CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-660

MEDICAL REVIEW(S)

Division NDA Review Summary

NDA: 21-660
Applicant: American BioScience, Inc. (ABI)
Proprietary Name: Abraxane™ (paclitaxel protein-bound particles for injectable suspension)

Regulatory History

Regulatory Landmarks

May 12, 1998: original IND 55,974 was submitted.

January 16, 2003: Product received Fast Track designation for metastatic breast cancer.

June 30, 2003: ABI submitted first piece of rolling NDA (CMC and non-clinical).

March 8, 2004: Division received the last piece of the rolling NDA (clinical).

January 8, 2005: PDUFA goal date for this standard review.

FDA met with the sponsor on several occasions to discuss trial designs that could serve as the basis for approval. The sponsor was developing a new formulation of paclitaxel that was cremophore-free and promised to be less toxic. FDA agreed that ABI could be compared to paclitaxel under the 505 b2 regulations, however, clinical studies would be necessary. FDA stated that objective response rate could be used as a comparative measure of paclitaxel activity. ABI was to be compared to Taxol in a non-inferiority analysis which would assure statistically at least 75% retention of the paclitaxel activity in the Taxol control arm. (Although the Agency often allows a standard of 50% retention of control effect, a more stringent standard was required because 1) response rate is a surrogate rather than a ultimate end point, and 2) the sponsor was relying on results from only a single study). Breast cancer was chosen as the disease for study because of the high response rate of breast cancer to single-agent Taxol. As discussed below, the sponsor exceeded the goal of demonstrating non-inferiority by demonstrating clearly superior response rates with ABI.

Indication

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.

Clinical/Statistical (See reviews by Drs. Scher, Dagher's, Drs. Yang & Sridhara's)

The clinical database supporting efficacy and safety in this setting includes two single-arm studies and one randomized, multi-center, international study enrolling 460 patients (Study CA012-0).

Study CA012-0 was a randomized, multi-center, open-label, phase 3 trial in breast cancer patients. It was conducted at 70 sites located in Russia/Ukraine, Canada, the U.S. and the United Kingdom. Patients were randomized to receive Abraxane (233 patients), 260 mg/m^2, as a 30-minute infusion, or 175 mg/m^2 paclitaxel injection (227 patients) as a 3-hour infusion. Fifty-nine

percent of patients received study drug as second-line or greater than second-line therapy. Seventy-seven percent of the patients had previous exposure to anthracyclines.

The primary efficacy endpoint was response rate based on reconciled (investigators and independent radiology experts) assessment of target lesions through cycle 6. The primary analysis was a sequential test with the following pre-specified testing order: non-inferiority test in the whole study population, superiority test in the whole study population, and superiority test in the subgroup of patients who received study treatment as the 1st line therapy. Based on the FDA clinical reviewer's adjudication of response status, there were 50 and 25 responders in the ABI-007 arm and Taxol arm, respectively. The observed response rates were 21.5% and 11.1%, respectively and the estimated ratio of response rates (ABI-007/Taxol) was 1.899 with a 95% confidence interval (CI) of 1.228 – 2.937. This suggests the superiority of ABI-007 with respect to the primary endpoint in the whole study population.

Table 1: Reviewer's Results of FDA-Confirmed *rec*TLRR (All Randomized Patients)

Reconciled Target Lesion Response Assessment Dataset	**ABI-007 [N = 233]**	**Taxol [N = 227]**
No. of FDA-Confirmed Responders	50	25
Response Rate (95% Binomial CI)	21.5% (16.19% – 26.73%)	11.1% (6.94% – 15.09%)
Ratio of Response Rates (ABI-007/Taxol) (95% CI)[a]	1.899 (1.228 – 2.937)	
P-value[b]	0.003	

[a] 95% CI of the ratio in superiority analysis based on the stratified Cochran-Mantel-Haenszel (CMH) test, stratified by 1st line vs. > 1st line therapy.
[b] P-value from the stratified CMH test.

Time to progression data also appeared favorable, but evaluation of this secondary endpoint was neither rigorous enough, nor mature enough, for definitive conclusions to be reached. Central review of the radiologic findings was only conducted for the first six cycles of therapy. The FDA statistical team evaluated TTP by two methods: 1) analyzing only the reconciled progression dates through cycle 6, and 2) analyzing all investigator-specified progression dates which were available beyond cycle 6. By both analyses the hazard ratio was about 0.75 and the p value was about 0.04.

Survival data was not mature enough for evaluation. The applicant will be required to submit survival data for review as a phase IV post-marketing commitment.

Abraxane has an acceptable safety profile compared to paclitaxel as evaluated in study CA012-0. Hypersensitivity reactions were fewer in the Abraxane arm compared with paclitaxel (4% vs. 12%), with no severe hypersensitivity reactions observed for Abraxane. The incidence of neutropenia was lower for patients in the Abraxane arm compared to paclitaxel (9% vs. 22%), despite a 49% higher dose of ABI-007. The incidence of sensory neuropathy was greater in the Abraxane treatment arm (71% vs. 56% for all grades and 10% vs. 2% for grade 3). However, it

appears that of the 24 patients with grade 3 neuropathy, 14 improved at a median of 22 days, 10 resumed treatment at a reduced dose, and 2 discontinued due to peripheral neuropathy.

Outside Consultation: This application was not presented at the Oncologic Drugs Advisory Committee. The review team discussed this application with three outside SGE consultants (two oncologists and a radiologist).

