 23 to 26 hours, and all other patients were dosed as outpatients. The dose range was 135 to 375 mg/m^2 given intravenously (IV) every 3 weeks with the first infusions for the first 3 enrolled patients given over 180 minutes and subsequent infusions for these patients and subsequently enrolled patients given over 30 minutes. No steroid or histamine blocker premedication was given prior to dosing. Dose escalation used the rule of 3 + 3 at a rate of 25% to 50% with increases by 50% if patients experienced < Grade 1 toxicity. Plasma samples were collected from 5 patients (all 4 patients assigned to 135 mg/m^2 and the first patient assigned to 200 g/m^2) and whole blood samples were collected from 11 patients receiving 200 to 375 mg/m^2 for PK analyses. Samples (5 mL each) were collected predose, at 15, 30, and 60 minutes, and at 1.5, 2, 4, 6, 8, 12, 18, 24, and 48 hours after the start of infusion. The limit of quantitation (LOQ) for paclitaxel was 5 ng/mL, with a linear range of — — for plasma and 5 to 1000ng/mL for whole blood.		

Methodology (continued): Tumor size was evaluated in 6 patients at baseline and posthaseline by computed tomography (CT) scan of the abdomen, magnetic resonance imaging (MRI), bone scan, and/or if indicated, a bone survey focused on symptomatic sites of bone metastases. Tumor response was evaluated per World Health Organization (WHO) guidelines. Toxicity grade was assessed using the National Cancer Institute (NCI) Common Toxicity Criteria (CTC). Vital signs were closely monitored during study drug dosing for signs of hypersensitivity.
Number of Patients (planned and analyzed): Planned Enrollment: approximately 20 patients. Enrolled: 19 patients; Intent-to-Treat (ITT) Population: 19 patients; Participants in the PK study: 16 patients.
Diagnosis and Criteria for Inclusion: Male and female patients were eligible if they had a biopsy proven diagnosis of advanced cancer, had failed standard therapy; had a Zubrod performance status of 0 to 3; had an expected survival of at least 6 weeks; and had hemoglobin > 9 g/dL, white blood cell (WBC) count ≥ 3000 cells/mm^3 (3.0 x 10^9/L), absolute neutrophil count (ANC) > 1500 cells/mm^3 (1.5 x 10^9/L), platelet count ≥ 100,000 cells/mm^3 (100 x 10^9/L), serum creatinine ≤ 2 mg/dL, and serum bilirubin ≤ 1.5 mg/dL.
Test Product, Dose and Mode of Administration, Lot Numbers: ABI-007 was administered at 135 to 375 mg/m^2 as a continuous IV infusion. It was supplied as a 30 mg/50 mL vial (Lot Numbers: C018-001, C018-002, C019-001, C019-002, C199-004).
Duration of Treatment: Patients received cycles of ABI-007 infused IV over 180 minutes for the first dose for the first 3 patients enrolled and over 30 minutes for subsequent infusions for these patients and for all infusions in subsequently enrolled patients. Cycles were to be repeated every 3 weeks. Individual patients received from 1 to 13 cycles with intervals between dosing cycles ranging from 19 to 69 days.
Criteria for Evaluation: The MTD was the dose level below the dose resulting in ≥ Grade 2 nonmyelosuppressive toxicity or ≥ Grade 3 myelotoxicity in at least 2 of 6 patients. *A minimum of 6 patients were to be treated at the MTD.* Safety variables included continuous adverse event (AE) monitoring, clinical laboratory values, vital sign measurements during study drug dosing, and physical examination findings. Dose-limiting toxicities were defined as ≥ Grade 2 nonmyelosuppressive toxicity or ≥ Grade 3 myelotoxicity. PK parameters included maximum observed plasma/blood concentration (C_{max}), time to reach C_{max} (t_{max}), terminal plasma/blood elimination rate constant (λ_z), apparent terminal elimination half-life ($t_{1/2}$), area under the plasma/blood concentration-time curve (AUC_∞), plasma/ blood clearance (CL), and volume of distribution (V_z). Exploratory assessments of response included bidimensional tumor measurements and evaluation of tumor response per criteria in the WHO guidelines.
Statistical Methods: Toxicities/AEs were coded to the closest lower level Medical Dictionary for Drug Regulatory Affairs (MedDRA) term and then mapped to an NCI CTC term. Toxicities/AEs were summarized by relationship to treatment, toxicity grade, and dose prior to onset. Clinical laboratory parameters and vital signs were summarized as changes and shifts from baseline to final on-treatment assignment, and by clinically significant abnormalities. Vital signs during study drug dosing were summarized by dose as changes from pre-infusion. Changes from baseline in physical examination findings were also evaluated.

Results:

- No premedication was given prior to ABI-007 dosing, and no hypersensitivity reactions were reported during 92 cycles at 135 to 375 mg/m^2 given within 30 minutes with few exceptions.
- The MTD was 300 mg/m^2 given IV over 30 minutes every 3 weeks. 9 patients received this dose in a total of 32 treatment cycles
- Dose limiting toxicities observed at 375 mg/m^2 were keratitis, blurred vision, sensory neuropathy, stomatitis, and Grade 4 neutropenia. These events were generally toxicity Grade 2 or 3, were reported after Cycle 1 dosing, and were generally transient
- There were 5 episodes of Grade 4 neutropenia, 4 of which were isolated, transient occurrences during Cycle 1 that did not generally recur despite additional cycles at the same dose. These 4 episodes were not associated with fever or other symptoms and were not considered to be dose-limiting by the investigator. The remaining case was reported as an SAE by the investigator, was the only Grade 4 SAE reported on-study, and was considered a dose-limiting toxicity
- Grade 3 treatment-emergent events were reported for 58% of patients. Grade 3 toxicities/AEs reported for more than 1 patient were fatigue (37%), sensory neuropathy (26%), constipation (16%), and stomatitis/pharyngitis and diarrhea (11% each)
- No deaths were reported on-study, and keratitis and blurred vision were the only treatment-related SAEs reported for more than 1 patient
- The most commonly reported treatment-related toxicities/AEs were expected for this therapeutic class of drug and included fatigue (84% of patients), nausea (63%), alopecia (58%), sensory neuropathy (53%), stomatitis/pharyngitis (53%), diarrhea (42%), Dermatology/Skin, other (42%), vomiting (37%), blurred vision (37%), fever (32%), anorexia (32%), Musculoskeletal, other (26%), and insomnia (26%).
- No clinically significant changes were observed in clinical chemistry values or vital sign measurements during dosing or postdosing
- ABI-007 appeared to have a linear PK for the clinically relevant dose range of 135 to 300 mg/m^2 given as a 30-minute infusion.
- Disposition of ABI-007 exhibited a biphasic decline in concentration
- Half-life ($t_{1/2}$) of ABI-007 was similar across different dose levels while both V_z and Cl decreased slightly as dose increased.
- Similar PK parameters were observed for the 135 mg/m^2 dose given over 3 hours or 30 minutes
- Exploratory analysis of response (n = 6) indicated 1 patient each achieved confirmed partial response and unconfirmed stable disease at 200 mg/m^2

Conclusions:

- No steroid or anti-histamine premedication was given prior to dosing, and no hypersensitivity reactions were observed with ABI-007 monotherapy
- The MTD for ABI-007 given IV over 30 minutes every 3 weeks was 300 mg/m^2
- Keratitis, blurred vision, sensory neuropathy, stomatitis, and Grade 4 neutropenia were the dose-limiting toxicities. Although ocular/visual events are not unexpected with this therapeutic drug class, careful monitoring for these events was incorporated into the Phase II clinical studies with ABI-007.
- ABI-007 monotherapy over the clinically relevant dose range (ie, 135 to 300 mg/m^2 given IV over 30 minutes every 3 weeks) resulted in Grade 3 and 4 toxicities/AEs for 58% and 5% of all patients, respectively
- Isolated, transient episodes of Grade 4 neutropenia occurred on Cycle 1 in 4 patients but generally did not recur despite continued treatment at the same dose. These events were not considered dose-limiting by the investigator and were not reported as SAEs. In general, hematologic toxicities were not important dose-limiting events for paclitaxel in the ABI-007 formulation administered over 30 minutes at up to 375 mg/m^2.
- The most commonly reported toxicities/AEs were all expected for this therapeutic drug class, ie, fatigue, myalgia, nausea, alopecia, and stomatitis. the only Grade 3 toxicities/AEs reported for more than 1 patient were fatigue, neuropathy – sensory, constipation, diarrhea, and stomatitis/pharyngitis
- No deaths were reported on-study, and no specific safety concerns were identified in the other SAEs or ADRs reported.
- No clinically significant changes from baseline were observed for clinical chemistry parameters or vital sign measurements
- Pharmacokinetics for ABI-007 exhibited bi-exponential disposition following IV infusion, appeared to be linear for the clinically relevant dose range of 135 to 300 mg/m^2 given over 30 minutes
- An exploratory evaluation of response to ABI-007 monotherapy provided results supporting the continuing development of ABI-007 for treatment of solid tumors/breast cancer.

Date of the Report: 06 January 2004

3. Study CA012-0

A Controlled Randomized, Phase III, Multicenter, Open Label Study of ABI-007 (A Cremophor®-Free, Protein Stabilized, Nanoparticle Paclitaxel) And Taxol® in Patients with Metastatic Breast Cancer

Study: Phase III, multi-center, open-label, controlled randomized study

Subjects: Subset of patients (n=12) enrolled for treatment of Metastatic Breast Cancer

Objectives: To evaluate the PK of ABI-007.

