

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

21-660

APPLICATION NUMBER:

PHARMACOLOGY REVIEW(S)



DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 21, 660
SERIAL NUMBER: 000
DATE RECEIVED BY CENTER: 03/07/04
PRODUCT: ABI-007
INTENDED CLINICAL POPULATION: —
SPONSOR: American Bioscience, Inc.
DOCUMENTS REVIEWED: Electronic submission
REVIEW DIVISION: Division of Oncology Drug Products (HFD-150)
PHARM/TOX REVIEWER: Margaret E. Brower, Ph.D.
PHARM/TOX SUPERVISOR: John Leighton, Ph. D.
DIVISION DIRECTOR: Richard Pazdur, M.D.
PROJECT MANAGER: Sheila Ryan

Date of original NDA review submission to Division File System (DFS): 12/17/04

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Executive Summary

I. Recommendations

A. Recommendation on Approvability: Approve

B. Recommendation for Nonclinical Studies: Approve

C. Recommendations on Labeling: See separate labeling review

II. Summary of Nonclinical Findings

A. Brief Overview of Nonclinical Findings

Abraxane is composed of a Cremophor-free formulation of paclitaxel formulated in human serum albumin. The name Abraxane refers to the clinical formulation of the drug product used in Phase 3 studies, which is to be used commercially. This name refers to the natural biosource material, *T. media*, and a ratio of 1:9:: paclitaxel: human serum albumin. Other biosource materials (manufactured by differing suppliers) of the drug used for pre-clinical and earlier clinical trials include paclitaxel. Suppliers of human serum albumin and ratios of paclitaxel to human serum albumin have also varied during the development of this Taxol analog. Names for the drug used for pre-clinical studies with these varying biosource and human serum albumin concentrations are known as Capxol and ABI-007. Pre-clinical pharmacokinetic studies comparing the differing biosource formulations and differing paclitaxel to HSA ratios have indicated only minor changes which would not significantly impact the comparative toxicity of the drug. However, since the natural biosource was utilized for Phase 3 studies and will be used commercially, it should be noted that this ABI-007 biosource exhibited a slightly higher systemic exposure, with an extended half-life compared to the biosources.

In general, acute toxicity and lethality of ABI-007 were significantly reduced as compared to Taxol, based on comparative lethal doses and MTDs. However, renal toxicity was observed in multiple toxicology studies with ABI-007-dosed rodents. Single-dose studies with ABI-007 in rats indicated renal toxicity at doses >540mg/m². In these studies, lethality was observed at doses >720mg/m² and myelosuppression was reduced compared to Taxol. Rats administered ABI-007 exhibited swollen nerve root axons of the spinal cord at 540mg/m², and urinary bladder hyperplasia, kidney fibrosis, adrenal hyperplasia, and testicular atrophy at doses ≥54mg/m²; these findings were not observed with concurrently administered Taxol animals. In rodent pharmacokinetics studies, ABI-007 appears to be rapidly distributed to tissues with a greater volume of distribution and longer serum half-life compared to Taxol.

Toxicology studies in dogs, and possibly swine were complicated by the immunological reaction of the human albumin to these animal models. Even so, neurotoxicity of ABI-007 in dogs appeared to be enhanced compared to that of Taxol.

Abraxane is embryotoxic and fetotoxic when administered to rats at doses ≥6mg/m², (approximately 0.02 of the daily maximum recommended human dose on a mg/m² basis) on gestation days 7-17. Significant changes in reproductive parameters included increase of early and late resorptions (4.5 fold), reduction in litter size and live fetuses (up to 3-fold), significant reduction in fetal BW and significant increase in numbers of fetuses with abnormalities. All fetuses were born dead or resorbed at 24mg/m² in this study. Biologically significant fetal anomalies included fused digits, bulging eyes, folded retinas, microphthalmia, dilation of brain ventricles, septal defects in heart vasculature, fused lungs, small eye sockets, presence of extra cervical ribs, and incomplete or absent ossification of ribs and sternum. Eye anomalies and extra cervical ribs were also observed at the lowest dose tested, 3mg/m². In another study, significant changes in reproductive parameters included significantly reduced sperm count and sperm motility, absence of implantations and viable embryos, absence of fertility index, significant reduction of dams with viable fetuses, and maternal lethality. Testicular atrophy/degeneration has also been observed in single-dose toxicology studies in rodents administered Abraxane at ≥54mg/m² and dogs administered 175mg/m².

B. Pharmacologic Activity

The effects of Taxol and ABI-007 on tumor free survival and tumor growth rate were compared for HT29 colon tumor, PC-3 prostate tumor, NCI-H522 lung tumor, SK-OV-3 ovarian tumor and MX-1 mammary tumor. Abraxane

was less toxic in tumor-bearing mice as measured by MTDs and LD₅₀. The LD₅₀ was calculated to be 47 and 30mg/kg/d for ABI-007 and Taxol, respectively. Antitumor activity of ABI-007 was similar to that of Taxol in some of these studies at these dose levels; in other studies, antitumor of ABI-007 was superior to that of Taxol. In a different study, the binding of ABI-007 to albumin, microtubules, and endothelial cells appeared to be superior to that of Taxol.

C. Nonclinical Safety Issues Relevant to Clinical Use

The incidence of Grade 3 sensory neuropathy was greater in Abraxane-treated patients in the Phase 3 comparative study of Abraxane vs. Taxol with lower frequency of neutropenia with Abraxane. Neurotoxicity appears to follow a similar pattern preclinically, although dog studies were complicated by the immunological reaction of the human serum albumin component of ABI-007. Differences in neurotoxicity between Abraxane and Taxol therapy have been addressed clinically. Testicular atrophy/degeneration was observed in multiple studies with Abraxane. Abraxane is embryotoxic and fetotoxic to rats at doses of 0.05 the maximum daily recommended human dose on a mg/m² basis. These findings have been addressed in the label. A study was submitted which justified the increase in shelf-life specification of _____ impurity _____ from _____

III. Administrative

A. Reviewer signature: _____

B. Supervisor signature: Concurrence - _____

Non-Concurrence - _____
(see memo attached)

C. cc: list:

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 21,660

Review number: 1

Sequence number/date/type of submission:

Information to sponsor: Yes (X) No ()

Sponsor: American BioScience, Inc, Santa Monica, CA

Manufacturer for drug substance :

Previous suppliers of paclitaxel for ABI-007:

Current supplier of paclitaxel for ABI-007:

— (natural biosource, *T. media*)

Sources of Human Serum Albumin (HSA): —

Current supplier of Human Serum Albumin: —

Reviewer name: Margaret E. Brower, Ph.D.

Division name: Oncology

HFD #: 150

Review completion date: December 1, 2004

Drug:

Trade name: Abraxane (previous name: Capxol)

Generic name: paclitaxel protein-bound particles for injectable suspension

Code name: ABI-007

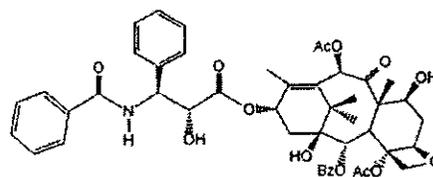
Chemical name: 5β, 20-epoxy-1, 2α, 4,7β, 10β, 13α-hexahydroxytax-11-en-9-one-4, 10-diacetate-2-benzoate-13-ester with (2'R, 3'S)-N-benzoyl-3-phenylisoserine

CAS registry number: 33069-62-4

Mole file number: N/A

Molecular formula/molecular weight: C₄₇H₅₁NO₁₄ /853.91

Structure:



Relevant INDs/NDAs/DMFs: IND 55,974 IND — IND — DMF — NDA 20262,
NDA — .ND 55,974

Drug class: cytotoxic

Intended clinical population: —

Clinical formulation:

Drug product/ formulation components (50mL vial):

Component	Concentration
Paclitaxel	100mg
Human serum albumin, USP	900mg

For administration, each vial is reconstituted with 20mL 0.9% Sodium Chloride Injection, USP, to give a suspension of fine particles containing 5mg paclitaxel/mL, pH

Route of administration: iv, 30m infusion of 260mg/m² q3w

Disclaimer: Tabular and graphical information are constructed by the reviewer from the sponsor's submission unless cited otherwise.

Data reliance : Except as specifically identified below, all data and information discussed below and necessary for approval of NDA # 21,660 are owned by American Bioscience, Inc. or are data for which American Bioscience, Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA # 21,660 that American Bioscience, Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that American Bioscience, Inc. does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA # 21,660.

Studies reviewed within this submission:Pharmacology

A069.1	Anticancer efficacy evaluation of American Bioscience compound ABI-007 against HT29 human tumor xenograft in athymic nude mice
A069.2	Comparison of effects of ABI-007 and Taxol in athymic nude mice with PC-3 human prostate tumor xenografts
A069.3	Comparison of effects of ABI-007 and Taxol in athymic nude mice with NCI-H522 lung tumor xenografts
A069.4	Anticancer efficacy evaluation of American Biosciences compound ABI-007, ABI-007HC and ABI-007LC against SK-OV-3 human ovarian tumor xenograft in athymic nude mice
SRI-LIF-97-171-9024-2	Toxicity determination and efficacy studies of VivoRx compounds Capxol VR-3 and Capxol VR-4
BIO-EL-1	Binding of paclitaxel to albumin, microtubules, and cells. Inhibition of binding by Cremophor-EL and comparative analysis of ABI-007 vs Taxol

Pharmacokinetics

A590.1	Distribution of [³ H]-labelled ABI-007 and Taxol in tumor bearing mice
A590.1.2	Distribution of [³ H]-labelled ABI-007 and Taxol in female tumor bearing mice
P1096001	Blood kinetics and tissue distribution of paclitaxel following a single intravenous dose of Capxol in the rat
P0202002	Pharmacokinetics and metabolism of ³ H-ABI-007 and Taxol following a single intravenous dose in the rat
NP001106	Blood kinetics study on 3 formulations of ABI-007 following a single intravenous dose in rabbits at 50mg/kg
P0297003	Blood kinetics of ³ H-paclitaxel derived radioactivity following single intravenous doses in the rat at 9, 30, 90 and 12-mg/kg
P0303014	Blood kinetics study comparing 3 biosources of paclitaxel in ABI-007 following a single intravenous dose in the rat at 50mg/kg

Toxicology

PR-0002	Pilot study of myelosuppression in rats with Capxol and Taxol following a single intravenous administration
PR-0003	Determination of the LD ₅₀ in mice for Capxol and Taxol following a single intravenous administration
PR-0004	LD ₅₀ of ABI-007 and Taxol following multiple iv administrations
PR-0007	Investigation of dose response to myelosuppression in rats following intravenous administration of Capxol
P0397006	Determination of the toxicity in rats of Capxol and Taxol following a single intravenous administration
P0897001	Fourteen day acute intravenous toxicity study of Capxol in beagle dogs
P0997006	Fourteen day acute intravenous toxicity study of Capxol in beagle dogs
LY-CHRON-001	Toxicity of systemic delivery of nanoparticle paclitaxel (ABI-007) in swine

Reproductive Toxicology

4701-001	Intravenous fertility and general reproduction toxicity of paclitaxel in male rats
4701-002	Intravenous developmental toxicity study of paclitaxel in rats

Special Toxicology

P0603001	Comparison of the 28-day toxicity of ABI-007 following a single intravenous dose of drug product containing usual and elevated levels of _____ in rats
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Studies not reviewed within this submission:

Drug History:

Abraxane is composed of a Cremophor-free formulation of the approved cytotoxic agent paclitaxel formulated in human serum albumin. Paclitaxel promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. The sponsors of Abraxane (also known as Capxol and ABI-007) have used multiple suppliers of paclitaxel, as well as human serum albumin since the IND was originally discussed and submitted in 1998. Three biosource materials have been studied during development of Abraxane: _____ and natural biosource. Phase 3 studies were conducted using the natural biosource, *Taxus media*, manufactured by _____ which is to be used commercially. The _____ drug product was also used as the source of several Phase 1 and Phase 2 studies. Three other sources of paclitaxel have been used in the development of the drug product:

- 1- Paclitaxel produced at _____ was used in pre-clinical and several Phase 1 and Phase 2 studies.
- 2- _____ was the supplier of paclitaxel in the original IND (IND 55,974) manufactured and used in Phase 1 clinical studies and pre-clinical studies.