Dosing Regimen: Each patient received 260 mg/m^2 IV inf 30 min every 3 weeks and subset group for PK were remained in hospital for 5 days during the first dose and treatment cycle.

Blood, urine, and feces samples were collected and analyzed by HPLC/MS* for paclitaxel and two metabolites, 6α-hydroxypaclitaxel and 3'-p-hydroxypaclitaxel. Blood samples were collected at pre-dose, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 9, 12, 15, 24, 36, 48, 60, and 72 hours. Urine samples were collected at predose and during time intervals: 0-6, 6-12, 12-24, 24-48, 48-72, 72-96, 96-120 hours. Feces samples were collected for 5 days.

Patients demographics: BW = 70 kg; BSA = 1.77 m^2; dose = 459 mg

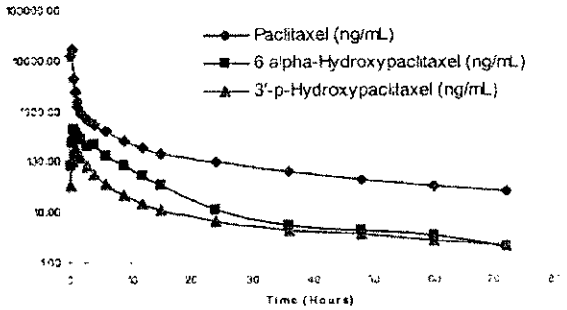
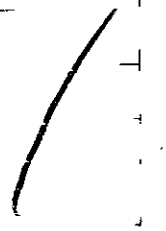


Figure 3.1 Paclitaxel, 6α-hydroxypaclitaxel and 3'-p-hydroxypaclitaxel Blood Concentration- Time Profiles (mean)

Table 3.1 Paclitaxel PK Parameters

Parameter	Mean	%CV	Range
C_{max} (ng/ml)	18741	27	
T_{max} (hr)	0.46	21	
AUC_∞ (hr*ng/ml)	17940	23	
CL (L/hr/m^2)	15.2	24	
$T_{1/2}$ (hr)	27.4	33	
λ_z (hr^{-1})	0.027	21	
V_z (L/m^2)	632	63	
Cl_u (L/hr/m^2)	0.62	51	



Paclitaxel displayed multi-phasic disposition with total CL of 15L/h/m^2, $t_{1/2}$ of 27 hrs and V_z of 632 L/m^2. Urine elimination only accounts for 4% of CL_{tot}.

Patient 09 showed extreme value on V_z (1831 L/m^2) and $t_{1/2}$ (55 hrs). –an outlier
Predose urine conc of paclitaxel was from 5.4-7.8 ng/ml for patients 2, 3, 4, 5, 6.

Table 3.2 PK Parameters for 6α-hydroxypaclitaxel and 3'-p-hydroxypaclitaxel

Metabolite	C_{max} (ng/m)	T_{max} (hr)	AUC_∞ (hr*ng/ml)	Parent/Metabolite AUC_∞ Ratio
6α-Hydroxypaclitaxel	591 (82)	1.11 (89)	2528 (145)	21.6 (81)
3'-p-Hydroxypaclitaxel	220 (74)	0.86 (47)	1075 (125)	58.9 (92)

The metabolites profiles follow similar pattern to the parent drug except that the metabolite concentrations are substantial lower. The T_{max} was delayed relative to that for parent drug due to the formation of metabolites.
Paclitaxel had a 22- and 59-fold greater exposure than 6α-hydroxypaclitaxel and 3'-p-hydroxypaclitaxel, respectively.

Large variability on C_{max} and AUC due to P05 and P06 having extreme values.

Table 3.3 Urinary and Fecal Excretion of Paclitaxel and Metabolites

Compound	% Dose	
	Urine	Feces
Paclitaxel	3.92 (39,	2.77 (74
6α-Hydroxypaclitaxel	0.15 (108	18.04 (65,
3'-p-Hydroxypaclitaxel	0.04 (79,	1.08 (80,

* method for paclitaxel and two metabolites: for blood; urine; and for feces.

Synopsis CA012-0

Sponsor Company Name: American BioScience, Inc. **Name of Finished Product:** ABI-007 (*nab* [nanoparticle, albumin-bound] Paclitaxel for Injectable Suspension) **Name of Active Ingredient:** Paclitaxel	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	*(For National Authority Use Only)*
Title of the Study: A Controlled, Randomized, Phase III, Multicenter, Open-Label Study of ABI-007 (A Cremophor®-Free, Protein-Stabilized, Nanoparticle Paclitaxel) and Taxol® in Patients With Metastatic Breast Cancer		
Investigators and Study Centers: This was an international, multicenter study conducted at 70 sites: 22 sites in North America (21 in the US and 1 in Canada), 20 sites in the U.K., and 28 sites in Russia/Ukraine. Four of the sites in Russia participated in a PK substudy.		
Publications: To date, no journal articles based on data from this study have been published. Data gathered in this study have been presented at 3 medical conferences as indicated in Appendix 16.1.11.		
Study Dates: From 01 November 2001 (first patient randomized) to 07 April 2003 (data cutoff date: date of 9-week assessment for last patient entered). Study is ongoing; patients will continue to receive treatment beyond 6 treatment cycles as long as Investigators determine that there is a continuing benefit to their patients.		**Phase of Development:** Phase III
Objectives: The primary objectives of this study were to compare the antitumor activity of ABI-007 with that of Taxol in patients with metastatic breast cancer and to evaluate the safety/tolerability of ABI-007 compared to that of Taxol. Secondary objectives were to evaluate time to disease progression (TTP) and survival, to evaluate changes from baseline in quality of life (QOL) and to determine the pharmacokinetics (PK) of ABI-007.		

Methodology:

This was a controlled, randomized, multicenter, open-label, Phase III, outpatient, noninferiority study. Eligible patients were randomized (1:1) to receive either 260 mg/m^2 ABI-007 infused IV over 30 minutes or 175 mg/m^2 Taxol infused IV over 3 hours. Treatment cycles were administered every 3 weeks. Within-country balance for anthracycline exposure was ensured by within-country stratification into anthracycline-exposed and -naive strata.

Patients without progressive disease (PD) after 6 cycles could continue their assigned treatment at the investigator's discretion. No premedication was required prior to ABI-007 dosing; however, premedication was given prior to Taxol dosing per the Package Insert. Imaging studies were performed at baseline; Weeks 5, 9, and 15; and end of treatment. These images also were evaluated by a central reader who was blinded to study drug assignment and to the investigator's selection of target and nontarget lesions and response assessment. Response was evaluated according to Response Evaluation Criteria in Solid Tumor (RECIST) guidelines. Telephone assessments of survival were made once a month for 3 months after the end of all cycles and every 3 months thereafter. QOL and peripheral neuropathy assessments were evaluated prior to dosing at each cycle. Clinical laboratory values via a central laboratory (hematology and clinical chemistry parameters) and vital signs were assessed throughout the study. For the PK substudy in 12 patients directly assigned to ABI-007 treatment (ie, not part of the randomized population), blood and urine samples were obtained predose, during dosing, and postdosing; fecal samples were collected daily during 5 days of inpatient care.

Number of Patients (planned and analyzed):

Synopsis Table 1. Study Populations

	ABI-007	Taxol	Total
Planned enrollment	230	230	460
evaluable	~ 210	~ 210	~ 420
anthracycline-exposed	≥ 100	≥ 100	≥ 200
Populations for analysis			
All Randomized (AR) Population	233	227	460
Intent-to-Treat (ITT) Population	229	225	454
Per-Protocol (PP) Population	211	218	429
Safety Population	229	225	454
ITT Population – prior therapy subsets			
anthracycline-exposed	176	175	351
anthracycline-naive	53	50	103
study drug as 1st-line therapy	97	89	186
study drug as > 1st-line therapy	132	136	268
PK substudy (these patients not included in any of the above categories)	12	0	12

Diagnosis and Criteria for Inclusion:

Eligible patients were nonpregnant, nonlactating females, ≥ 18 years of age with histologically or cytologically confirmed measurable metastatic breast cancer and expected survival ≥ 12 weeks; were candidates for single-agent paclitaxel therapy; had failed prior adjuvant or metastatic chemotherapy; had not received paclitaxel or docetaxel due to metastatic carcinoma; had appropriate washouts; had not relapsed with breast cancer within 1 year of adjuvant Taxol or docetaxel; had no other malignancy within 5 years (except nonmelanoma skin cancer, cervical intraepithelial neoplasia [CIN], or in-situ cervical cancer [CIS]); had acceptable clinical laboratory levels at baseline; had Eastern Cooperative Oncology Group (ECOG) status of ≤ 2 at baseline; and did not have pre-existing peripheral neuropathy of ≥ 1 per National Cancer Institute (NCI) Common Toxicity Criteria (CTC).

Test Product, Dose and Mode of Administration, Lot Numbers:

ABI-007 (a Cremophor-free, protein-stabilized, colloidal nanoparticle suspension of paclitaxel) at 260 mg/m^2 over 30 minutes by IV infusion. Unit strength – 100 mg/50 mL vial (reconstituted suspension 5 mg/mL paclitaxel).
Lot Numbers: C101-001; C101-002; C101-003; C102-001; and C102-003.

Reference Therapy, Dose and Mode of Administration, Lot Number(s):

Taxol® (paclitaxel) Injection (Bristol-Myers Squibb) 175 mg/m^2 given over 3 hours by IV infusion. Unit strength = 6 mg/mL. Product is commercially available and was supplied by the Sponsor. Lot Numbers: 0K35175, 0L36871, 1A39935, 1D36332, 1E41928, 1E47934, 1F51597, 1F51598, 1K43584, 1K57419, 1L41327, 1L43680, 1M37265, 1M37269, 2B50417, 2C65657, 2E532, 2E59016, 2E59019, 2E65637, 2K62575, L136859, and L156859.

Duration of Treatment:

Study participation included a potential 4-week anthracycline washout, a 3-week Baseline Period, 18 weeks of treatment (6 treatment cycles given at 3-week intervals), and a 30-day follow-up period. Patients completing 6 cycles without PD could continue study drug dosing at 3-week intervals, at the investigator's discretion.

Criteria for Evaluation:

Efficacy: Two types of response were assessed according to RECIST guidelines: target lesion and overall (target and nontarget lesion); confirmation of complete response (CR) and partial response (PR) required response duration ≥ 4 weeks. Three datasets were used: investigators' assessment; assessments by an Independent Radiology Laboratory (IRL) who were blinded to study drug assignment and to the investigator's selection of target and nontarget lesions and response assessment; and a reconciliation of these datasets according to a predefined algorithm.

The primary efficacy endpoint was the target lesion response rate (TLRR) which was based on the Reconciled Response Assessment Dataset (*rec*TLRR). The *rec*TLRR includes only target responses confirmed by Cycle 6 and represents a rigorous, conservative, prospective approach to minimize bias. The protocol-specific *rec*TLRR results in an underestimate of response rate relative to those based on target and nontarget lesions (ie, the overall response rate [ORR]) for all cycles of therapy using the Investigator Response Assessment Dataset (*inv*ORR). The *inv*ORR is emphasized more than *rec*TLRR in this report because the *inv*ORR is more clinically meaningful and is comparable with literature reports of response rates to taxanes. Furthermore, the primary efficacy tests of noninferiority and superiority, which were based on *rec*TLRR, were met and surpassed, and analyses of *inv*ORR and *rec*TLRR yield the same conclusion with regard to the relative efficacy of ABI-007 versus Taxol.

Secondary efficacy measures included overall response (*inv*ORR); time to disease progression, patient survival; time to first response (target lesion and overall), duration of response (target lesion and overall), number of cycles to maximum response (target lesion and overall); and QOL assessments (ie, ECOG performance status, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire [EORTC-QLQ]-C30 scores, and weight).

PK: PK parameters included elimination rate constant, half-life, volume of distribution, maximum blood concentration (C_{max}), time of occurrence for maximum blood concentration (T_{max}), area-under-the-curve from time zero to time infinity (AUC_∞), clearance, and urinary clearance.

Safety: The final overall judgment to confirm that the safety of ABI-007 was not worse than that of Taxol was a clinical judgment based on the comparative analyses described in the subsections below and the clinical significance of the adverse events. Safety assessments included discontinuations from the study; treatment exposure including dose interruptions and reductions, dosing delays, and cumulative dose; treatment-emergent adverse events (AEs), serious adverse events (SAEs), and toxicities (per NCI CTC); clinical laboratory values (hematology and clinical chemistry parameters), including maximal degree of myelosuppression, incidence of Grade 4 neutropenia, and time to recovery from Grade 4 neutropenia; peripheral neuropathy assessments (physician and patient-rated); vital signs; use of growth factors and steroids; 12-lead electrocardiogram (ECG) results; and echocardiogram/multigated (radionuclide) angiogram (MUGA) results.

Statistical Methods:

Efficacy: The primary efficacy analysis was multiple nested testing as follows: noninferiority of the target lesion response (CR + PR) rate (*rec*TLRR) for ABI-007 compared to Taxol was tested stratified by 1st line versus >1st line therapy; if noninferiority was shown, the superiority of ABI-007 compared to Taxol was tested stratified by 1st line versus > 1st line therapy; and if the second test was positive, then the superiority of ABI-007 to Taxol was tested for 1st line therapy patients only. The test of noninferiority was whether the ratio of percentage of patients with response after ABI-007 (p_A) to that after Taxol (p_T) was ≤ 0.75 (H_0) or > 0.75 (H_a). The primary efficacy analysis was performed for the Reconciled Response Assessment Dataset of the intent-to-treat (ITT) Population. For each step of the primary efficacy analysis, the point estimate and confidence interval (CI) of the ratio p_A/p_T was presented along with the percentage of patients with confirmed CR or PR and the 95% binominal CI for the confirmed PR or CR response rate for ABI-007 and Taxol. Secondary efficacy analyses included the primary analysis performed for the all randomized (AR) and per protocol (PP) Populations, and analysis of prognostic factors (including age category and country) with a possible influence on response. Analyses similar to the primary efficacy analysis were performed for overall response. Treatment differences in time to first confirmed response, duration of response, time to disease progression, and patient survival were analyzed using Kaplan-Meier methods (using PROC LIFETEST). Numbers of cycles to maximum confirmed target and overall response was summarized by cycle and treatment. Treatment differences in QOL measures were analyzed using a 2-way analysis of variance (ANOVA) with treatment and country as factors. ECOG performance status also was

analyzed as the worst score in each treatment cycle and any time during the study.

PK: PK parameters for individual data sets were determined by noncompartmental analysis. Plots of individual patient profiles (whole-blood concentration versus time; urine concentration versus time) were evaluated. Mean whole-blood concentration versus time plots were analyzed for all dose levels (semi-log plot). Recovery of dose in feces was calculated.

Safety: AEs and toxicities were analyzed in terms of incidence of treatment-emergent events. Events were coded using the Medical Dictionary for Regulatory Affairs (MedDRA). MedDRA coded terms were further classified to the NCI CTC. Incidence rates were presented overall and by maximum intensity and strongest relationship to study drug for each treatment group. Treatment exposure was summarized by dose reductions and reasons for reductions, dosing delays, cumulative dose (mg and mg/m^2), average dose intensity (mg/m^2/week), and percentage of protocol dose. Clinical laboratory assessments were analyzed as change from baseline to each visit, shifts (relative to normal range) from baseline to final on-treatment evaluation, and incidence of most severe NCI CTC grade in each treatment cycle and any time during the study. Myelosuppression was evaluated by nadir, hematology values in each treatment cycle, and any time during the study for each treatment group. Time to recovery from Grade 4 (and from Grade 3 or 4) neutropenia, with and without growth factor treatment, was evaluated. Patient assessment of peripheral neuropathy was evaluated using the Functional Assessment of Cancer Therapy (FACT)-Taxane (Version 4) "Additional Concerns" subscale and analyzed as change from baseline in total score to each visit for each treatment group. Physicians assessed peripheral neuropathy at each visit using the NCI CTC for "neuropathy-sensory", this was analyzed as change from baseline as well as worst overall score. Vital signs during each treatment cycle were analyzed as mean change from predose to minimum, maximum, and end of dosing for each treatment group. Incidence of clinically significant vital signs was summarized. ECGs were analyzed as changes from baseline to follow-up categorized as improved, no change, or worsened. Echocardiograms and MUGAs were analyzed as the incidence of abnormalities at each visit and left ventricular ejection fraction (LVEF) at each visit by treatment group.

Results:

Disposition: Approximately half of the treated patients in both arms received ≥ 6 cycles (ABI-007: 56%; Taxol: 50%). Most patients came off therapy because they had progressive disease (ABI-007: 46%; Taxol: 55%). Treatment-related toxicities/AEs resulted in discontinuation from therapy for 11 and 6 patients in the ABI-007 and Taxol group, respectively, an additional 4 and 3 patients, respectively, with progressive disease discontinued for treatment-related toxicities/AEs. Non-treatment-related toxicities/AEs resulted in discontinuation from therapy for 5 and 4 patients, respectively; an additional 3

and 7 patients, respectively, with progressive disease discontinued for non-treatment-related toxicities/AEs. Death was the reason for discontinuation of therapy for 1 patient in the ABI-007 group. As of the data cut-off date of 07 April 2003, 3 patients in the ABI-007 group and 2 in the Taxol group continue to be treated on study.

Demographics: All patients were female. 97% were Caucasian, and 83% were postmenopausal. Mean (S.D.) age was 53.2 (10.10) years; 86% of patients were < 65 years of age. Patients were enrolled at sites in Russia/Ukraine (353 patients; 77% of patients), the UK (67; 15%) and the US/Canada (40; 9%). Pathology at baseline was primarily ductal carcinoma (52%), carcinoma/adenocarcinoma (24%), lobular carcinoma (10%), and cancer/malignancy (10%). The dominant lesion site for most patients was liver (42%) or lung (34%). Most patients had a baseline ECOG performance status of 0 (36%) or 1 (60%). At baseline, most patients had been exposed to chemotherapy (86%), anthracyclines (77%), or hormonal therapy (56%); 54% had received anthracycline treatment for metastatic disease. Most patients (59%) had received prior chemotherapy for metastatic disease; 41% had no prior chemotherapy in the metastatic setting and received ABI-007 and Taxol in this study as 1st-line therapy. No important differences between the treatment groups were noted in these parameters.