3- _____, provided a single lot of technical grade paclitaxel used in exploratory pharmacodynamics studies in mice.

Sources of the (HSA) human serum albumin have also changed during the development of Abraxane. The HSA supplied by _____ (current supplier) were subsequently utilized.

Pre-clinical pharmacokinetic studies comparing the differing biosource formulations and differing paclitaxel to HSA ratios have indicated only minor changes which would not significantly impact the comparative toxicity of the drug.

**APPEARS THIS WAY
ON ORIGINAL**

2.6.2 PHARMACOLOGY:**2.6.2.1 Brief summary**

The efficacy of Taxol and ABI-007 were compared as to their effects on tumor free survival and tumor growth rate for HT29 colon tumor, PC-3 prostate tumor, NCI-H522 lung tumor, SK-OV-3 ovarian tumor and MX-1 mammary tumor (See table below). ABI-007 was less toxic in tumor-bearing mice as measured by MTDs and LD₅₀. The LD₅₀ was calculated to be 47 and 30mg/kg/d for ABI-007 and Taxol, respectively. Antitumor activity of ABI-007 was similar to that of Taxol in some of these studies at these dose levels; in other studies, antitumor of ABI-007 was superior to that of Taxol. In a different study, the binding of ABI-007 to albumin, microtubules, and endothelial cells appeared to be superior to that of Taxol.

2.6.2.2 Primary pharmacodynamics:

Study #	Animal model	Design	Results
A069.1	NCr-nu mice w/ HT29 human colon tumor	Multiple iv dose – efficacy of increasing doses of ABI-007 or Taxol	MTD: 20mg/kg ABI-007, 13.4mg/kg Taxol. Antitumor activity of ABI-007 superior at specified doses
A069.2	NCr-nu mice w/ PC-3 human prostate tumors	Multiple iv dose – efficacy of increasing doses of ABI-007 or Taxol	MTD: 20mg/kg ABI-007, 13.4mg/kg Taxol. Antitumor activity of ABI-007 similar to Taxol
A069.3	NCr-nu mice w/ NCI-H522 human lung tumors	Multiple iv dose – efficacy of increasing doses of ABI-007 or Taxol	MTD: 20mg/kg ABI-007, 13.4mg/kg Taxol. High rate of response to both ABI-007 and Taxol
A069.4	NCr-nu mice w/ SK-OV-3 human ovarian tumors	Multiple iv dose – efficacy of increasing doses of 3 ABI-007 formulations or Taxol	MTD: 20mg/kg ABI-007, 13.4mg/kg Taxol. All 3 ABI-007 formulations superior to Taxol (formulations differed in ratio of paclitaxel to albumin)
SRI-LIF-97-171.9024.2	NCr-nu mice w/ MX-1 human mammary tumors	Multiple iv dose – efficacy of increasing doses of ABI-007 or Taxol	Tumor-free survival for ABI-007 treated mice superior MTD differs for this study ABI-007 (45mg/kg/d) 100% survival to 103d Taxol (30mg/kg/d) 40% survival to 103d Control: no survival after 47d

Several pharmacology studies were performed to investigate efficacy. These studies indicated that tumor accumulation of ABI-007 was higher than that of Taxol. Mice administered paclitaxel formulated as ABI-007 exhibited decreased plasma AUC and increased tumor AUC compared to mice administered paclitaxel formulated as Taxol.

Study # BIO-EL-1 Binding of paclitaxel to albumin, microtubules, and cells. Inhibition of binding by Cremophor-EL and comparative analysis of ABI-007 versus Taxol

The binding of paclitaxel to human serum albumin, microtubules and endothelial cells were inhibited by clinical levels of Cremophor/ethanol. The binding of the ABI-007 formulation to human serum albumin, microtubules and endothelial cells appeared to be superior to that of Taxol.

Mechanism of action: The mechanism of action of ABI-007 can be described as the facilitation of active transport of albumin-bound paclitaxel into a tumor site by an albumin receptor. While targeting the vascular endothelium, the intratumoral concentration of the drug is increased by utilizing an amplification effect imparted by angiogenesis, resulting in increased efficacy while expecting to minimize exposure to normal tissue.

Drug activity related to proposed indication: no specific data submitted preclinically

2.6.2.3 Secondary pharmacodynamics No data submitted

2.6.2.4 SAFETY PHARMACOLOGY:

Neurological effects: No safety pharmacology studies submitted

Cardiovascular effects: No safety pharmacology studies submitted

Pulmonary effects: No safety pharmacology studies submitted

Renal effects: No safety pharmacology studies submitted

Gastrointestinal effects: No safety pharmacology studies submitted

Abuse liability: No safety pharmacology studies submitted

Other: No safety pharmacology studies submitted

2.6.2.5 Pharmacodynamic drug interactions No studies submitted

2.6.3 PHARMACOLOGY TABULATED SUMMARY

[See above summary]

2.6.4 PHARMACOKINETICS/TOXICOKINETICS:

2.6.4.1 Brief summary

Pre-clinical studies indicate that ABI-007 is similar to Taxol in several parameters. Metabolism and excretion are similar to that of Taxol; excretion is primarily fecal and these drugs are largely eliminated within 48h of dosing. However, ABI-007 exhibits a greater volume of distribution and longer half-life compared to Taxol. Distribution is rapid with highest tissue distribution in prostate, liver, seminal vesicles, lung, pancreas, spleen, GI and kidney; in a separate study, tissue concentration was highest in liver, testes and ovaries. In general, tissues with highest ³H-ABI-007 derived radioactivity concentrations are involved in metabolism/excretion, contain a high proportion of dividing cells, or are highly perfused. Mice administered paclitaxel formulated as ABI-007 exhibited decreased plasma AUC and increased tumor AUC compared to mice administered paclitaxel formulated as Taxol.

Similar pharmacokinetics were exhibited for differing albumin:paclitaxel ratios of ABI-007 and differing formulations using natural, _____ biosource for ABI-007. However, since the natural biosource was utilized for Phase 3 studies and will be used commercially, it should be noted that this ABI-007 biosource exhibited a slightly higher systemic exposure, with an extended half-life compared to the _____ biosources. For this study, study authors indicate measurement of whole blood paclitaxel.

2.6.4.2 Methods of Analysis

[See individual study reviews]

2.6.4.3 Absorption (incorporated in studies below)

2.6.4.4 Distribution

Study title: Blood kinetics and tissue distribution of paclitaxel following a single intravenous dose of Capxol in the rat

Key Findings:

- Rapid distribution of ³H-Capxol from blood to tissues
- Tissue distribution highest: prostate, liver, seminal vesicles, lung, pancreas, spleen, GI, kidney
- AUC_{0-24h} 60% of total radioactivity are metabolites

Study no: P1096001

Volume #, and page #: vol 2, p. 1

Conducting laboratory and location: —

Date of study initiation: November 18, 1996

GLP compliance: yes

QA report: yes (X) no ()

Drug, lot #, radiolabel, and % purity: ³H-Paclitaxel, lot #124-131-0023, —, [portion of ³H-Paclitaxel formulated to ³H-Capxol], radiochemical purity — onradiolabeled paclitaxel, lot 960911, —

Formulation/vehicle: diluted with 0.9% NaCl (Taxol vehicle not specified, although historically diluted with 0.9%NaCl).

Dosing:

Species/strain: rat/Sprague Dawley (males only)

#/sex/group (main study): 10

Satellite groups used for toxicokinetics: none

Age: 7-8w

Weight: not provided

Doses in administered units: 5.1mg/kg Capxol (84.6uCi/g); 4.9mg/kg Taxol (radiolabeled; details unspecified)

Specific activity: 62,909dpm/ug (³H-paclitaxel in dosing solution)

Route, form, volume, and infusion rate: iv, dose volume 1.67mL/kg

Method of Analysis: LC/MS

Blood collection: 2, 5, 15, 30m, 1, 2, 3, 4, 5, 6, 8, 12, 24h

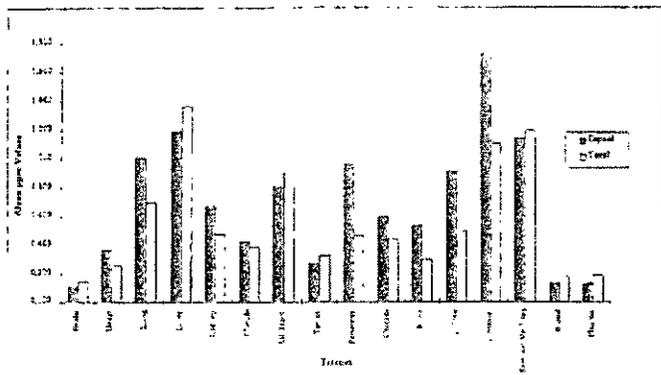
Total radioactivity and parent compound level following administration of Capxol ↓ bi-phasicly over 5h post-dose followed by linear ↓ to 24h. AUC_{0-24h} exposure for parent paclitaxel was 60% of total radioactivity due to metabolism. The following tissues exhibited the highest total radiolabel distribution (up to 5X paclitaxel blood level): prostate, liver, seminal vesicles, lung, pancreas, spleen, GI tract, kidney (See Sponsor's graph below). With exception of pancreas, tissues with highest concentrations are involved in metabolism/excretion (liver, GI, kidney), contain a high proportion of dividing cells (seminal vesicles, prostate), or are highly perfused (lung and spleen).

Blood levels following Capxol administration were lower than following similar Taxol dose, indicating more rapid distribution out of blood (2m post-dose sample). Similar pattern of metabolism were observed for both Capxol and Taxol. However, the rate of metabolism was significantly slower for Capxol as 44% of blood reactivity remains as paclitaxel 24h post-dose, compared to 22.4% for Taxol. Predominantly fecal excretion was exhibited with both drugs, with only minimal excretion via urine.

Treatment	AUC ₀₋₂₄ (ug eq.hr/mL)	Cmax (ug eq/mL)	t _{1/2β} (h)
Paclitaxel concentration			
³ H-Capxol	3.7	4.0	11.4
³ H-Taxol	5.4	11.8	7.2
Total Radioactivity			
³ H-Capxol	6.1	4.2	19
³ H-Taxol	10.2	13.5	19.7

Tissue radioactivity levels were higher 24h following Capxol administration as compared to Taxol administration for 9 of 14 assayed tissues. Tissue/blood ratios were higher for Capxol-dosed animals with lower paclitaxel-blood levels, indicating rapid distribution of Capxol from blood to tissues.

Tissue Radioactivity Levels Expressed as ppm Paclitaxel Equivalents
24 Hours Following a Single Intravenous Administration of
³H-Taxol™ at 4.9 mg/kg or ³H-Capxol™ at 5.1 mg/kg



Summary:

Total radioactivity of ABI-007 decreased biphasically over 5h post-dose followed by linear decrease to 24h. The distribution of ³H-Capxol from blood to tissues appears to be rapid; tissue distribution was highest in prostate, liver, seminal vesicles, lung, pancreas, spleen, GI and kidney. Metabolites comprised 60% of Capxol AUC_{0-24h} total radioactivity. Metabolism was slower for ³H-Capxol as compared to ³H-Taxol, with 44% of blood radioactivity remaining as paclitaxel 24h post-dose, compared to 22% for ³H-Taxol.

2.6.4.5 Metabolism (Studies grouped as Metabolism/Excretion)

2.6.4.6 Excretion

Study title: Blood kinetics of ³H-paclitaxel derived radioactivity following single intravenous doses of Capxol in the rat at 9, 30, 90, and 120mg/kg

Note: Doses administered to animals varied from doses indicated in study title (see below).

Key study findings:

- ³H-ABI-007 slowly metabolized in vivo; 7-19% unchanged at 24h
- Exposure increases disproportionately with increasing dose

Study no: P0297003

Volume #, and page #: Vol 2, p, 1; Electronic submission

Conducting laboratory and location:

Date of study initiation: April 2, 1997

GLP compliance: yes

QA report: yes (X) no ()

Drug, lot #, radiolabel, and % purity:

³H-paclitaxel, lot# : 124-131-0028 (— purity), 127-097-0053 (— , purity);
nonradiolabeled paclitaxel: lot# 960911. (— purity; nonradiolabeled Capxol: lot# A5-05, purity not provided

³H-Capxol batches # A4-75, A5-03 formulated from above paclitaxel; noted purity —

Dose/group (5M): paclitaxel doses: 9.1, 26.4, 116.7, 148.1mg/kg

radioactive dose: 38.6, 35.6, 39.3, 36.8uCi respectively

Blood sample collection: 2, 5, 15m, 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24h post-dose

24h HPLC analysis indicated 7-19% of blood radioactivity as unchanged paclitaxel, indicating a slow rate of metabolism. Exposure increases disproportionately with increasing dose, suggesting saturation of clearance.

Dose (mg/kg)	AUC _{0-24h} (ug•eq hr/mL)	Normalized AUC	Cmax (ug•eq/mL)	t _{1/2} (h)
5.1	6.1	1.19	4.2	19
9.1	11.5	1.26	7.2	22.3
26.4	43.5	1.65	29.5	16
116.7	248.9	2.13	283.3	8.5
148.1	355.3	2.40	414.2	9.3

Study title: Pharmacokinetics and metabolism of 3H-ABI-007 and Taxol following a single intravenous dose in the rat

Key study findings:

- Highest tissue distribution in liver, testes and ovaries, ³H-ABI-007; lung, liver, testes, ³H-Taxol
- Primary route of excretion: feces
- ³H-ABI-007 excreted in urine as metabolite, feces as paclitaxel

Study no: P0202002

Volume #, and page #: Vol 2, p.1; Electronic submission March, 2004

Conducting laboratory and location: _____

Date of study initiation: July 24, 2002

GLP compliance: yes

QA report: yes (X) no ()

Drug, lot #, radiolabel, and % purity: ³H-ABI-007, ³H-paclitaxel (lot# 424-218-003, 424-242-0147)

Non-radiolabeled paclitaxel (lot#15359/N) manufactured by _____, purity final drug _____

³H-Taxol as control

Formulation/vehicle: reconstituted with 0.9% NaCl

Dosing:

Species/strain: rat/Sprague Dawley

#/sex/group (main study): 5 (2 misdosed animals replaced)

Satellite groups used for toxicokinetics or recovery: none

Age: 7-8w M; 11-12w F

Weight: 182-223g

Doses in administered units: ³H-Taxol: 5.93mg/kg M, 5.98mg/kg F; ³H-ABI-007: 7.69mg/kg M, 7.79mg/kg F

Route, volume, and infusion rate: iv, dose volume 5ml/kg, final diluted concentration: 1mg paclitaxel/mL

Method of Analysis: LC/MS (measured ³H-paclitaxel derived from ABI-007 and Taxol)

Urine/fecal sample collection: 0-4, 4-8, 8-12, 12-24, 24-36, 36-48, 48-72, 72-96, 96-120h following dosing

The highest concentration of ³H-ABI-007 derived radioactivity was found in the liver, testes and ovaries; distribution was similar in males and females (See Sponsor's graphs below). In comparison, the highest concentration of ³H-Taxol derived radioactivity was found in the lung, liver and testes. As with previous studies, the primary route of excretion was the feces; fecal excretion was 82 and 78% of administered dose of ABI-007 in males and females, respectively, between 8-120h (compared to 77 and 75% in Taxol-treated males and females for the same time interval). The majority of this fecal radioactivity was excreted within 48h following dosing. Comparative excretion in the urine was 8.10% and 12.45% in males (between 4 and 120h) and females (between 0 and 120h) administered Taxol, respectively, and 9.51% and 14.07% in males and females administered ABI-007, respectively for the same time intervals. Little radioactivity was observed in tissue samples after 5d post-dose.

Comparison of Radioactive Residues in Various Tissues of Sprague-Dawley Rats Following Intravenous Administration of ¹⁴C-Taxol and ³H-ABI-007
M. K. Kim

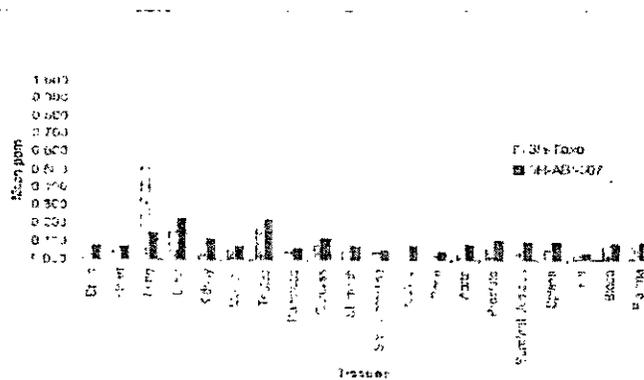
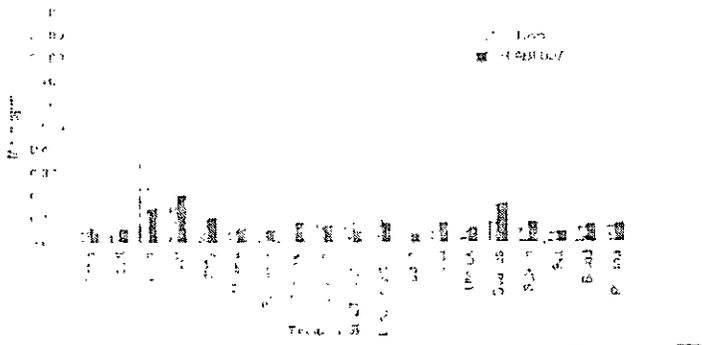


Figure 2: Comparison of Radioactive Residues in Various Tissues of Sprague-Dawley Rats Following Intravenous Administration of ¹⁴C-Taxol and ³H-ABI-007
M. K. Kim



2.6.4.7 Pharmacokinetic drug interactions No studies submitted

2.6.4.8 Other Pharmacokinetic Studies

Study title: Blood kinetics study comparing three biosources of paclitaxel in ABI-007 following a single intravenous dose in the rat at 50mg/kg

Note: Natural biosource to be utilized commercially

Key study findings:

- Similar pharmacokinetics for paclitaxel from 3 different biosources
- Exposure of paclitaxel slightly higher for natural biosource
- Terminal t_{1/2} of paclitaxel extended w/ natural biosource
- C_{max} of paclitaxel slightly higher for natural biosource

Study no: P0303014

Volume #, and page #: Vol 2, p. 1, Electronic submission: March, 2004

Conducting laboratory and location:

Date of study initiation: April 21, 2003

GLP compliance: yes

QA report: yes (X) no ()

Drug, lot #, radiolabel, and % purity: Three ABI-007 paclitaxel formulations, manufactured using differing biosource material:

- #C018-001(Capxol) biosource from
- #C199-004, biosource from
- #C102-005, biosource from

Formulation/vehicle: diluted with 0.9% NaCl

Dosing:

Species/strain: rat/Sprague Dawley (males only)

#/sex/group (main study): 8 (2 animals replaced due to misdosing)

Satellite groups used for toxicokinetics or recovery: none

Age: 8-9w

Weight: 254-280g

Doses in administered units: 50mg/kg

Route, form, volume, and infusion rate: iv, dose volume 5ml/kg, final diluted concentration: 10mg paclitaxel/mL

Method of Analysis: LC/MS

Blood collection: 5, 15, 30m, 1, 2, 4, 8, 24, 48, 72h

ABI-007 biosource	Dose (mg/kg)	AUC last (ng x h/mL) (normalized value)	AUC inf (ng x h/mL) (normalized value)	Terminal t _{1/2} (h)	Cmax (ng/mL) (normalized value)
(natural)	50.5	48022 (951)	48122 (953)	7.8	26214 (519)
	49.5	50072 (1012)	50164 (1013)	6.1	24129 (487)
	50.7	51915 (1024)	52046 (1027)	9.6	24829 (490)

The 3 formulations appeared to have similar pharmacokinetic parameters. Normalized AUC indicate that exposure was slightly higher with the natural biosource and lower with the biosource. Terminal t_{1/2} was also extended with the natural biosource formulation. Normalized Cmax indicates slightly higher levels in the formulation at 72h following dosing, with paclitaxel levels in the formulation slightly lower.

An earlier study comparing 3 formulations of ABI-007 was conducted in November, 2000 (Blood kinetics study on three formulations of ABI-007 following a single intravenous dose in the rat at 50mg/kg; study #NP001106). However, since the 3 formulations were only identified by lot #, which were traced to , a written review of this study was not completed. The study author indicated that the 3 formulations had similar pharmacokinetics.

2.6.4.9 Discussion and Conclusions

Pre-clinical studies indicate that ABI-007 is similar to Taxol in several parameters. Metabolism and excretion are similar to that of Taxol; excretion is primarily fecal and is largely completed within 48h of dosing. However, ABI-007 exhibits a greater volume of distribution and longer half-life compared to Taxol. Distribution is rapid with highest tissue distribution in prostate, liver, seminal vesicles, lung, pancreas, spleen, GI and kidney; in a separate study, tissue concentration was highest in liver, testes and ovaries. In general, tissues with highest ³H-ABI-007 derived radioactivity concentrations are involved in metabolism/excretion, contain a high proportion of dividing cells, or are highly perfused. Mice administered paclitaxel formulated as ABI-007 exhibited decreased plasma AUC and increased tumor AUC compared to mice administered paclitaxel formulated as Taxol.

Similar pharmacokinetics were exhibited for differing albumin:paclitaxel ratios of ABI-007 and differing formulations using natural, _____, biosource for ABI-007. However, since the natural biosource was utilized for Phase 3 studies and will be used commercially, it should be noted that this ABI-007 biosource exhibited a slightly higher systemic exposure, with an extended half-life compared to the _____ biosources. For this study, study authors indicate measurement of whole blood paclitaxel; specifics are not provided.

2.6.4.10 Tables and figures / comparative TK summary

See individual studies for appropriate tables and figures. Toxicokinetics conducted with reproductive toxicity studies indicated significant clearance of ABI-007 within 24h.

**APPEARS THIS WAY
ON ORIGINAL**

2.6.5 PHARMACOKINETICS SUMMARY

Study #	Species	Study design	Results
A590.1	NCr-nu/nu mice w/ MX-1 tumors	Single ABI-007 dose: 21.7mg/kg, 8.7-9 uCi Taxol: 19.5mg/kg, 6.9-8.7uCi	ABI-007: $t_{1/2}$ longer in blood and plasma, V_d increased in blood and plasma, plasma AUC ↓, tumor AUC ↑ compared to Taxol Distribution into RBC to > extent
A590.1.2	NCr-nu/nu mice w/MX-1 tumors	Single 20mg/kg dose of 3H paclitaxel formulated as ABI-007 or Taxol	Decreased V_d for Taxol, plasma AUC ↓, tumor AUC ↑ compared to Taxol
P1096001	Rat	Single dose of 3H paclitaxel formulated as ABI-007 (5.1mg/kg)	Tissue distribution highest: prostate, liver, seminal vesicles, lung, pancreas, spleen, GI, kidney. Metabolism slower for ABI-007
P0202002	Rat	Single dose 3H paclitaxel as: Taxol (5.93mg/kg M, 5.98mg/kg F) ABI-007 (7.69mg/kg M, 7.79mg/kg F)	Highest tissue distribution in liver, testes and ovaries, 3H -ABI-007; lung, liver, testes, 3H -Taxol Fecal excretion primary between 8-120h: 82 and 78% of administered dose of ABI-007 in M and F; 77 and 75% in Taxol-treated M and F Fecal excretion primarily within 48h of dosing
NP001106	Rat	Single dose blood kinetics of 3 formulations of ABI-007 containing human albumin: naclitaxel ratios of	Similar pharmacokinetics for 3 formulations
P0297003	Rat	Single dose blood kinetics and tissue distribution of 3H -ABI-007 at doses of 9.1, 26.4, 116.7, and 148mg/kg	3H -ABI-007 slowly metabolized in vivo; 7-19% unchanged at 24h Exposure increases disproportionately with increasing dose for 3H -Capxol
P0303014	Rat	Single 50mg/kg dose blood kinetics of 3 batches of ABI-007 with different biosource	Similar pharmacokinetics for paclitaxel from 3 biosources, although exposure slightly higher and terminal $t_{1/2}$ of paclitaxel extended with natural biosource C_{max} of paclitaxel slightly higher for biosource

Note:

Three biosource materials were used in the development of Abraxane: _____ and natural biosource paclitaxel. The majority of the pre-clinical studies were conducted using the _____ biosource. The pharmacokinetic study above (P0303014) indicates similar kinetics for the 3 biosource, with minor difference. These data indicate that the natural biosource exhibited a slightly higher systemic exposure, with an extended half-life compared to the _____ biosources. The Phase 3 clinical trial was conducted with the natural paclitaxel biosource for ABI-007, *T media*. This biosource will also be used as the commercial source. See more extensive pharmacokinetics summary above and Drug History, p. 7 of this NDA.