Efficacy: The patient population for this study had poor prognostic factors in that 76% had ≥ 3 metastatic lesions; 79% had visceral (lung, abdominal, or liver) disease; 86% had prior chemotherapy; and 59% had relapsed after > 1st-line therapy. The *in*vORR was statistically significantly greater in patients receiving ABI-007 (260 mg/m^2 IV q3w) than in patients receiving Taxol (175 mg/m^2 IV q3w) for all patients, patients receiving 1st-line therapy, patients receiving ≥ 1st-line therapy, patients with prior anthracycline therapy (adjuvant or metastatic), and patients with prior metastatic anthracycline therapy (see Synopsis Table 2 and Synopsis Figure 1 below). Of the 76 patients in the ABI-007 group with confirmed overall responses, 74 were PR and 2 were CR; of the 42 in the Taxol group, 39 were PR and 3 were CR.

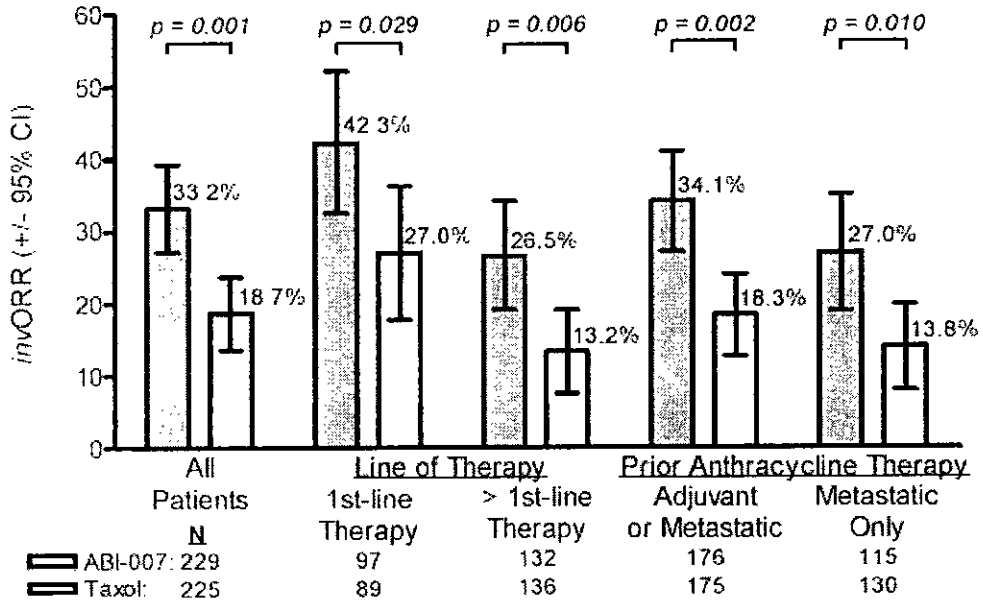
These results were confirmed using the dataset from the blinded review of tumor images by independent radiologists: response rates in the ABI-007 group were statistically significantly higher than those in the Taxol group (21.4% vs 10.3%; P = 0.002). As anticipated, the blinded analysis yielded lower response rates because the central readers at the independent radiology laboratory (IRL) had only radiologic images for review and could not include lesions measurable only on physical examination. In addition, the IRL reviewed data up to Cycle 6 while the *in*vORR includes data for all cycles.

Synopsis Table 2. *inv*ORR for All Patients, by Line of Therapy, and by Prior Anthracycline Therapy (ITT Population)

	*inv*ORR		
	ABI-007	**Taxol**	***P-value***
All Patients	33.2%	18.7%	*0.001*
Patients Receiving 1st-line Therapy	42.3%	27.0%	*0.029*
Patients Receiving > 1st-line Therapy	26.5%	13.2%	*0.006*
Patients with Prior Anthracycline Therapy (Adjuvant or Metastatic)	34.1%	18.3%	*0.002*
Patients with Prior Metastatic Anthracycline Therapy	27.0%	13.8%	*0.010*

(See Synopsis Figure 1 below for number of patients in each group.)

Synopsis Figure 1. *inv*ORR for All Patients, by Line of Therapy, and by Prior Anthracycline Therapy (ITT Population)



The prospectively defined analysis of the primary efficacy endpoint consisted of 3 nested tests, conducted sequentially: noninferiority (all patients), superiority (all patients), and superiority in patients receiving study drug as 1st-line therapy for metastatic disease. The *rec*TLRR was statistically significantly greater for the ABI-007 group as compared to the Taxol group for all patients (24.0% vs 11.1%; P < 0.001) and for patients receiving 1st-line therapy (34.0% vs 18.0%; P = 0.013).

The efficacy of ABI-007 was statistically significantly greater than that of Taxol among patients < 65 years old (n = 392; *inv*ORR: 34.2% vs 18.7%; P < 0.001) and among patients with visceral (liver, lung, or abdominal) dominant site lesions (n = 358; *inv*ORR: 33.5% vs 18.7%; P = 0.002). *inv*ORRs were also greater for ABI-007 among patients ≥ 65 years old (n = 62; 26.7% vs 18.8%; P = 0.754) and among patients with nonvisceral dominant site lesions (n = 93; 34.0% vs 18.6%; P = 0.074), but these results did not reach statistical significance due to the smaller number of patients in these subsets. Prognostic factors had no statistically significant effect on *inv*ORR, for all patients and within each country (US/Canada, UK, Russia/Ukraine).

The robustness of the conclusion of superior efficacy for ABI-007 is demonstrated by the consistency of the results when analyzed using:

- different response rates (*rec*TLRR, *inv*ORR),
- different populations (ITT, AR, PP),
- different response assessment datasets (Investigator, IRL, Reconciled), and
- different patient subsets (all patients, 1st-line therapy, > 1st-line therapy, patients with prior anthracycline exposure, patients with prior anthracycline exposure in a metastatic setting) (Synopsis Table 3).

All of these analyses showed that response rates in the ABI-007 group were at least 50% greater than those in the Taxol group.

Synopsis Table 3. Ratio of ABI-007/Taxol Response Rates for Investigator and IRL Response Assessment Datasets (ITT Population)

Response Assessment Dataset	Patient Population	Response	Ratio[a]	95% CI	*P-value*
Investigator	All	Overall	1.75	1.27-2.42	*0.001**
		Target	1.82	1.32-2.50	*0.001**
	1st-line therapy	Overall	1.57	1.04-2.37	*0.029**
		Target	1.64	1.09-2.47	*0.014**
	> 1st-line therapy	Overall	2.00	1.20-3.36	*0.006**
		Target	2.06	1.23-3.44	*0.004**
	Prior Anthracyclines	Overall	1.74	1.21-2.50	*0.002**
		Target	1.80	1.25-2.58	*0.001**
	Prior Metastatic Anthracyclines	Overall	1.95	1.15-3.29	*0.010**
		Target	2.01	1.20-3.38	*0.007**
IRL	All	Overall	2.04	1.28-3.25	*0.002**
		Target	2.65	1.47-4.77	*0.001**
	1st-line therapy	Overall	2.15	1.17-3.96	*0.009**
		Target	2.49	1.20-5.17	*0.009**
	> 1st-line therapy	Overall	1.89	0.91-3.93	*0.083*
		Target	2.94	1.10-7.86	*0.023**
	Prior Anthracyclines	Overall	2.17	1.23-3.85	*0.005**
		Target	3.06	1.44-6.49	*0.002**
	Prior Metastatic Anthracyclines	Overall	1.84	0.87-3.88	*0.104*
		Target	2.72	1.00-7.43	*0.040**

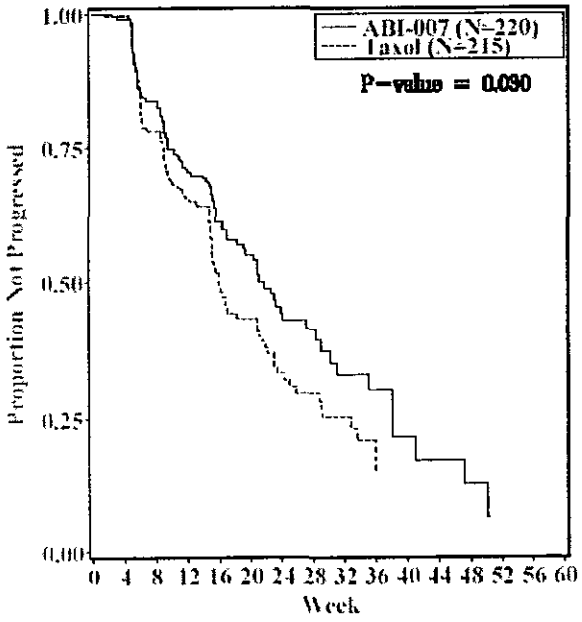
[a] Ratio of response rates (ABI-007/Taxol)

CI = confidence interval; * P < 0.05

APPEARS THIS WAY
ON ORIGINAL

Time to disease progression (TTP) was statistically significantly greater for the ABI-007 group (Investigator Response Assessment Dataset: 21.9 vs 16.1 weeks, P = 0.030; Reconciled Response Assessment Dataset: 16.6 vs 15.4 weeks, P = 0.016). TTP was higher for the ABI-007 group for patients receiving 1st-line therapy (28.4 vs 21.1 weeks, P = 0.056).

Synopsis Figure 2. Time to Disease Progression (ITT Population; Investigator Response Assessment Dataset)



Note: P-value from log-rank test.