2.6.6 GENERAL TOXICOLOGY:

2.6.6.1 Overall toxicology summary

General toxicology:

Single-dose studies with ABI-007 in rats indicated renal toxicity at doses >540mg/m², lethality at doses > 720mg/m², and reduced myelosuppression compared to Taxol. Comparative lethality studies in mice indicated LD_{10s} of 1116 and 15mg/m², for ABI-007 and Taxol, respectively. In another single-dose toxicity study, rats administered ABI-007 exhibited swollen nerve root axons of the spinal cord at 540mg/m², and urinary bladder hyperplasia, kidney fibrosis, adrenal hyperplasia, and testicular atrophy at doses >54mg/m²; these findings were not observed with concurrently administered Taxol animals.

Administration of a single iv dose of 175mg/m² ABI-007, ABI-007 vehicle, and processed human serum albumin to beagle dogs resulted in CNS toxicity including multifocal granulomatous meningitis, acute congestion and acute hemorrhage of the cerebrum, cerebellum, brainstem, hippocampus and basal ganglia. Many of these CNS effects may have been an immunological reaction of the human serum albumin to dogs, or a combination of the HSA and other residual solvents (e.g. _____). It should be noted that an increased incidence of congestion of the hippocampus and testicular atrophy/degeneration was exhibited in dogs administered Capzol relative to Capzol vehicle control and "processed" human serum albumin. A second study was conducted with the same lot of ABI-007 in beagle dogs at the same dose. Histopathology was not conducted, and CNS effects were not evident. However, soft brain tissue and increased CSF were noted in Capzol-treated males relative to Capzol-treated females. No explanation was provided for the difference in findings, or why the extent of hypersensitivity was not similar in both studies.

Administration of a single iv dose of 22-132mg/m² ABI-007 to Yorkshire swine resulted in increased body temperature, leukopenia, and severe dose-related neutropenia. HD animals exhibited emesis, loose stool, depression and loss of appetite. Some of these findings may be a result of an immunological reaction to the HSA, as with many results noted in the dog studies.

Genetic toxicology: none

The genetic toxicology data constitutes prior approved FDA findings for Taxol, as described in the drug's approved labeling. The genetic toxicology portion of the label for Abraxane is identical to that of Taxol, with minor modifications.

Carcinogenicity: none

Reproductive toxicology:

ABI-007 is maternally toxic, embryotoxic and fetotoxic when administered to rats at doses ≥ 6 mg/m², (about 0.02 the daily maximum recommended human dose on a mg/m² basis). Maternal toxicity was observed as a 10 to 52% decrease in body weight for animals administered 6-48mg/m². Significant changes in reproductive parameters included increase of early and late resorptions (4.5 fold), reduction in litter size and live fetuses (up to 3-fold), significant reduction in fetal BW and significant increase in numbers of fetuses with abnormalities. All fetuses were born dead or resorbed at 24mg/m² in this study. Biologically significant fetal anomalies included fused digits, bulging eyes, folded retinas, microphthalmia, dilation of brain ventricles, septal defects in heart vasculature, fused lungs, small eye sockets, presence of extra cervical ribs, and incomplete or absent ossification of ribs and sternum. Eye anomalies and extra cervical ribs were observed at the lowest dose tested, 3mg/m². This dose was not maternally toxic.

In another study, ABI-007 was embryotoxic and fetotoxic when administered to male rats at doses ≥ 42 mg/m² (about 0.16 the daily maximum recommended human dose on a mg/m² basis) that were then bred with untreated female rats. Significant changes in reproductive parameters included reduced sperm production and sperm motility, absence of implantations and viable embryos, absence of fertility index, and significant reduction of dams with viable fetuses.

Testicular atrophy/degeneration has also been observed in single-dose toxicology studies in rodents administered ABI-007 at ≥ 54 mg/m² and dogs administered 175mg/m².

Special toxicology:

_____ is the primary process impurity of ABI-007. In order to justify an increase in shelf-life specification to _____, rats were administered ABI-007 with an enhanced impurity level of _____ compared to ABI-007 with a normal impurity level of _____. RBC, WBC, and platelet counts were increased in animals administered ABI-007 containing the enhanced impurity level. Severe testicular degeneration was exhibited in both ABI-007 groups. Increase in the shelf-life specification for _____ from _____ was approved; changes in the hematological indices were significant in males only. Paclitaxel with enhanced impurity level did not display any overt toxicological change. Hematological indices of both groups recovered within 28 days.

2.6.6.2 Single-dose toxicity

Study title: Determination of the LD50 in mice for Capxol and Taxol following a single intravenous administration

Study no: PR-0003

Reviewed with IND 55,974 (See appendix for review)

Key study findings:

- Capxol LD50 and LD10 = 447.4 and 371.5mg/kg, respectively
- Comparative Taxol LD50 and LD19 = 7.5 and 5.1mg/kg, respectively

Study title: Determination of the toxicity in rats of Capxol and Taxol following a single intravenous administration

Study no.: P0397006

Reviewed with IND 55,974 (See appendix for review)

Doses: 5, 9, 30, 90, 120mg/kg Capxol; 5, 9, 30mg/kg Taxol

- Taxol lethality at 30mg/kg (d4)
- Capxol lethality at 90mg/kg (1/12, d15)
- Piloerection, lethargy, staggering gait all Taxol groups and 90 and 120mg/kg Capxol

Key study findings (not observed in Taxol treated animals):

- Spinal cord/swollen nerve root axons in 1/6 90mg/kg Capxol treated
- BUN levels ↑ in dose-related manner in males administered 30, 90, 120mg/kg Capxol from 1.25 - 2.9-fold concurrent vehicle controls
- Urinary bladder hyperplasia at 30 and 120mg/kg
- Kidney fibrosis/mineralization (may be attributed to Capxol or chloroform component)
- Adrenal hyperplasia at 9, 30, and 90mg/kg
- Atrophy/tubular necrosis of testes, epididymis at 9, 30, 90, 120mg/kg Capxol
- Uterine decidualoma at 120mg/kg

Study title: Pilot study of myelosuppression in rats with Capxol and Taxol following a single intravenous administration

Study no.: PR-0002

Reviewed with IND 55,974 (See appendix for review)

Dose Capxol and Taxol: 5mg/kg

Key study findings:

- Leukopenia (up to 7-fold) of Taxol- and Cremophor vehicle-treated rodents as compared to Capxol and HAS

Study title: Investigation of dose response to myelosuppression in rats following intravenous administration of Capxol

Study no.: PR-0007

Reviewed with IND 55,974 (See appendix for review)

Dose Capxol: 30, 90, 120, 200mg/kg

Key study findings:

- Lethality at 120 (2/3) and 200 (3/3)mg/kg
- Dose-related leukopenia and BW loss
- Polyuria, reported at 90 and 120mg/kg, possibly a result of the chloroform component of Capxol
- Kidney lesions at 90 and 120mg/kg

Study title: Fourteen day acute intravenous toxicity study of Capxol in beagle dogs

Study no: P0997006

Reviewed with IND 55,974 (See appendix for review) Study initiated September, 1997 and completed November, 1997

Animals were administered "unprocessed" (indicated as "Capxol vehicle control") and "processed" HSA, as well as 175mg/m² Capxol+HSA. The "unprocessed" HSA was obtained from a commercial lot of human serum albumin, known as _____, and manufactured by _____

Key study findings:

- Multifocal granulomatous meningitis, acute congestion and acute hemorrhage of the cerebrum, cerebellum, brainstem, hippocampus and basal ganglia observed in dogs administered Capxol vehicle control, Capxol, and processed HSA.
- Increased incidence of acute congestion of the hippocampus in Capxol-treated dogs
- CNS effects may be an immunological reaction of human serum albumin to dogs or a combination of the HSA and other residual solvents (e.g. _____)
- Testicular atrophy/degeneration in Capxol-treated dogs

Comments:

The Capxol administered to dogs in "safe passage" Study # P0997006, with a concentration of 37mg paclitaxel/vial was the same lot number as the Capxol administered with Study # P0897001.(see study below), with a concentration of 30mg paclitaxel/vial. The source of both formulations was _____ acclitaxel, manufactured at _____

As indicated below(Study P0897001) and above (Study P0997006), dogs administered 175mg/m² Abraxane in the two multiple dose dog studies did not exhibit similar findings. The difference in paclitaxel concentration is small, and would not account for these differences. If the CNS effects observed above were the result of an immunological reaction to the human serum albumin, these same effects would be expected in the similar study reviewed below.

Study title: Fourteen day acute intravenous toxicity study of Capxol in beagle dogs

Key study findings:

- Significantly increased WBC, reticulocytes study days 8, 15
- 1/4 dogs soft brain tissue, increased CSF, histopathology not conducted

Study no: P0897001

Volume #, and page #: Vol 3, p. 1; electronic file: March 19, 2004

Conducting laboratory and location: _____

Date of study initiation: August, 1997 (completion September, 1997)

GLP compliance: No signed GLP statement, although study text indicated GLP compliance

QA report: yes (X) no ()

Drug, lot #, and % purity: Capxol (30mg paclitaxel/vial) lot#:97101000, purity not indicated
Formulation/vehicle: Human serum albumin formulation/0.9% NaCl diluent

Methods: No unique aspects identified

Dosing:

Species/strain: Beagle dogs

#/sex/group (main study): 2M, 2F (no vehicle control group)

Satellite groups: none

Age: 9-11 months

Weight: 6.5 – 11.3kg

Doses: 175mg/m² (single dose)

Duration of observation: 14d

Route, volume, and infusion rate: iv, 5mg paclitaxel/mL, infusion rate 1mL/min

Observations	Capxol M	Capxol F
Mortality (daily)	none	
Clinical observations (postdose, daily)	Loose stool, bloody stool, depressed appetite, emesis, depression, slightly depressed body temperature	
Body weight (d1, 8, 15) ^a	↓12% (d8), ↓7% (d15)	↓12% (d8), ↓13% (d15)
Food consumption (daily) ^b	M1: ↓100% d2-4, ↓70% d5 M2: ↓100% d2-7, ↓80% d8	F1: ↓100% d2, 3 F2: ↓100% d2-4, ↓45% d5
Hematology (predose, d8, 15) ^a	WBC: ↑63% (d8), ↑40% (d15) Reticulocytes: ↑15% M, ↑169% F (d8); ↑3-fold M, ↑7-fold F (d15)	
Clinical chemistry (predose, d8, 15)	UR	
Gross pathology (d14) See histopath inventory listing	M1: Lungs: congested; Testes: soft M2: Brain: ↑CSF, soft Testes: Soft, fluid consistency	F1: UR F2: GI: congestion at jejunum
Histopathology	Not performed	

^a As compared to weights measured prior to dosing

^b As compared to FC prior to dosing; days indicated for depressed FC are days following dosing, ie. day2 = 1st day following dosing.

Study title: Toxicity of systemic delivery of nanoparticle paclitaxel (ABI-007) in swine

Key study findings:

- Hypersensitivity pneumonitis may be associated with Human Albumin
- Atrophy of prostate

Note: Paclitaxel may have amplified the immunological reaction of the Human Albumin in swine following administration of ABI-007, manifesting as hypersensitivity pneumonitis. This may be a explanation for the lack of similar changes in the control HSA group administered an HSA dose corresponding to HD ABI-007. Mononuclear cell aggregates of the brain were observed in HSA control and ABI-007- dosed swine.

Dogs also exhibited effects which may be a result of the use of Human Albumin (see studies BTC P0997006 and BTC P0897001).

Study no: LyChron-001

Volume #, and page #: Vol 3, p. 1; electronic file: March 19, 2004

Conducting laboratory and location: American BioScience, Menlo Park, CA

Date of study initiation: not indicated

GLP compliance: No

QA report: yes () no (X) Study narrative indicated performance of study under GLP

Drug, lot #, and % purity: ABI-007, lot#: C101-001, purity not indicated

Formulation/vehicle: Human serum albumin, lot APP00717, → HSA/mg paclitaxel; vehicle control administered 60mgHSA/kg

Methods: No unique aspects identified

Dosing:

Species/strain: Yorkshire swine

#/sex/group (main study): 3 males

Satellite groups: none

Age: not indicated

Weight: 30-35kg

Doses: 1, 3, 6mg/kg [single dose]

Duration of observation: 14d

Route, volume, and infusion rate: iv (auricular vein, iliac artery), volume: 6, 18, 36mL, infusion rate: 10mL/min

Observations	HSA control	1mg/kg	3mg/kg	6mg/kg
Mortality (daily)				1 (d5) ^a
Clinical signs (daily)		UR	diarrhea	D2-8: diarrhea, emesis, depression, depressed appetite
Body weights (daily) ^b		UR	↓10% (d13)	↓14% d5; ↓12% d13
Body Temperature ^b		UR	↑4°C d5 ↑2.5°C d13	↑1-2°C d1-10
Food consumption (daily) ^b		UR	UR	UR
Hematology (predose, 5, 10, 14d) ^b		UR		
WBC (d5)			↓46%	↓47-50%
WBC (d14) ^c			↑32%	↑45%
Neutrophils (d5)			↓90%	↓20%
Neutrophils (d14) ^c			↑30%	↑56%
Clinical chemistry (predose, 5, 10, 14d) ^b		UR	UR	UR
Gross pathology (d14)	Lungs: 1/3MD diffuse necrotizing bronchopneumonia; mild edema and consolidation remaining swine (consistent with swine enzootic pneumonia) Prostate: atrophy Spleen: congested			
Histopathology (d14)	N=3 (w/exception of HD N=2 due to death)			
Brain/mononuclear cell aggregates – meninges, cerebral cortex (minimal-mild)	1		2	1
Heart/chronic epicarditis (minimal-mild)		2		1
Lungs/bronchopneumonia			1	
Liver/congestion			1	
Kidneys/lymphocytic aggregates (mild)		1		
Prostate glands/absence due to hypotrophy or castration	3	3	3	2

^a Cause of death: aspiration pneumonia considered a result of anesthesia and tracheal intubation

^b Compared to concurrent controls; HD increase in body temperature associated with unspecified gastrointestinal symptoms

^c Recovery of MD WBC and neutrophils by d14

Summary:

Increased body temperature was observed at 3 and 6mg/kg. Depressed WBC were observed at 3 and 6mg/kg with severe neutropenia exhibited at 3mg/kg on day 5. These findings reversed by d14. This findings may be the result of

hypersensitivity pneumonitis associated with the human serum albumin. Atrophy of the prostate was observed at all ABI-007 doses as well as the HSA control animals.

2.6.6.3 Repeat-dose toxicity

Study # SRI-LIF-97-171-9024.2

Study name: Toxicity determination and efficacy studies of VivoRx compounds Capxol VR-3 and Capxol VR-4

Methods: Study was repeat dose pharmacology/toxicology study (athymic nude mice implanted with MX-1 tumors dosed for 5 days at 45-100mg/kg formulated as Taxol or ABI-007 with albumin: paclitaxel ratios of — and — Study conducted as a pharmacology study with only determination of lethality.

Findings:

X LD10s: 45mg/kg/day for albumin:paclitaxel ration of — and 67mg/kg/day for albumin:paclitaxel ratio of —

Histopathology Inventory for NDA # 21,660

Study	P0897001	LyChron-001
Species	dog	swine
Adrenals		
Aorta		
Bone Marrow smear		
Bone (femur)		
Brain	X#	X
Cecum		
Cervix		
Colon		
Duodenum		
Epididymis	X#	X
Esophagus		
Eye		
Fallopian tube		
Gall bladder		
Gross lesions		
Harderian gland		
Heart	X#	X
Ileum		
Injection site		
Jejunum		
Kidneys	X#	X
Lachrymal gland		
Larynx		
Liver	X#	X
Lungs	X#	X
Lymph nodes, cervical		
Lymph nodes mandibular		
Lymph nodes, mesenteric		
Mammary Gland		
Nasal cavity		
Optic nerves		
Ovaries		
Pancreas		
Parathyroid		
Peripheral nerve		
Pharynx		
Pituitary		
Prostate	X#	X
Rectum		
Salivary gland		

Sciatic nerve	X#	X
Seminal vesicles		
Skeletal muscle		
Skin		
Spinal cord		
Spleen	X#	X
Sternum		
Stomach		
Testes	X#	X
Thymus		
Thyroid		
Tongue		
Trachea		
Urinary bladder		
Uterus	X#	
Vagina		
Zymbal gland		
Standard List		
Ascending coronary artery		X

X, histopathology performed

X#, no histopathology performed, tissues stored for future evaluation

*, organ weight obtained

2.6.6.4 GENETIC TOXICOLOGY: NONE

The genetic toxicology data constitutes prior approved FDA findings for Taxol, as described in the drug's approved labeling. The genetic toxicology portion of the label for Abraxane is identical to that of Taxol, with minor modifications.

2.6.6.5 CARCINOGENICITY: NONE

2.6.6.6 REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY:

FERTILITY AND EARLY EMBRYONIC DEVELOPMENT

Study title: Intravenous fertility and general reproduction toxicity study of paclitaxel in male rats

Key study findings:

- Significant reduction in male fertility at 7mg/kg/week; infertility at 16mg/kg/week
- Reduced to absence of pregnancy at 7 and 16mg/kg
- Increased early resorptions at 2mg/kg

Study no.: 4701-002

Volume #, and page #: Electronic submission March, 2004 ; hardcopy submission: Vol 3, p. 1

Conducting laboratory and location: —

Date of study initiation: January, 2002

GLP compliance: Y

QA reports: yes (X) no ()

Drug, lot # and % purity: paclitaxel, lot #101-001, purity not provided

Formulation/vehicle: Human albumin lot#N-043; purity —

Methods:

Species/strain: — CD(SD)IGS BR VAF/plus rats

Age/weight: males: 71d/335-384g; females at 1st cohabitation period: 65d/218-284g

Test material: identified as paclitaxel + human albumin (not identified as ABI-007); paclitaxel:albumin ratio of 1:9 as indicated for to-be-marketed drug product

Doses employed: see table below 0, 0.5, 2, 7, 16, 32mg/kg/week for 12w (beginning 11w prior to 1st cohabitation and through the 1st week of cohabitation)

Route of administration: iv

Number/sex/group: 30 males

Parameters and endpoints evaluated: see below

Dose administration: weekly for 12w [HD terminated following 5w due to mortality]

Cohabitation: 4 cohabitation periods of 14d maximum

Recovery period: d92 –termination (inclusive of cohabitation 2-4)

Unique Methods: Since dosing was conducted on a weekly basis, effects on fertility, reproductive performance and embryotoxicity may not be a full reflection of the total dose. Study purpose was indicated as evaluation of male reproductive functions, mating behavior and fertilization.

Dosage (mg/kg/week)	Concentration (mg/mL)	Dose volume (mL/kg)
0 (saline control)	0	6.4 ^a
0 (vehicle control)	0	6.4 ^a
0.5	5	0.1
2	5	0.4
7 ^b	5	1.4
16	5	3.2
32 ^c	5	6.4

^a Dose volume in control groups adjusted from 6.4 mL/kg to 3.2 mL/kg on study day 31

^b 7mg/kg administered instead of 8mg/kg; 7mg/kg produced mortality, clinical signs of toxicity, reductions in BW and FC, and reproductive toxicity presumed by sponsor to be similar to findings at 8mg/kg

^c dosing terminated following 5th weekly dose due to excessive mortality and toxicity

Results:

mg/kg/week

Observations/males	0.5	2	7	16	32
Mortality (2X/d) (day of death/# doses administered)	1 (d192/12)	1 (d29/5)	3 (d15/3, d22/4, d51/8)	9 (1@d15/3, 1@d29/5, 1@d40/6, 2@d58/9, 4@d78-84/12)	30 (6@d15-33/3 12@22-29/4, 12@29-31/5)
Clinical signs (daily; hourly on dosing days) ^a	Dose-dependent ↑ in incidence of findings associated w/ mortality. Labored respiration, bradypnea, dehydration, emaciation, hypothermia, ↓ motor activity, ataxia, comatose, inability or limited use/hindlimbs, loss/righting reflex, hunched posture, inflammation/limbs, digits, alopecia, soft feces, ungroomed coat, excess salivation, lacrimation, chromodacryorrhea Recovery occurred for many findings in animals remaining alive following dosing.				
Body weight (weekly) ^{b,c} Recovery BW (compared to concurrent vehicle control)			↓14%	↓35%	↓36 ^d
d92			↓14%	↓34%	
d141			↓10%	↓28%	
d148				↓27%	
d211				↓21%	
Food consumption (weekly) ^b d1-71 mean consumption d15-29			↓12%	↓23%	↓37-45%
Gross pathology N=30 Testes/small/dicolored/flaccid Epididymides/small			10 16	27 23	29 23

/mass			1	2	
Prostate/small				4	9
Seminal vesicles/small			1	4	13
Thymus/small				4	7
Spleen/small					8
Absolute organ weights ^c					
Left epididymis			↓45%	↓67%	
Right epididymis			↓47%	↓65%	
Heart				↓30%	
Liver				↓24%	
Prostate		↓12%	↓27%	↓45%	
Testes			↓17%	↓78%	

^a Females examined weekly prior to gestation and on d 0, 7, 10, 13 for females assigned to 1st, 2nd, and 3rd cohabitation period. Females assigned 4th cohabitation examined d 0, 7, 10, 13, 15, 18, 21

^b Weekly BW and FC for females prior to gestation and d 0, 7, 10, 13 (cohab 1-3), 15, 18, 21 (cohab 4)

^c Terminal BW (d78) compared to concurrent vehicle control

^d BW d29 compared to concurrent vehicle control

^e Compared to concurrent controls (organs weighed included heart, liver, spleen, kidneys, testes, epididymes, seminal vesicles and prostate) All organs recovered with exception of epididymes and prostate

Notes:

1. Following completion of 1st cohabitation, ½ males sacrificed, with remaining males assigned to recovery.
2. Evaluation of cauda epididymal sperm concentration and motility using computer-assisted sperm analysis.
3. Females assigned to 1st, 2nd or 3rd cohabitation periods sacrificed d13; females assigned to 4th cohabitation period sacrificed d21. Gross necropsy of thoracic, abdominal and pelvic organs performed. # of corpora lutea/ovary recorded. Uterus examined for pregnancy, number and distribution of implantation sites and viable and nonviable embryos, and early and late resorptions.
4. Each fetus weighed, examined for gross alterations and identified by litter #, and uterine distribution. Approx. ½ fetuses/litter examined for soft tissue alterations. One-half fetuses/litter examined for skeletal alterations.