Median time to death was not statistically different for the ABI-007 and Taxol groups (39.9 vs 37.9 weeks, P = 0.636); at the time of this analysis, 35% of patients had died. Among patients who achieved responses, mean time to first overall response was similar in the ABI-007 and Taxol groups (7.86 vs 9.24 weeks; P = 0.197; Investigator Response Assessment Dataset). Similarly, duration of overall response among those who achieved overall response was not statistically different between the groups (18.3 vs 26.9 weeks; P = 0.856; Investigator Response Assessment Dataset). Among patients who achieved an overall CR or PR, maximum responses occurred at Cycles 2 or 3 in 91% of responders in the ABI-007 group and 81% of responders in the Taxol group (Investigator Response Assessment Dataset). Measures of quality of life (ECOG status, EORTC QLQ, and weight) were not notably different between the groups.

Pharmacokinetics: Following ABI-007 administration, blood pharmacokinetic parameters for paclitaxel (mean $T_{1/2}$ and mean clearance) were similar to those reported following Taxol administration (27.4 vs 20.2 hours and 15.2 vs 12.2 L/h/m^2, respectively). Mean urinary recovery of unchanged paclitaxel (4%) following ABI-007 administration also was similar to that noted following Taxol administration (range: 1.3% to 12.6% of dose) and indicates extensive nonrenal clearance. The percent of the total dose excreted in the feces was approximately 45%.

Safety: Overall, the toxicity of ABI-007 was comparable to that of Taxol as assessed by patient disposition, dose delivered, discontinuations for toxicities/AEs, dose reductions, and incidence of specific toxicities/AEs. Performance status was well maintained and was not statistically significantly different between the treatment groups. Compliance with the treatment regimen was high in both groups (96% in the ABI-007 group and 94% in the Taxol group received at least 90% of the protocol-specified dose). Patients in the ABI-007 group received an average paclitaxel dose intensity 49% greater than that received by patients in the Taxol group (mean [S.D.]: 85.13 [3.118] vs 57.02 [3.008] mg/m^2/week, respectively). Premature discontinuations from study and dose interruptions, reductions, and delays due to toxicities/AEs occurred in fewer than 10% of patients in each group; no statistically significant differences between the groups were noted in these parameters. Dose reductions due to toxicities/AEs occurred more frequently in the ABI-007 group (7% vs 4%), while dose interruptions and dose delays due to toxicities/AEs occurred more frequently in the Taxol group (3% vs 6%; 3% vs 7%, respectively).

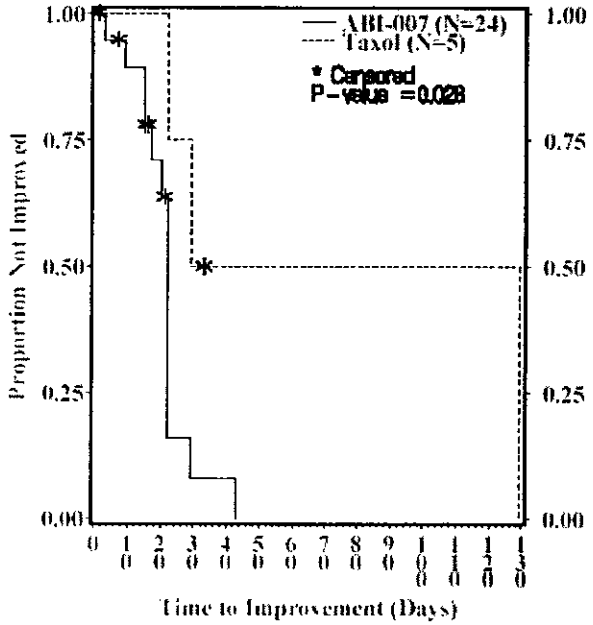
The most commonly reported toxicities/AEs during the study were expected for paclitaxel and included (ABI-007 group; Taxol group) alopecia (90%; 94%), neuropathy sensory (71%; 56%), fatigue (47%; 38%), neutrophils (hereafter neutropenia) (34%; 49%), arthralgia (35%, 32%), myalgia (28%; 32%), nausea (30%; 21%), infection with unknown absolute neutrophil count (ANC) (24%, 20%), and diarrhea (26%; 15%).

Despite the higher dose, Grade 4 neutropenia occurred less frequently for the ABI-007 group (9% vs 22%, P < 0.001) with a higher mean neutrophil nadir (1.67 vs 1.31 x 10^9/L, P = 0.046), suggesting that the Cremophor-EL may contribute to this toxicity in patients administered Taxol. Febrile neutropenia was uncommon, and there were no septic deaths in either group.

As expected with a higher dose of paclitaxel in ABI-007 (260 mg/m^2) compared with Taxol (175 mg/m^2), Grade 3 sensory neuropathy was more common in the ABI-007 arm (10% vs 2%, P < 0.001) but resolved rapidly (Synopsis Figure 3) and was easily managed with dose interruption and reduction. There were no episodes of Grade 4 sensory neuropathy in either arm. Grade 3 sensory neuropathy improved rapidly to Grade 2 or 1 by a median of 22 days in the 24 patients in the ABI-007 group, while in the Taxol group, the median time to improvement was 79 days in 5 patients (P = 0.028, log-rank test). By

day 28 after its first occurrence, the number of patients with persistent Grade 3 sensory neuropathy was the same (n = 4) in both arms of the study. No difference in physician or patient grading of peripheral neuropathy was found between the treatment groups when these parameters were analyzed on the basis of total paclitaxel dose administered (P > 0.2).

Synopsis Figure 3. Patients with Grade 3 Sensory Neuropathy: Time to Improvement to Grade 1 or 2 (Based on AE Data)



Note: P-value from log-rank test.

The incidence of severe (Grade 3 or 4) toxicities/AEs coded as hypersensitivity and related Grade 3-4 toxicities/AEs occurring on the day of dosing (chest pain) was low (no patients in the ABI arm; 3 and 2 patients, respectively, in the Taxol arm); flushing occurred more frequently in the Taxol group (<1% vs 9%, P < 0.001). In the Taxol group, predosing corticosteroids and antihistamines were administered to all but 1 patient (~99%) and at 95% of cycles. In contrast in the ABI-007 group, predosing corticosteroids and antihistamines were administered to 8% of patients and at 2% of cycles.

Gastrointestinal toxicities/AEs occurred more frequently in the ABI-007 group (eg, any grade of nausea: 30% vs 21%, P = 0.041), a difference likely related to the anti-emetic effect of the steroid premedications required for the Taxol regimen as well as the higher

dose of paclitaxel. Gastrointestinal toxicities/AEs were easily managed and were rarely Grade 3 or 4 (worst toxicity during any cycle ≤ 4% of patients). The toxicity/AE most frequently reported as a serious adverse event (SAE) was neutropenia (ABI-007: 10%; Taxol: 21%); no other SAE showed a notable difference in incidence between the treatment groups. The next most frequent SAEs were "cancer related", ie, disease progression and events related to disease progression (ABI-007: 8 patients; Taxol: 9), elevated gamma-glutamyltransferase (GGT) (9; 6); infection (4; 6); febrile neutropenia (4; 3), hyperuricemia (3; 3), and fractures (5; 1). Six patients in the ABI-007 group and 8 in the Taxol group died while enrolled in the study; in all cases, death was caused by progression of the patients' breast cancer.

No clinically significant differences between the treatment groups were noted in vital signs, LCG, and echocardiogram/MUGA assessments. The incidence of toxicities/AEs in the ABI-007 group were not higher in patients ≥ 65 years of age.

Overall, toxicity was comparable in the ABI-007 and Taxol groups as assessed by patient disposition, dose delivered, discontinuations for toxicities/AEs, dose reductions, and incidence of specific toxicities/AEs. While the overall safety profile of ABI-007 is similar to that of Taxol, the absence of Cremophor-EL in the ABI-007 preparation obviates the need for premedication and special IV tubing, results in less neutropenia, and may permit more rapid improvement from sensory neuropathy.

Conclusions:

This Phase III study demonstrated that ABI-007 has superior efficacy to Taxol in patients with metastatic breast cancer as well as in patients with metastatic breast cancer receiving 1st-line therapy. The safety profile of ABI-007 is similar to that of Taxol, and ABI-007 is not more toxic than Taxol. Specifically:

- The patient population for this study had poor prognostic factors in that 76% had > 3 metastatic lesions; 79% had visceral (lung, abdominal, or liver) disease; 86% had prior chemotherapy; and 59% had relapsed after > 1st-line therapy.
- The *in*vORR in patients receiving ABI-007 (33.2%) was significantly higher than the *in*vORR in patients receiving Taxol (18.7%) (P = 0.001)
- In patients receiving chemotherapy for metastatic breast cancer for the first time (1st-line patients), the *in*vORR in patients receiving ABI-007 (42.3%) was significantly higher than the *in*vORR in patients receiving Taxol (27.0%) (P = 0.029).
- The *in*vORRs with ABI-007 were higher, and statistically significant, in those patients who had failed prior chemotherapy (34.1% vs 18.3%, P = 0.002), and in patients with poor prognostic indicators such as in those with liver metastases (26.1% vs 13.4%; P = 0.030) and lung metastases (43.2% vs 25.3%; P = 0.035).
- *in*vORR was not affected by age group (< 65 vs ≥ 65 years) or country of enrollment.

- In the prospectively defined analysis of the primary efficacy endpoint, *rec*TLRR was statistically significantly greater for the ABI-007 group as compared to the Taxol group for all patients (24.0% vs 11.1%; P < 0.001) and for patients receiving 1st-line therapy (34.0% vs 18.0%; P = 0.013).
- The robustness of the efficacy conclusions is demonstrated by the consistent finding of statistically significant superiority of ABI-007 over Taxol in analyses of different datasets, populations, and patient subsets
- The median time to tumor progression was longer for patients receiving ABI-007 than for patients receiving Taxol, both for all patients (21.9 vs 16.1 weeks, P = 0.030) and for patients receiving 1st-line therapy (28.4 vs 21.1 weeks, P = 0.056).
- 98% of cycles of ABI-007 were administered without steroid premedication, and severe hypersensitivity reactions did not occur in any of these patients, confirming the ability to safely administer a solvent-free paclitaxel without the need for premedication. In contrast, even though 95% of the doses of Taxol were administered with steroids and antihistamines, these patients showed a significantly higher incidence of flushing than in those patients receiving ABI-007 without premedication.
- Both treatments were well tolerated with 98% of patients receiving the planned dose on both arms. Patients in the ABI-007 group received an average paclitaxel dose intensity 49% greater than that received by patients in the Taxol group (mean [S.D.]: 85.13 [3.118] vs 57.02 [3.008] mg/m^2/week, respectively).
- Consistent with this higher dose of paclitaxel delivered with ABI-007, the incidence of Grade 3 sensory neuropathy was 10% versus 2% in the patients receiving Taxol. There were no reports of Grade 4 sensory neuropathy or severe motor neuropathy in either arm. The Grade 3 sensory neuropathy improved rapidly in the ABI-007 patients within a median of 22 days and was thus easily managed. In contrast, and consistent with current clinical experience, recovery of the neuropathy after Taxol administration was significantly prolonged with a median of 79 days. This finding suggests that the Cremophor component of Taxol may be responsible for prolonged neuropathy, while neuropathy due to paclitaxel alone improves more rapidly.
- Despite the higher dose of paclitaxel delivered, there was significantly less Grade 4 neutropenia with ABI-007 (9%) compared to Taxol (22%), suggesting that Cremophor-EL may contribute to bone marrow damage and loss of white blood cells.
- Elderly patients were not at greater risk for toxicities due to ABI-007 than younger patients (< 65 years).
- In patients receiving study drugs as 1st-line therapy, the safety profiles of ABI-007 (n = 97) and Taxol (n = 89) were similar to those noted in the overall study population.
- The protocol-specified endpoints were achieved and exceeded.

Date of the Report: 10 February 2004

4. Study CA008-0

A Phase I Comparative Pharmacokinetic Study of a Cremophor®-Free, Protein Stabilized, Nanoparticel Formulation of Paclitaxel (ABI-007) and Taxol® in Patients with Advanced Solid Tumors

Study: Phase I, multi-center, open-label, controlled randomized study

Subjects: 26 patients with advanced solid tumors

Objectives: To compare the PK of Abraxane and Taxol

Dosing Regimen: Twenty-six patients were randomly assigned to receive either Abraxane 260 mg/m^2 over 30 minutes (n=14) or Taxol 175 mg/m^2 over 3 hours (n=12).

The plot of the mean paclitaxel concentration vs. time is presented in Figure 4.1. A summary of the estimated PK parameters for paclitaxel administered as both Abraxane and Taxol are listed in Table 4.1.

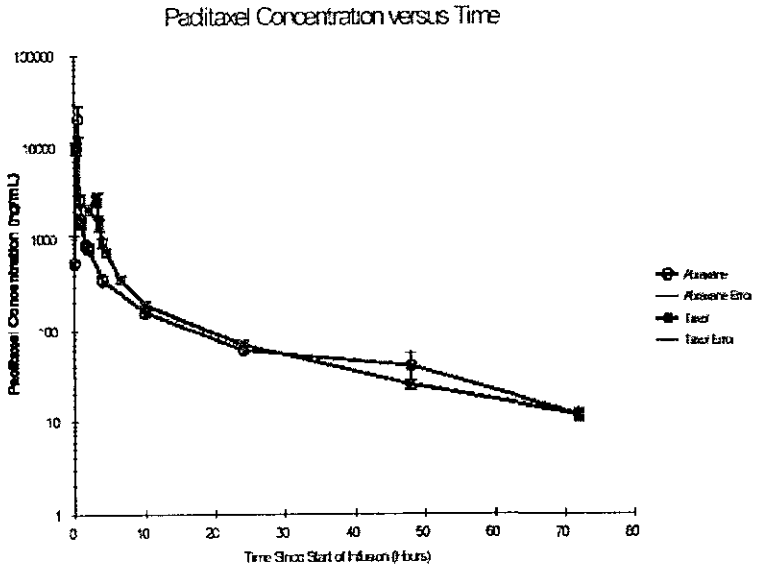


Figure 4.1 Plot of Mean Paclitaxel Concentration versus Time with Standard Error Bars for both ABI-007 (Abraxane) and Taxol

The paclitaxel AUC_{inf} for Abraxane 260 mg/m^2 and Taxol 175 mg/m^2 are not significantly different. However, the dose adjusted AUC_{inf} for Abraxane and paclitaxel formulated with Cremophor-EL (Taxol) is consistent with the known sequestration of paclitaxel in Cremophor micelles[1]. The terminal elimination rate constants (λ_z) are nearly

identical and the apparent volume of distribution (Vz) is larger when administered as Abraxane when compared to Taxol.

Table 4.1 Summary of Paclitaxel PK Parameters for Abraxane and Taxol

Parameter	ABI-007			Taxol			
	Mean	%CV	Range	Mean	%CV	Range	p-value
Cl (L hr/m²)	21.13	43.8		14.76	31.8	10.20 - 28.75	0.048
Vdss (L/m²)	230.7	51.3		156.3	43.2	99.7 - 346.6	0.211
Vz (L/m²)	663.8	48.1		433.4	31.1	308.7 - 809.3	0.040
AUCinf (ng-hr/mL)	14788.6	15.3		12602.7	21.0	6087.1 - 17081.2	0.521
AUCinf/dose corrected (ng-hr/mL)	56.81	46.3		71.90	21.1	34.78 - 98.06	0.049
Cmax (ng/mL)	22998.6	112.5		3543.3	57.2	1530 - 9380	0.001
Cmax/dose corrected (ng/mL)	88.69	111.2		20.11	55.8	8.8 - 52.1	0.001
Tmax (hr)	0.36	15.2		2.65	27.6	1.0 - 3.5	0.001
λz (hr⁻¹)	0.033	16.9		0.031	13.0	0.026 - 0.040	0.477
$t_{1/2}$ (hr)	21.6	17.2		20.5	11.6	17.5 - 26.3	0.479
AUC%extrap (%)	2.8	41.3		2.8	52.6	1.4 - 6.8	0.983

SYNOPSIS

Sponsor Company Name: American BioScience, Inc **Name of Finished Product:** ABI-007 (Paclitaxel Albumin Nanoparticle for Injectable Suspension) **Name of Active Ingredient:** Paclitaxel	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume Page	(For National Authority Use Only)
Title of the Study: Phase I, Comparative Pharmacokinetic Study of a Cremophor®-Free, Protein Stabilized, Nanoparticle Formulation of Paclitaxel (ABI-007) and TAXOL® in Patients with Advanced Solid Tumors		
Investigators and Study Centers: Eight sites in Russia. See Appendix 2		
Publications: Hawkins, MJ, Lane, JR, Clark M, et al. Comparative Pharmacokinetic (PK) Study of a Cremophor-free, Protein Stabilized, Nanoparticle Formulation (ABI-007) and a Cremophor-based Formulation of Paclitaxel (P) in Patients with Advanced Solid Tumors 16th EORTC-NCI-AACR Symposium, October 2004. Abstract 539 (Appendix 4)		
Study Dates: 24-Oct-2003 (First patient enrolled) to 27-Sept-2004 (All data in-house and entered into database) 1-Sept-2004 (SAE report cutoff date)		**Phase of Development:** Phase I
Introduction and Objectives: ABI-007, a Cremophor®EL-free[1], albumin-bound formulation of paclitaxel, has been shown in a Phase I clinical study in breast cancer solid non-hematological tumors to be tolerated at higher doses (300 mg m^2 every 3 weeks) than Taxol®[2] (Paclitaxel Injection, Bristol-Myers Squibb). In addition, ABI-007 can be administered with much faster infusion times (as compared with Taxol administration), with no reported severe hypersensitivity or fluid retention reactions associated with its use, and without the need for premedication. In addition, preclinical data indicated that paclitaxel distributed into the tissues more rapidly with ABI-007 than with Taxol. In Phase II studies of ABI-007, preliminary evidence suggests that ABI-007 may be effective (as measured by incidence of partial response or stable disease) in patients with metastatic breast cancer. Weekly dosing of ABI-007 is being evaluated because previous studies with paclitaxel have reported this dosing schedule greatly reduces side effects, such as neuropathy and myelosuppression, and may result in increased response rates. A Phase III		

[1] Cremophor® EL is a registered trademark of BASF Aktiengesellschaft
[2] Taxol® is a registered trademark of Bristol-Myers Squibb Co.