Mating and Fertility following 4 cohabitation periods

Parameter measured	Saline c	Veh c	0.5mg/kg	2	7	16
1st cohabitation						
# rats in cohabitation	30	30	30	29	27	25
Fertility index ^a	93.3	89.6	93.1	93.1	0	25
Rats pregnant/rats cohab	93.3	86.7	90	93.1	0	4
2nd cohabitation						
# rats in cohabitation	15	15	15	14	13	15
Fertility index ^a	93.3	84.6	100	84.6	0	0
Rats pregnant/rats cohab	93.3	73.3	100	78.6	0	0
3rd cohabitation						
# rats in cohabitation	15	15	15	14	13	15
Fertility index ^a	93.3	86.7	100	100	66.7	0
Rats pregnant/rats cohab	93.3	86.7	100	100	61.5	0
4th cohabitation						
# rats in cohabitation	15	15	15	14	13	15
Fertility index ^a	100	86.7	100	92.8	61.5	0
Rats pregnant/rats cohab	100	86.7	93.3	92.8	61.5	0

^a # pregnancies/# rats mated

Sperm count and motility

Parameter measured	Saline c	Veh c	0.5mg/kg	2	7	16
Main study						
Sperm count	189.6	215.3	201.7	184	26.8	15.5
Motility %	87.6	89.5	89	79.4	5.1	0
Recovery						
Sperm count	174.3	150.3	159.3	162.6	94.7	8
Motility %	88.5	79.1	91.1	94.2	48.8	4

Litter observations (mean incidence)

Parameter measured	Saline c	Veh c	0.5mg/kg	2	7	16
1 st cohabitation						
Implantations	15.8	15.7	15	15.6	0	1
Viable embryos	15.1	15.2	14.3	14.8	0	0
2 nd cohabitation						
Implantations	15.2	14.6	14.2	15.2	0	0
Viable embryos	14.1	14.3	13.8	14.7	0	0
3 rd cohabitation						
Implantations	14.9	15.2	15.3	14.8	14.8	0
Viable embryos	14.4	14.3	14.9	13.7	14.2	0
4 th cohabitation						
Implantations	14.7	15	13.6	15.9	14.1	0
Live fetuses	14.1	14.7	12.9	14.4	13.6	0
Dams w/viable fetuses ^a	15	13	14	13	8	0
External anomalies ^b						
Hindlimbs/extra digits				1/1 ^c		
Eyes/folded retina				1/1		
Incomplete ossification/ sternum			1/1	1/1		
Hindlimb/irregular shape				1/1		

^a BW of live fetuses averaged 5.20-5.64g

^b litters/fetuses evaluated: saline control 15/212; vehicle control 13/191; 0.5mg/kg 14/181; 2mg/kg 13/187; 7mg/kg 8/109; 16mg/kg not evaluated

^c litter incidence/fetal incidence

Summary

Significant reduction in male fertility was observed at 7mg/kg/week with absence of sperm and infertility at 16mg/kg/week. The number of motile sperm and total sperm count was significantly reduced at 7 and 16mg/kg. Reduced mating index was observed at 7mg/kg at the 1st cohabitation; significantly reduced mating indices were observed at 16mg/kg at the 1st-4th cohabitation. Pregnancy in mated animals was reduced to absent at 7 and 16mg/kg; 7 and 16 mg/kg groups were infertile in 1st and 2nd cohabitation. Increased early resorptions were observed at 2mg/kg; fetal alterations were minimal at this dose.

EMBRYOFETAL DEVELOPMENT**Study title: Intravenous developmental toxicity study of paclitaxel in rats****Key study findings:**

- Maternal and developmental toxicity at doses >1mg/kg/d
- Teratogenicity at 1 to 2mg/kg/d
- NOAEL: 0.5mg/kg/d

Study no.: 4701-001

Volume #, and page #: Volume 3, p. 1, Electronic submission: March , 2004

Conducting laboratory and location: —

Date of study initiation: January, 2002

GLP compliance: Y

QA reports: yes (X) no ()

Drug, lot #, radiolabel, and % purity: paclitaxel (not identified as ABI-007), Lot # C101-001, purity not provided

Formulation/vehicle: Human albumin Lot #N-043

Methods:

Species/strain: — CD(SD)IGS BR VAF/Plus

Test material: identified as paclitaxel + human albumin (not identified as ABI-007); paclitaxel:albumin ratio of 1:9 as indicated for to-be-marketed drug product

Doses employed: saline control, vehicle control, 0.5, 1, 2, 4, 8mg/kg/day

Route of administration: iv daily on days 7-17 (Dosing discontinued for all 8mg/kg animals following d7)

Study design: 5d cohabitation following acclimation; females w/copulatory plug or observed sperm assigned to individual housing (day 0)

Number/sex/group: Females 28/group (3F for toxicokinetics for all groups with exception of vehicle control with 25 animals total); males used for breeding purposes only (not considered test animals)

Age: 75d

Weight: 272-378g

Results: mg/kg/day

Observations/females	0.5	1	2	4	8
Mortality (2X/d) ^b (# dead or sac moribund@day/death/ #dosages)			1@d21/11	2@d17/10 10@d17-20 /11	2@d14/7 5@d14-15/8 10@d15-17/9 1@d17/10 6@d18-20/11
Clinical signs and abortion (daily; hourly on dosing days 1 and 2)	1mg/kg females: localized alopecia 2, 4, and 8mg/kg females: dehydration, [perivaginal bleeding (possibly assoc/GI bleeding or litter resorption) decedents only], soft feces, chromorrhinorrhea, alopecia, stained fur, ptosis, hunched posture, ↓ motor activity, (limited use of hindlimbs, loss of righting reflex, head tilt at 8mg/kg), ataxia, labored respiration, emaciation, chromodacryorrhea, tip-toe walk, mouth ulceration, hypothermia				
Body weight (weekly) ^c		↓10%	↓35%	↓52%	↓45%
Food consumption (0, 7, 10, 12, 15, 18, 21) ^c d1-21 mean consumption			↓33%	↓49%	↓37%
Toxicokinetics (d17: predose, 6, 24h postdose) ^a	See below				
Gross pathology (d21) ^b	2, 4, 8mg/kg: small thymus, large adrenal glands, discolored/mottled areas of liver, discolored/thin-walled stomach, [ulcerations of stomach, adhesions, gastric perforations (4, 8mg/kg)], [gaseous distention of stomach and spleen, discolored adrenals (8mg/kg)]				
Organ weights (uterus, heart, liver, spleen, kidneys, ovaries) ^c					
Liver			↓19%	↓22%	↓18%
Ovaries			↓18%	↓42%	↓50%
Heart			↓15%	↓18%	↓9%

^a Toxicokinetic samples not taken from 2 remaining females in HD group due to mortality and adverse clinical observations

^b Necropsy observations for decedents included GI lesions, gastric wall thinning, ulcerated stomach, small spleen, enlarged adrenals. All litters were early resorptions.

^c compared to concurrent vehicle controls

Toxicokinetics – Mean blood paclitaxel concentrations (ng/mL) at day 17

Dose group	Predose	6h postdose	24h postdose
0	< LOQ ^a	< LOQ	< LOQ
0.5	8.3	28.2	8.8
1	16.2	57.7	24.7
2	36.9	108.3	45.9
4	56.9	130.5	52.2

^a LOQ: Level of Quantitation (level not provided)

Mean levels of paclitaxel were increased ~3-4 fold at 6h, returning to predose levels at 24h, indicating significant clearance within the 24h period.

Observations (mean incidence) N=24 for pregnant controls; N= 25, 24, 23, 12, 1 for 0.5, 1, 2, 4, 8mg/kg)

Finding	Saline	Vehicle c	0.5mg/kg	1mg/kg	2mg/kg	4mg/kg	8mg/kg
Implantations	15.2	15.9	14.8	15.2	14.5	15.4	15
Litter size	14.8	15.4	14.3	13.2	5.6	0	0
Live fetuses	14.8	15.4	14.3	13.2	5.5	0	0
Litters w/1 or >1 live fetuses ^a	24	24	25	24	19	0	0
Resorptions	0.4	0.5	0.5	2	9	15.4	15
Early resorptions	0.4	0.5	0.5	1.8	7.6	15.4	15
Dams w/all conceptuses dead or resorbed (%)					17.4	100	100
Fetal BW ^b				↓18%	↓38%		
Fetuses with anomalies /litter	2.9	1.6	4.2	6.9	26.5		
External anomalies(%) ^c							
Fore/hindlimbs					5.3		
/splayed digits					5.3		
/fused digits					10.5		
Eyes/bulge	4.2			4.2	41.2		
/folded retina	8.3		20	37.5	5.9		
/microphthalmia	4.2				5.9		
Brain/dilation of ventricles					5.9		
Heart/septal defect					5.9		
Vessels					5.9		
/innominate artery short					5.9		
/innominate a. absent			4.0	4.2			
/artery misplacement					5.9		
Lungs/lobes fused or absent			4.0		5.9		
Skull/small eye socket				4.2	5.3		
Vertebra/presence of extra cervical rib	4.2	12.5	16	12.5	31.6		
Ribs/wavy					5.3		
/incomplete ossification				4.2	10.5		
Sternum/not ossified					10.5		
Sternum /asymmetric				4.2			

^a Total incidence

^b compared to concurrent fetal weights (vehicle control)

Summary

Maternal and developmental toxicity was observed at doses ≥ 1 mg/kg/d. Developmental toxicity at 1, 2, 4 and 8 mg/kg ABI-007 included increased postimplantation loss (primarily early resorptions), fetal mortality, reduction in fetal body weight and increased fetal alterations. Teratogenicity was observed at 0.5 to 2 mg/kg/day. Dose related increased mortality was exhibited at 2-8 mg/kg/day; no litters or live fetuses were observed at 4 or 8 mg/kg. Maternal toxicity was observed as a 10 to 52% decrease in body weight for animals administered 6-48 mg/m².

PRENATAL AND POSTNATAL DEVELOPMENT: NONE**Reproductive and developmental toxicology conclusions:**

Significant reduction in male fertility was observed at 7 mg/kg/week with absence of sperm and infertility at 16 mg/kg/week. The number of motile sperm and total sperm count was significantly reduced at 7 and 16 mg/kg. Reduced mating index was observed at 7 mg/kg at the 1st cohabitation; significantly reduced mating indices were observed at 16 mg/kg at the 1st-4th cohabitation. Pregnancy in mated animals was reduced to absent at 7 and 16 mg/kg; 7 and 16 mg/kg groups were infertile in 1st and 2nd cohabitation. Increased early resorptions were observed at 2 mg/kg; fetal alterations were minimal at this dose.

In a separate study, maternal and developmental toxicity was observed at doses > 1 mg/kg/d. Developmental toxicity at 1, 2, 4 and 8 mg/kg ABI-007 included increased postimplantation loss (primarily early resorptions), fetal mortality, reduction in fetal body weight and increased fetal alterations. Teratogenicity was observed at 0.5 to 2 mg/kg/day. Dose related increased mortality was exhibited at 2-8 mg/kg/day; no litters or live fetuses were observed at 4 or 8 mg/kg.

LABELING RECOMMENDATIONS: See separate labeling review

2.6.6.7 LOCAL TOLERANCE

No studies submitted

2.6.6.8 SPECIAL TOXICOLOGY STUDIES:

Study title: Comparison of the 28-day toxicity of ABI-007 following a single intravenous dose of drug product containing usual and elevated levels of _____ rats

Key study findings:

- Suppression of RBC, WBC + \uparrow platelets increased in _____ groups compared to _____ groups
- Paclitaxel with enhanced impurity level did not display any overt toxicological change
- Hematological indices of both groups recovered within 28 days
- Severe testicular degeneration both ABI-007 male groups
- Approval to increase shelf-life specification from _____

Study no: P0603001

Volume #, and page #: Separate submission on October 28, 2004

Conducting laboratory and location: _____

Date of study initiation: November, 2003

GLP compliance: Y

QA reports: yes (X) no ()

Drug, lot #, and % purity: ABI-007 w/ _____ (lot #C102-004; purity not provided; designated as ABI-007A); ABI-007 _____ (lot # 24246-14; purity not provided; designated as ABI-007B)

[Boosted impurity level for specification justification]

Formulation/vehicle: 0.09% NaCl

Species/strain/age/wt: Sprague Dawley rats/8-11 w/226-304g

Methods: Groups of 4rats/sex dosed 1X with control, ABI-007A or ABI-007B and sacrificed d8 and d29.