randomized trial comparing the efficacy and safety of ABI-007 260 mg m^2 to those of Taxol 175 mg m^2 in patients with metastatic breast cancer has been completed, with significantly higher efficacy results for the ABI-007 group as compared to the Taxol group (Response Rate 33.2% vs 18.7%, p 0.001, Time to Progression 21.9 weeks vs 16.1 weeks, p 0.03, respectively) The purpose of this study is to determine the pharmacokinetic (PK) parameters of paclitaxel formulated in ABI-007 (administered as a single 260 mg m^2 IV dose over 30 minutes) and in Taxol (administered as a single 175 mg m^2 IV dose over 3 hours) in patients with advanced solid tumors This study is complete. This report summarizes the disposition, demographics, and toxicities adverse events (AEs) of the patients enrolled as of the data cutoff date of 27-Sept-2004. Serious adverse events (SAEs) are reported up to 1-Sept-2004
Methodology: This was a randomized, Phase I, open-label clinical study investigating 2 formulations of paclitaxel, ABI-007 and Taxol, administered at doses and schedules that have been compared in a large-scale, randomized, phase III trial in patients with advanced breast cancer. A total of 27 patients were randomized (1:1) in blocks of 4 to either ABI-007 (260 mg m^2 administered over 30 minutes) or Taxol (175 mg m^2 administered over 3 hours). Blood samples were collected before, during, and after study drug infusion on Cycle 1. Enrollment and randomization continued until PK sampling had been completed for 12 patients assigned to each study drug. After Cycle 1, patients were allowed to continue on study with further cycles of their assigned study drug (repeated at 3-week intervals) until either progressive disease or unacceptable toxicity occurred. Dose modification for toxicity was permitted. Patient survival was monitored poststudy on a monthly basis for 6 months and every 3 months thereafter for a total of 2 years. The protocol is attached as Appendix 1.
Number of Patients (planned and analyzed): 24 to 28 patients were planned to be enrolled in this study (12 patients in each treatment arm). A total of 27 patients were enrolled (14 patients in the ABI-007 treatment arm and 13 patients in the Taxol arm).
Diagnosis and Criteria for Inclusion: **Inclusion Criteria:** A patient will be eligible for inclusion in this study only if all of the following criteria are met. 1. Recurrent metastatic cytologically/histologically proven advanced solid tumor that is considered to be not curable with standard treatment modalities 2. Male or non-pregnant and non-lactating female, and 18 years of age - If a female patient is of child-bearing potential, as evidenced by regular menstrual periods, she must have a negative serum pregnancy test (β-hCG) documented during screening - If sexually active, the patient must agree to utilize contraception considered

adequate and appropriate by the investigator

3. No other malignancy (except non-melanoma skin cancer, cervical intraepithelial neoplasia [CIN], in-situ cervical cancer, or lytic bone metastasis)
4. Expected survival of ≥ 8 weeks
5. Baseline hematology values
   - ANC ≥ 1.5 x 10^9 L (1500 cells mm^3)
   - Platelets ≥ 100 x 10^9 L (100,000 cells mm^3)
   - Hgb ≥ 9 g dL
6. Baseline blood chemistry values:
   - AST (SGOT), ALT (SGPT), and alkaline phosphatase ≤ 2.5 x upper limit of normal (ULN)
   - Total bilirubin and creatinine within normal range

Exclusion Criteria: A patient will not be eligible for inclusion in this study, if any of the following criteria apply:

1. Brain metastasis
2. A history of allergy or hypersensitivity to the study drugs or their excipients
3. Eastern Cooperative Oncology Group (ECOG) / Zubrod performance status of ≥ 3
4. Serious concurrent illness
5. Pre-existing peripheral neuropathy of ≥ Grade 1
6. Received taxane chemotherapy within the previous 6 months, or anthracycline within the previous 3 weeks or any other investigational drug within the previous 4 weeks
7. Not expected to tolerate any dose of the study drugs to which the patient may be randomized
8. Unlikely to complete the study through the follow-up visit
9. Acquired immunodeficiency syndrome (AIDS)
10. If the patient is taking any anti-cancer medication or a protease inhibitor, such as ritonavir, saquinavir, indinavir or nelfinavir, the investigator will inform the patient about the proper washout period, based on drug package inserts. The investigator will document the designated washout period in the patient's source documentation.

Test Product, Dose and Mode of Administration, Lot Numbers: ABI-007, a Cremophor EL-free, protein-stabilized nanoparticle formulation of paclitaxel, was administered IV over 30 minutes at 260 mg m^2. Treatment consisted of 1 dose, with the possibility of remaining on treatment at 3-week intervals until either progressive disease or unacceptable toxicity occurs.

ABI-007 was supplied as a 100 mg 50 ml vial (lot number C102-004)

Reference Therapy, Dose and Mode of Administration, Lot Numbers: Taxol® (paclitaxel) Injection (Bristol-Myers Squibb) 175 mg m^2 given over 3 hours by IV infusion. Unit strength = 6 mg mL. Product is commercially available and was supplied by the Sponsor. Lot Number 1M37265

Duration of Treatment: Study participation included (i) up to a 3-week period to complete baseline assessments, (ii) 1 chemotherapy cycle during which PK samples were collected; (iii) additional every-3-weeks treatment cycles until either progressive disease or unacceptable toxicity occurs, and (iv) a follow-up evaluation within 30 days of study completion or early termination. In addition, a poststudy phone follow-up was conducted to assess survival on a monthly basis for 6 months and every 3 months thereafter for a total of 2 years.

Criteria for Evaluation:

The pharmacokinetic parameters were determined by noncompartmental analysis and included the maximum blood concentration (C_{max}), the area under the blood concentration vs time curve (AUC_{inf}), the half-life of the apparent terminal portion of the concentration vs time curve ($T_{1/2}$), the blood clearance (CL), and the volume of distribution (V_z).

The safety/tolerability endpoints were incidence of treatment-emergent adverse events (AEs) and serious adverse events (SAEs), nadir of myelosuppression, changes from baseline in clinical chemistry values, and number (%) of patients experiencing dose modifications, dose interruptions, and/or premature discontinuation of study drug.

Antitumor activity was evaluated in patients with measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) guidelines.

Statistical Methods: The primary endpoint is to determine the PK parameters of paclitaxel formulated in ABI-007 (administered as a single 260 mg m^2 IV dose over 30 minutes) and in Taxol® (administered as a single 175 mg m^2 IV dose over 3 hours). Noncompartmental analysis will be performed using standard approaches. The pharmacokinetic parameters for ABI-007 and Taxol will be determined by noncompartmental analysis and include the maximum blood concentration (C_{max}), the area under the blood concentration vs time curve (AUC_{inf}), the half-life of the apparent terminal portion of the concentration vs time curve ($T_{1/2}$), the blood clearance (CL), and the volume of distribution (V_z). Mean values for each drug will be determined.

Antitumor activity will be evaluated in patients with measurable disease according to RECIST guidelines as summarized below.

Percentage change in lesion size will be evaluated by the following formulae:

1.When determining complete response or partial response:

$$\frac{(\text{Post value} - \text{Baseline value})}{(\text{Baseline value})} \cdot 100$$

2. when determining progressive disease:

$$\frac{(\text{Post value} - \text{Smallest value since treatment started})}{(\text{Smallest value since treatment started})} \times 100$$

AEs will be analyzed in terms of treatment-emergent AEs (defined as any AEs that begin or worsen in intensity after the start of study drug through 30 days after the last dose of study drug). All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), and the MedDRA (lower level) terms will be mapped to the appropriate NCI Common Toxicity Criteria (CTC) term. The incidence of treatment-emergent toxicities will be summarized by NCI CTC term. AEs coded to MedDRA preferred terms also will be summarized by system organ class and preferred term. Tables summarizing the incidence of treatment-emergent toxicities/AEs will be presented for all events, all events by intensity, all events by relationship to study drug, treatment-related events by intensity, SAEs, SAEs by intensity, SAEs by relationship, and events that led to premature discontinuation of study drug. All SAEs, events that led to premature discontinuation of study drug, and deaths will be listed.

Analyses of other safety endpoints, including laboratory assessments, vital signs, ECG evaluations, and concomitant medications will be presented in the final report for this study.

Results:

This interim report summarizes the disposition, demographics, and toxicities/adverse events of the patients enrolled as of the data cutoff date of 27-Sept-2004. In addition, reports of SAEs received up to 1-Sept-2004 are described. Results are presented by treatment group.

Disposition

Twenty-seven patients were enrolled in the study and all 27 patients received at least 1 dose of study drug (Treated Population) (Summary Table 3.0).

To date, 26 patients (96%) have discontinued therapy, and 1 patient (4%) continues on study (Summary Table 3.0). Discontinuations from the study were due to progressive disease (10 patients [38%]), investigator discretion (9 [35%]), progressive disease with unacceptable toxicity (2 [8%]), patient discretion (2 [8%]), unacceptable toxicity (1 [4%]), loss to follow-up (1 [4%]), and other (1 [4%]) (Summary Table 3.0).

Demographics and Disease Characteristics (Summary Tables 4.0 and 11.0):

Sex: 22 (81%) women, 5 (19%) men

Age (mean ± SD, range): 52.2 ± 9.77 years; 34 to 71 years

Race/ethnicity: 25 (93%) White, Non-Hispanic and Non-Latino; 2 (7%) White, Hispanic or Latino

Weight - mean ± SD, range): 71.4 ± 11.38 kg, 47 to 100 kg

Prior Chemotherapy: 26 (96%) of all patients received prior chemotherapy - 6 (22%) received prior neo-adjuvant therapy, 11 (41%) received prior adjuvant therapy; out of 18 patients that received prior metastatic therapy, 12 (67%) received 1st line therapy; 4 (22%) received 2nd line therapy, and 2 (11%) received 3rd line therapy.

Pharmacokinetics.