Dosing: 50mg/kg (300mg/m2)

Note: — considered “usual” level of — , the primary impurity found in ABI-007

Observations	ABI-007 + —		ABI-007 + —	
	M	F	M	F
Mortality (2X/d)	none			
Clinical obs (daily)	none			
BW (d1, 8, 15, 22, 28, 29) ^a	↓12-15%	↓6-7%	↓13-14%	↓5%
Hematology (d8, 29) ^{b,c}				
WBC	↓35%	↓19% (↓28)	↓50%	↓28% (↓26)
RBC		↓27% (↓17)	↓35%	↓33% (↓11)
HGB		↓26% (↓15)	↓48%	↓35% (↓11)
HCT		↓28% (↓18)	↓46%	↓34% (↓11)
PLT		↑24% (↑10)	↑128%	↑91% (↑10)
Clinical chemistry (d8, 29)	UR			
Gross necropsy (d8, 29)	Testes: Discoloration, atrophy in — groups (d29) Single animals/ — groups: white material/enlarged bladder (d8), hemorrhagic lung (d29)			
Organ weights - absolute (d8, 29) ^a				
Day 8 (day 29)				
Left kidney	↓13		↓15 (↓13)	
Right kidney	↓12		↓13 (↓18)	
testes	↓49 (↓67)		↓46 (↓68)	
Histopathology (d8, 29)	N=8/sex		8	
Testes/degeneration (severe)	8			
Kidney/interstitial nephritis		1		1

^a compared to concurrent controls

^b Day 8 comparative values. Differential leukocyte count was not performed d8 due to cell degradation from use of incorrect collection tube

Note: excessive — indicated to be associated with artifactual differences in WBC, RBC, HGB, HCT, and PLT parameters of ABI + — group

Note: calculations performed on values provided for analyses of all results provided despite claims by sponsor of excessiv — Study is satisfactory for justification to increase shelf-life specification from —

^c Comparative values of samples not affected by excess — in sample tubes calculated in parentheses for females; male data not provided for boosted impurity group

The sponsor has claimed that artifactual differences in WBC, RBC and PLT parameters were caused by excess — in sample tubes. Changes from concurrent controls are significantly greater for the boosted — group in males when samples with and without “artifactual changes” are compared on d8. Without affected samples, calculations indicate that changes from controls are slightly increased in the — group for females. At day 29, hematology parameters of treated males and females are comparable to controls.

Increase in the shelf-life specification for — from — is approved; changes in the hematological indices significant in males only. Paclitaxel with enhanced impurity level did not display any overt toxicological change. Hematological indices of both groups recovered within 28 days.

2.6.6.9 DISCUSSION AND CONCLUSIONS

Neurotoxicity appears to be slightly enhanced with ABI-007 when administered to animals compared to Taxol. Rodents administered a single dose of ABI-007 exhibited swollen nerve root axons of the spinal cord at 540mg/m2, as well as urinary bladder hyperplasia, kidney fibrosis, adrenal hyperplasia, and testicular atrophy at doses >54mg/m2. These findings were not observed with concurrently administered Taxol animals. Administration of ABI-007 to beagle dogs was complicated by the immunological reaction to the human serum albumin portion of the drug product formulation. Dogs administered 175mg/m2 exhibited severe CNS effects with ABI-007, as well as the drug vehicle control and processed human serum albumin. However, an increased incidence of congestion of the hippocampus was observed in dogs administered ABI-007. Since histopathology was not conducted in a second dog study at the same dose level, the level of CNS toxicity in this study could not be determined. Testicular atrophy/degeneration was exhibited in dogs and rodents administered ABI-007. This finding was repeated in reprotoxicity studies, where male infertility, and maternal toxicity and mortality were associated with embryoletality and fetolethality at doses of 6mg/m2.

TABLES AND FIGURES See individual studies for appropriate tables and figures.

2.6.5 TOXICOLOGY TABULATED SUMMARY

General Toxicology - Non-GLP studies

Study #	Species	Study design	Results
PR-0003	Mouse	Single dose acute toxicity	ABI-007 LD ₅₀ : 447.4mg/kg, LD ₁₀ : 371.5mg/kg Taxol LD ₅₀ : 7.53mg/kg, LD ₁₀ : 5.13mg/kg
PR-0004	Mouse	LD ₅₀ of ABI-007 and Taxol following multiple iv administrations	ABI-007 LD ₅₀ : 76.2mg/kg Taxol LD ₅₀ : 8.07mg/kg
PR-0002	Rat	Single dose – effect on myelosuppression, iv toxicity	ABI-007 exhibited less myelosuppression compared to Taxol
PR-0007	Rat	Dose response effect on myelosuppression, iv	Myelosuppression exhibited by d3; ↑WBC on d10 inversely related to dose Kidney lesions at 90, 120mg/kg Lethality at 120 and 200mg/kg

**APPEARS THIS WAY
ON ORIGINAL**

General Toxicology - GLP studies

P0397006	Rat	Single dose acute toxicity Abraxane: 5, 9, 30, 90, 120mg/kg Taxol: 5, 9, 30mg/kg	Abraxane findings (not observed w/Taxol): Swollen spinal cord, nerve root axons @ 90mg/kg ↑BUN, urinary bladder hyperplasia Kidney fibrosis Adrenal hyperplasia Atrophy/necrosis testes, epididymis
P0897001	Dog	Single dose acute toxicity in M and F dogs dosed 175mg/m ² ABI-007	Soft brain tissue, ↑CSF, histopathology not conducted Vasculitis, ↑WBC, reticulocytes CNS observed below not exhibited
P0997006	Dog	Single dose acute toxicity in M and F dogs dosed 175mg/m ² ABI-007, ABI-007 vehicle, HSA	Multifocal granulomatous meningitis, acute congestion, acute hemorrhage of cerebrum, cerebellum, brainstem, hippocampus and basal ganglia in dogs dosed ABI-007, vehicle control, or — HSA Acute congestion of hippocampus Testicular atrophy CNS effects may be immunological reaction of human serum albumin to dogs
LYCHRON-001	Swine	Single dose acute toxicity in swine dosed 1, 3, 6mg/kg ABI- 007, HSA	↑ body temperature at 3, 6mg/kg ↓WBC, severe neutropenia

Reproductive Toxicity

Study #	Species	Study design	Results
4701-001	Rat	Developmental toxicity	Maternal and developmental toxicity at doses >1mg/kg/d. Teratogenicity at 1 to 2mg/kg/d. Fetal deaths at doses >2mg/kg. NOAEL: 0.5mg/kg
4701-002	Rat	Fertility and early embryonic development	Significant reduction in male fertility at 7mg/kg/week; infertility at 16mg/kg/week. ↑ early resorptions at 2mg/kg/week Minimal incidence of fetal alterations, primarily observed at 2mg/kg/week

OVERALL CONCLUSIONS AND RECOMMENDATIONS:

Conclusions:

Abraxane is a composed of a Cremophor-free formulation of the cytotoxic agent paclitaxel formulated in human serum albumin. Toxicology studies in dogs, and possibly swine were complicated by the immunological reaction of the human albumin to these animal models. Even so, neurotoxicity of Abraxane may be slightly enhanced compared to that of Taxol. However, in general, acute toxicity and lethality are significantly reduced, as indicated by comparative lethal doses and MTDs. Abraxane appears to be rapidly distributed to tissues with a greater volume of distribution and longer serum half-life compared to Taxol.

Unresolved Toxicology Issues: None

Recommendations: Approval

Suggested labeling: To be completed in separate labeling review

Reviewer Signature _____

Supervisor Signature _____ **Concurrence** Yes _____ No _____

APPENDIX/ATTACHMENTS:**Addendum to review:****IND 55,974 Review #1 Reviewed: June, 1998**

PR-0003 Determination of the LD₅₀ in mice for Capxol and Taxol following a single intravenous administration. Conducted by VivoRx Pharmaceuticals, Santa Monica, CA in 1996. The study was not conducted according to GLP. Capxol LD₅₀ = 447.4mg/kg, Capxol LD₁₀ = 371.5mg/kg
 species: CD-1 % mice
 drug: Capxol (formulation 1: lot A4-16, — (formulation 2: lot A4-33, — , (formulation 2: lot A4-34, — , Taxol
 vehicle: Capxol control (Human Albumin, single dose 4.94g/kg), Taxol control (Cremophor, 1ml/6mg paxlitaxel)
 dosage: Capxol: 30, 103, 367, 548, 822mg/kg; Taxol: 4, 6, 9, 13.4, 20.1mg/kg
 age; weight: 8-9wks., 18-35g
 route: single iv dose, injection volume= 15ml/kg
 observation: 28 days

Results**Mortality**

Capxol mortality was 100% at 548 and 822mg/kg and 0% at doses #367mg/kg. Linear extrapolation of Capxol LD₅₀ and LD₁₀ was 447.4 and 371.5mg/kg, respectively. Taxol mortality was 100% at doses ≥13.4mg/kg. The Taxol LD₅₀ and LD₁₀ was 7.53 and 5.13mg/kg, respectively. Capxol formulations varied in concentration as indicated above; 30 and 103mg/kg animals were administered lot 16, 367 and 548mg/kg animals were administered lot 34 and 822mg/kg animals were administered lot 33.

P0397006 Determination of the toxicity in rats of Capxol and Taxol following a single intravenous administration. Conducted by — in 1997. The study was indicated to have been conducted according to GLP; however, a signed statement was not provided.
 species: Sprague Dawley rats (6/dose/sex)
 drug: Capxol; lot #A4-97; Taxol, lot #B6F41A
 vehicle: HSA (drug product formulation vehicle)
 dosage: 5, 9, 30, 90, 120mg/kg Capxol; 5, 9, 30mg/kg Taxol; dose volume 5ml/kg
 age; weight: 7-9wks; 182-272g
 route: iv

Observations

Clinical signs	Following dosing, 1 and 4hr post-dose, daily thereafter
Body weights	Days 0, 1, and weekly to day of necropsy
Hematology	prior to necropsy (day 8 or 31)
Clinical chemistry	prior to necropsy
Gross pathology	at necropsy
Histopathology	at necropsy

Mortality and clinical signs

Dose (mg/kg)	Mortality	Day of death	Clinical signs
Albumin vehicle			none
Capxol/5			piloerection
/9			piloerection
/30			none
/90	1/12	day 15	none
/120			piloerection
Taxol/5			piloerection
/9			piloerection, staggering gait
/30	12/12	day 1(2/12) day 2(2/12) day 3 (5/12) day 4 (3/12)	prostration, staggering gait , piloerection

Body weight

Body weights of animals administered 90 and 120mg/kg Capxol were 9 from study day 8 to study termination. Body weights of % appeared to be depressed to a greater extent (916-22% and 16-38%, respectively, on day 8 and 12 and 14%, respectively, at study termination) compared to & (12% and 12-14%, respectively, on day 8 and 2 and 5%, respectively, at study termination).

Hematology There were no biologically significant changes in hematological parameters.

Clinical chemistry: % change from control of animals administered Capxol - % and &

Parameter (gender)	5mg/kg	9mg/kg	30mg/kg	90mg/kg	120mg/kg%
Glucose/d8 /d31 (%)	918 -	921 -	940 -	929 -	964 942
BUN/ d8 (%)	-	-	81.25-fold	81.9-fold	82.9-fold
Glucose/d8 /d31 (&)	932 -	919 -	935 -	937 -	933 -

BUN levels normalized in Capxol-treated males by day 31. Females were not similarly effected.

Gross pathology (limited to Capxol findings):

- Testes- small in 2/6 30mg/kg, 2/6 90mg/kg, 3/6 120mg/kg %
- Seminal vesicle- small in 1/6 120mg/kg%
- Ovary; uterus- thickening in 1/6 9mg/kg&
- Liver-mottled in 1/6 9mg/kg&
- Spleen-enlarged, white lesions in 1/6 90mg/kg&

Histopathology: With the exception of metaplasia of the vagina (as indicated below), the following histopathological changes were not observed in Taxol-treated animals.

Histopathology findings in Capxol-treated rats at day 8 and 31					
Organ/Finding	Capxol (mg/kg) - incidence at day 8 and (31) N=3%, 3&				
	5	9	30	90	120
Testes/ atrophy of seminiferous tubules	-	1	3, (3)	3, (2)	3, (3)
/multifocal tubular necrosis and mineralization	-	-	3, (3)	2, (2)	3, (3)
Epididymis/tubular atrophy	-	1	3, (3)	2, (2)	3, (3)
/lymphocytic interstitial infiltrate	-	-	3	2	-
Vagina/mucus metaplasia*	-	(1)	1, (1)	1, (1)	2, (2)
Uterus/deciduoma	-	-	-	-	(2)
/neutrophilic endometrial infiltrate	-	(2)	-	-	-
Sciatic nerve/lymphocytic infiltrate	-	-	-	-	1
Urinary bladder/urothelium hyperplasia	-	-	1	-	2
Spinal cord/swollen nerve root axons	-	-	-	1	-
Adrenals/bilateral cortical nodular hyperplasia	-	1	1	2	-

*Observed in 1/3 5- and 9mg/kg Taxol dosed &

PR-0002 Pilot study of myelosuppression in rats with Capxol and Taxol following a single intravenous administration. Conducted by VivoRx Pharmaceuticals, Santa Monica, CA in 1997. The study was not conducted according to GLP. WBC depression of Taxol and Cremophor-treated animals was significantly greater (up to 7-fold) than Capxol and HSA-treated animals.

species: Sprague Dawley rats (4%/group for Capxol and Taxol; 2%/group for vehicle controls)
 drug: Capxol (lot# A4-16, A4-34, A4-93); Taxol (lot# G6F19A)
 vehicle: HSA (Capxol); Cremophor (Taxol)
 dosage: 5mg/kg
 age;weight: 12-14wks; 350-450g
 route: single dose iv

Body weights and white blood cell counts were performed on days 1, 3, 7, 10 and 14.

Percent change of WBC following administration of paclitaxel or vehicle control as compared to predose counts				
Day	Capxol	Taxol	HSA	Cremophor
1	-23.66	-55.47	2.95	-61.36
3	-10.39	-42.3	0.7	-28.07
7	-6.85	-50.43	4.73	-23.51
10	31.46	-24.11	4.3	-11.39
14	10.82	-5.43	3.35	-11.39

Body weights of Taxol-treated rats were depressed to a greater extent compared to Capxol-treated rats following dosing and remained depressed to study day 14. Body weights of Capxol-treated rats recovered by day 7.

PR-0007 **Investigation of dose response to myelosuppression in rats following intravenous administration of Capxol.** Conducted by VivoRx Pharmaceuticals, Santa Monica, CA in 1997. The study was not conducted according to GLP. Capxol was lethal at 200mg/kg. The occurrence of leukopenia and body weight loss in Capxol-dosed animals was dose related.

species: Sprague Dawley % rats
 drug: Capxol (batch # 197070)
 vehicle: saline control
 dosage: 0, 30, 90, 120, 200mg/kg
 age;weight: 10-12wks; 360-420g
 route single iv bolus dose (dose volume 10ml/kg)

Observations

WBC counts Day 0, 1, 3, 7, 10, 14
 Body weight Day 0, 1, 3, 7, 10, 14
 Gross pathology Day 14

Note: Labeling of groups (Groups A-E) are reversed in tabular results compared to Experimental Design notation. Urine volume was not indicated to have been collected from test animals; however, observations of polyuria are reported by study author.

Percent change in WBC (compared to predose) following administration of Capxol						
Dose (mg/kg)	Mortality (Day of death)	Day 1	Day 3	Day 7	Day 10	Day 14
0	0/3	-0.11	-0.68	17.52	29.9	5.47
30	0/3	13.8	-62.05	-18.8	58.25	-2.7
90	0/3	-12.01	-60.25	-29.32	100.1	6.13
120	2/3 (day6)*	-17.47	-31.17	-57.2	237.1	232.7
200	3/3 (day 0, 15m postdose)	-	-	-	-	-

*Data on days 1 and 3 from 2/3 rats and days 7, 10, and 14 from 1/3 rats

The occurrence of leukopenia and body weight loss in Capxol-dosed animals was dose related with few exceptions. Polyuria, which may have been a result of the chloroform component of Capxol, was reported in animals administered 90 and 120mg/kg of the drug. 8 WBC observed during study week 2 may have been a result of dehydration due to polyuria. The large volume of Human Albumin administered during dosing of 200mg/kg Capxol may have contributed to the lethality observed in this group. Multiple kidney lesions were reported in 1/3 animals administered 90 and 120mg/kg Capxol. Gross findings were not tabulated.

P0997006 **Fourteen day acute intravenous toxicity study of Capxol in beagle dogs.** Conducted by _____ in 1997. Study was conducted according to GLP with exception of hematological analyses by _____, which is not in GLP compliance. Multifocal granulomatous meningitis, acute congestion and acute hemorrhage of the cerebrum, cerebellum, brainstem, hippocampus and basal ganglia were observed in dogs administered • _____ • Albumin and Capxol. Acute congestion of the hippocampus was observed at a greater incidence in Capxol-treated animals. These effects may be an immunological reaction of the Human Albumin to dogs or a combination of the Albumin and other residual solvents in the drug product. Atrophy, degeneration and hemorrhage of the testes and intratubular giant cells of the epididymis were observed in Capxol-treated %.

species: beagle dogs

drug: Capxol, lot #97102001, 37mg paclitaxel/vial

vehicle: Albumin from Capxol drug product (lot 97130001); Human Serum Albumin from commercial lot (lot NG7852A)

dosage: 175mg/m² Capxol

age:weight: 10-15months; % 10.8-13.9kg; & 8.1-10.6kg

route: iv

Observations

Clinical signs and

body temperature daily

Body weights day 1, 8

Food consumption daily

Hematology day 1, 8, prior to sacrifice

Clinical chemistry day 1, 8, prior to sacrifice

Gross pathology day 15

Histopathology day 15

Mortality and clinical signs:

One % and one & dog administered Human Serum Albumin were sacrificed moribund on study day 12.

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Clinical observations of dogs (n=4) administered Capxol or HSA			
Dose Group	Following dosing	1-4hr following dosing	day 2-15
Capxol vehicle	1/4dogs: vomiting, restlessness, 8salivation and body temperature	1/4 dogs: depressed, 9 response to stimulus	day 4-6 in 2/4 dogs: loose stool day 15 in 1/4: depressed, 9 response to stimulus, edema of face, ears, extremities, vomiting
Capxol	no change	1/4 dogs: depressed, 9 response to stimulus, 8 body temperature, bloody stool	day 2-6, 15 in 2%, day 2-15 in 1&, day 3, 5, 6 in 1&: depressed, 9 response to stimulus, edema of face, ears, extremities, vomiting, soft stool, poor appetite, dehydration
HSA	no change	no change	sporadically on days 2-15 in 3/4dogs: depressed, 9response to stimulus, loose stool, edema of face and extremities, ecchymosis on ventrum and ears, enlarged lymph nodes, dehydration, vomiting, hemorrhage of gums (2/4 dogs sacrificed day 12)

One & administered Capxol exhibited body temperature of 39.3°C on 5 study days. Abnormal hematology (high leukocyte counts with 8 numbers of immature neutrophils) and clinical chemistry values (8 ALK PHOS, LDH, CPK) for this dog, as well as the 8 in body temperature, suggested possible infection even though the animal was quarantined for 7 days prior to study initiation and reported to be normal upon release. One % administered Capxol and 3/4 dogs administered HSA exhibited high body temperature on a single study day.

Hematology and Clinical Chemistry

On day 8, the WBC count of one & administered Capxol (indicated above) was 2.8-fold 8 compared to the concurrent control mean WBC count; the animal appeared to recover by day 15. In addition, on day 8, the following serum chemistry values of this dog were 8 compared to the concurrent control mean values: alkaline phosphatase (86.8-fold), LDH (84.7-fold) and CPK (82.4-fold). The LDH and CPK of the animal remained 8 on day 15. There were no other remarkable changes in hematology or serum chemistry.

Gross Pathology

- Capxol/Capxol vehicle: Brain-8 cerebrospinal fluid
 - Spleen, mesenteric lymph nodes- enlarged and/or hemorrhagic
 - Face and extremities-edema
 - Stomach and intestines- hemorrhagic and/or congested
 - Testes- edema
- HSA (additional findings): Brain- congestion, dura mater adhered to skull and brain
 - Kidney, lung- hemorrhagic
 - Prostate- enlarged

Histopathology: (N=2/sex/group)

Organ/Finding	Capxol vehicle control		Capxol		HSA	
	%	&	%	&	%	&
Cerebrum/ Acute congestion	1		1			1
/ Multifocal granulomatous meningitis		1	1			
/ Reactive meningeal vessels		1				1
Cerebellum/ Acute congestion		1			1	2
Brainstem/ Acute hemorrhage	1	1	1			2
Hippocampus/ Acute congestion			1	2		2
/ Multifocal granulomatous meningitis					1	
/ Reactive meningeal vessels					1	1
Basal ganglia/ Acute congestion		1	1			
/ Multifocal granulomatous meningitis		1	1			1
/ Reactive meningeal vessels		1	1			1
Testes/ Seminiferous tubule atrophy/ degeneration			2			
/ Extensive focal hemorrhage			1			
Epididymus/ Bilateral intratubular giant cells			1			
Lung/ Proliferative chronic interstitial pneumonia				1		1

Gastrointestinal findings were similar in Capxol and control animals.

Histopathology Inventory for IND # 55974

Study		
Species	dog	rat
Adrenals		X
Aorta		X
Bladder		X
Bone Marrow smear		
Bone (femur)		X
Brain	X	X
Cecum		X
Cervix		X

Colon	X	X
Duodenum	X	X
Epididymis		X
Esophagus		X
Eye		X
Fallopian tube		
Gall bladder	X	
Harderian gland		
Heart	X	X
Hyphophysis		
Ileum		X
Injection site		
Jejunum	X	X
Kidneys	X	X
Lachrymal gland		
Larynx		
Liver	X	X
Lymph nodes, cervical	X	
Lymph nodes mandibular		
Lymph nodes, mesenteric	X	X
Lungs	X	X
Mammary Gland		X
Nasal cavity		
Optic nerves		X
Ovaries	X	X
Pancreas		X
Parathyroid		X
Peripheral nerve		
Pharynx		
Pituitary		X
Prostate	X	X
Rectum		X
Salivary gland		
Sciatic nerve	X	X
Seminal vesicles		X
Skeletal muscle		X
Skin	X	
Spinal cord		X
Spleen	X	X
Sternum		
Stomach	X	X
Testes	X	X
Thymus		
Thyroid		X
Tongue		X
Trachea		X
Uterus	X	X
Vagina		X
Zymbal gland		
Omentum		X
Gross lesions		X
Lymph nodes, mediastina	X	
Lymph nodes, popliteal	X	

Other relevant materials (Studies not reviewed, appended consults, etc.): none

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 21, 660
SERIAL NUMBER: 000
DATE RECEIVED BY CENTER: 03/07/04
PRODUCT: ABI-007
INTENDED CLINICAL POPULATION: Metastatic breast cancer
SPONSOR: American Bioscience, Inc.
DOCUMENTS REVIEWED: Electronic submission
REVIEW DIVISION: Division of Oncology Drug Products (HFD-150)
PHARM/TOX REVIEWER: Margaret E. Brower, Ph.D.
PHARM/TOX SUPERVISOR: John Leighton, Ph. D.
DIVISION DIRECTOR: Richard Pazdur, M.D.
PROJECT MANAGER: Sheila Ryan

Date of supplemental labeling submission to Division File System (DFS): 1/7/05

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Executive Summary

I. Recommendations

- A. Recommendation on approvability: The non-clinical studies submitted to this NDA provide sufficient information to support the use of ABI-007 (ABRAXANE) for treatment of patients with metastatic breast cancer who have failed initial chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy.
- B. Recommendation for non-clinical studies: None

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