For both ABI-007 and Taxol, paclitaxel displayed multiphasic disposition. AUC_{inf}, λ_z, and $T_{\frac{1}{2}}$ were similar for both formulations. Plasma clearances and volumes of distribution were clinically different and reached statistical significance for CL and V_z. Differences in T_{max}, C_{max}, and dose-adjusted C_{max} were attributed to differences in dose and duration of administration. When analyzed with data from other clinical trials, ABI-007 AUCs were linear with respect to dose from 80 to 300 mg m^2. The observed parameters were similar to those reported for Taxol and to previous clinical trials for ABI-007.

The pharmacokinetics are fully described in a separate pharmacokinetics study report for study CA008-0.

Efficacy

The confirmed complete or partial overall response rate in the treated population is presented in In-Text Table 1 and in Summary Table 15.0.

In-Text Table 1: Confirmed Complete or Partial Overall Response Rate

Variable	ABI-007 260 mg/m^2 (N=14)	Taxol 175 mg/m^2 (N=13)
Number of Patients with Confirmed Complete or Partial Overall Response	5	2
Confirmed Complete or Partial Overall Response Rate (%)	35.7	15.4
95% Confidence Interval (CI)	12.76, 64.86	1.92, 45.45
Type of Confirmed Overall Response	5	2
Complete Response	0	1 (50%)
Partial Response	5 (100%)	1 (50%)

Five patients (36%) in the ABI-007 group and 11 patients (85%) in the Taxol group have died or had disease progression as of the data cutoff date for this report. The median progression-free survival was 5.9 months (95% CI 5.3- 6.3) and 3.5 months (95% CI 2.1-6.2), respectively (Summary Table 18.0).

Safety/tolerability

The most frequently reported treatment-emergent toxicities ALs (per NCI CTC) are summarized in In-Text Table 2 and in Summary Table 22.0.

In-Text Table 2: Incidence of Treatment-Emergent Toxicities/AEs*

NCI CTC Term	ABI-007 260 mg/m^2 n (%)	Taxol 175 mg/m^2 n (%)
Patients with ≥ 1 Toxicity	14 (100)	12 (92)
Neurology: Neuropathy-sensory	12 (86)	7 (54)
Dermatology Skin: Alopecia	11 (79)	9 (69)
Constitutional Symptoms Fatigue	10 (71)	4 (31)
Pain: Myalgia	10 (71)	4 (31)
Pain: Arthralgia	9 (64)	5 (38)
Blood Bone Marrow: Neutrophils	6 (43)	8 (62)
Gastrointestinal: Nausea	5 (36)	2 (15)
Constitutional Symptoms: Fever	3 (21)	4 (31)
Gastrointestinal: Anorexia	4 (29)	0
Blood bone Marrow: Leukocytes	3 (21)	1 (8)
Pulmonary: Cough	3 (21)	1 (8)

* Most commonly reported (≥ 20% of patients in either treatment group)
Source data: Summary Table 22.0

The most frequently reported Grade 3-4 treatment-emergent toxicities AEs (Summary Table 22.1), and the most frequently reported Grade 3-4 treatment-related, treatment-emergent toxicities AEs (Summary Table 22.3) are summarized in In-Text Table 3

In-Text Table 3: Grade 3 and 4 Treatment-Emergent Toxicities/AEs and Treatment-Emergent, Treatment-Related Toxicities/AEs (*Italicized*)

NCI CTC Term	ABI-007 260 mg/m²		Taxol 175 mg/m²	
	Grade 3 n (%)	Grade 4 n (%)	Grade 3 n (%)	Grade 4 n (%)
Patients with ≥ 1 Toxicity	4 (29)	2 (14)	4 (31)	5 (38)
Patients with ≥ 1 Treatment-Related Toxicity	*4 (29)*	*2 (14)*	*4 (31)*	*4 (31)*
Blood Bone Marrow: Neutrophils	3 (21)	2 (14)	4(31)	4 (31)
Treatment-Related	*3 (21)*	*2 (14)*	*5 (38)*	*3 (23)*
Pulmonary: Dyspnea	0	0	1 (8)	0
Pain: Abdominal Pain or Cramping	0	0	1 (8)	0
Hepatic: Alkaline Phosphatase	1 (7)	0	0	0
Treatment-Related	*1 (7)*			
Cancer Related	0	0	0	1 (8)
Infection Febrile Neutropenia Febrile Neutropenia	0	0	0	1 (8)
Treatment-Related	*0*	*0*	*0*	*1 (8)*
Pulmonary: Pneumothorax	0	0	0	1 (8)

Source data: Summary Tables 22.1 and 22.3

Table 22.2 summarizes treatment-emergent toxicities/AEs and their relationship to study drug. A listing of all toxicities and AEs is presented in Listing 21.0.

Treatment-emergent serious toxicities/AEs were reported for 2 (14%) patients in the ABI-007 group and 5 (38%) patients in the Taxol group (Summary Table 22.4). The most frequently reported treatment-emergent serious toxicity/AE (per NCI CTC) was Blood Bone Marrow: Neutrophils reported for 2 (14%) patients in the ABI-007 group and 4 (31%) in the Taxol group. The other serious toxicities (reported for 1 [8%] patient each in the Taxol group) were Cancer Related, Infection Febrile Neutropenia: Febrile Neutropenia, and Pulmonary: Pneumothorax.

Summary Table 22.5 summarizes treatment-emergent serious toxicities/AEs and their relationship to study drug. The most frequently reported treatment-related (possibly, probably, or definitely related) treatment-emergent serious toxicity AE was blood/bone marrow - neutrophils, reported for 2 (14%) patients in the ABI-007 group and 3 (23%) patients in the Taxol group.

Patients with serious toxicities or SAEs are listed in Summary Table 22.32.

Toxicities AEs that led to premature discontinuation of study drug were reported for 3 (23%) patients in the Taxol group (Summary Table 3.0); the reasons for discontinuation were grade 2 elevated alkaline phosphatase (possibly related to treatment), grade 3 malignant neoplasm progression (not related to treatment), and grade 3 elevated ALT and AST (possibly related to treatment). No patients in the ABI-007 group discontinued for unacceptable toxicity or progressive disease with unacceptable toxicity. Patients with toxicities or AEs that led to premature discontinuation of study drug are listed in Summary Table 22.33.

There were no on-study deaths (Summary Tables 3 and 22.34).

Narratives for SAEs are attached in Appendix 3.

Conclusions:

- Toxicities AEs in this study were consistent with this patient population and indicated no additional safety concerns relating to ABI-007 administration at 260 mg m^2.
- The clearance and volume of distribution for ABI-007 were approximately 50% more than those of Taxol, and can be explained by the entrapment of paclitaxel by Cremophor micelles.
- The C_{max} for ABI-007 was 6.8-fold higher than that of Taxol and was due to the higher dose and shorter infusion duration for ABI-007.
- Pharmacokinetics of ABI-007 were linear with respect to dose (when analyzed with data from other clinical trials).

Date of the Report: *6 Oct 2004*

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**21,660**	**Brand Name**	**Abraxane**
OCPB Division (I, II, III)	**I**	**Generic Name**	***nab* paclitaxel**
Medical Division	**Oncology**	**Drug Class**	antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization.
OCPB Reviewer	**Angela Yuxin Men, M.D., Ph.D.**	**Indication(s)**	**Metastatic breast cancer**
OCPB Team Leader	**Brian Booth, Ph.D.**	**Dosage Form**	**100 mg paclitaxel + 900 mg Albumin Human , USP/vial, Final Conc: 5 mg/mL**
		Dosing Regimen	**260 mg/m^2 inf 30 min every 3 wk**
Date of Submission	**Mar 19, 2004**	**Route of Administration**	**IV infusion**
Estimated Due Date of OCPB Review	**Oct., 2004**	**Sponsor**	**American Science, Inc.**
PDUFA Due Date		**Priority Classification**	**Standard**
i. Division Due Date	**Dec., 2004**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x	8	8	
I. Clinical Pharmacology				
Mass balance:	x	1	1	
Isozyme characterization:	x			
Blood/plasma ratio:				
Plasma protein binding:	x	1	1	
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-	NA			
single dose:				
multiple dose:				
Patients-				
single dose:	NA			
multiple dose:	x	3	3	
Dose proportionality -				
fasting / non-fasting single dose:	NA			
fasting / non-fasting multiple dose:	x	1	1	
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				

In-vitro:	x			
Subpopulation studies -				
ethnicity:	x	1	1	
gender:				
pediatrics:				
geriatrics:	x	1	1	
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:	x	3	3	
Phase 3:	x	1	1	
PK/PD:	NA			
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -	NA			
Data rich:				
Data sparse:				
II. Biopharmaceutics	NA			
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies	NA			
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	x			
Total Number of Studies		20	20	

a. Filability and QBR comments		
ii.	"X" if yes	**Comments**
iii. Application filable?	Yes	
iv. Comments sent to firm?	Yes	Plasma/blood concentration needed
QBR questions (key issues to be considered)	1) **Hepatic impairment patient** 2) **Drug-drug interaction** 3) **PK/PD correlation**	
Other comments or information not included above		
Primary reviewer Signature and Date	**Angela Yuxin Men**	
Secondary reviewer Signature and Date	**Brian Booth**	

CC: NDA 21-660, HFD-850(Electronic Entry or Lee), HFD-XXX(CSO), HFD-860(TL, DD, DDD), CDR (B. Murphy)

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Angela Men
1/3/05 01:20:16 PM
BIOPHARMACEUTICS

Brian Booth
1/4/05 03:01:11 PM
BIOPHARMACEUTICS