Chemistry, Manufacturing and Controls (see Dr. Y. Hsieh's review)

Abraxane is a formulation of microparticles of paclitaxel coated with human albumin. The mean particle size of albumin bound paclitaxel particles is between — nm. The drug product is provided as a sterile, lyophilized cake of 100 mg of paclitaxel and approximately 900 mg of human albumin in a 50 mL — glass vial. Currently marketed paclitaxel drug products use a Cremophor-EL formulation. Abraxane can be stored at 25°C/60% RH. An expiration dating period of 24 months under the recommended storage conditions has been granted. For administration, each vial of Abraxane is reconstituted with 20 mL 0.9% Sodium Chloride Injection, USP to give a suspension of microparticles containing 5 mg paclitaxel per mL. Reconstituted drug product solution should be used immediately, but may be refrigerated at 2°-8°C (36°-46°F) for a maximum of 8 hours if necessary. Adequate information on the drug product has been provided to assure its identity, strength, purity and quality.

The active ingredient, paclitaxel, is an antitubulin agent, exhibiting a unique anti-mitotic activity. The drug product is manufactured from paclitaxel obtained — *Taxus media* (commonly known as Anglojap Yew). It is a white to off-white powder with poor water solubility. Complete information on the drug substance is provided in DMF No — Adequate information and data have been provided to support the use of the — material in the manufacturing of the Abraxane drug product.

Nonclinical (see Drs. Brower & Leighton's reviews)

Abraxane is a cytotoxic agent that functions as a microtubule inhibitor, promoting the assembly of microtubules and preventing depolymerization. To support the NDA, the applicant submitted nonclinical studies reports that evaluated the efficacy of paclitaxel protein-bound particles; general toxicology and reproductive toxicity studies; and pharmacokinetic and biodistribution studies. A study to justify an increased level of an impurity was also provided. ABI conducted these studies. Information on the mechanism of action and genetic toxicology of paclitaxel was obtained from product labels from previously reviewed NDA applications.

Single dose toxicology studies of paclitaxel formulated as protein-bound particles compared to cremophor-formulated paclitaxel did not raise any new concerns that were not addressed in clinical development. Developmental toxicity of paclitaxel protein-bound particles was assessed in a fertility and early embryonic toxicity study in which male rats were mated with untreated females. An embryo-fetal developmental toxicology study (Segment II) was also conducted in female rats. Results from both these studies indicated that paclitaxel protein-bound particles are a developmental toxicant. Pregnancy Category D is recommended.

ABI conducted a comparative toxicology to justify an increase in shelf-life specification of — — primary — impurity of ABI-007, from —

Clinical Pharmacology and Biopharmaceutics (see Dr. Men's review)

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%. The applicant did not study the safety and pharmacokinetics of Abraxane in hepatically-impaired patients.

Tradename and Labeling Consultation (see DMETS & DDMAC reviews)

The Division of Medication Errors and Tech Support (DMETS) had no objection to the use of the proprietary name, Abraxane. Additionally, DMETS provided label & labeling recommendations in their reviews.

The Division of Drug Marketing, Advertising and Communications (DDMAC) found the proprietary name acceptable from a promotional perspective. DDMAC reviewers Joseph Grillo and Iris Masucci reviewed and commented on the draft labeling submitted in the application.

Data Integrity Issues (see Dr. Gan's Clinical Inspection Summary)

The Division requested that the Division of Scientific Investigation (DSI) inspect 5 sites in Russia (2 in Moscow, 3 in St. Petersburg).

Dr. Gan concluded that the clinical investigators at the five Russian sites "did not always adhere to good clinical practices governing the conduct of clinical investigations". However, Dr. Gan found the data from the sites adequate for efficacy evaluation. He noted that adverse events are underreported in Russia compared to the U.S., Canada and the U.K. for 4 of the 5 sites. Therefore, Dr. Gan recommended, for assessing adverse events, the Division consider using data reported by study subjects (patient) on the study questionnaire instead of physician's report.

Pediatric Considerations

Metastatic breast cancer does not exist in children so the Division granted a full waiver to the applicant regarding conduct of pediatric studies.

Conclusions

The study results from the randomized, multi-center, open-label, Study CA012-0 support the breast cancer efficacy claim based on the primary endpoint, reconciled target lesion response rate. Response rate served as a surrogate for the antitumor effects of the active ingredient, paclitaxel, in breast cancer patients. Comparing the effects of Abraxane and Taxol on this surrogate in breast cancer patients, the sponsor was able to reference the proven efficacy of

Taxol in breast cancer through the 505(b)(2) process. Through this process Abraxane is granted the same breast cancer indication as found in the Taxol label.

Although the regulatory goal was for Abraxane to demonstrate at least 75% preservation of the Taxol response rate, the Abraxane study exceeded this goal by showing a superior response rate to Taxol. The study also suggested that Abraxane might be superior with respect to a secondary endpoint, time to progression.

The applicant agreed to the following phase 4 commitments:

1. Submit survival data and analysis results from the randomized study CA012-0 when 80% of the patients have died. Data should be available for submission approximately June 2005.
2. Evaluate Abraxane safety and pharmacokinetics in subjects with hepatic impairment, to allow the determination of dosing adjustment for this population. The final report should be available for submission by December 2006

Grant Williams, MD
Deputy Director, Division of Oncology Drug Products

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Grant Williams
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MEDICAL OFFICER

Clinical Review of a New Drug Application

NDA Number:	21-660
Submission Number:	N-000
Drug Trade Name:	ABRAXANE™ for Injectable Suspension
Established Name:	Paclitaxel protein-bound particles for injectable suspension
Therapeutic Class:	Cytotoxic antineoplastic (taxane)
Applicant:	American Biosciences, Inc.
Review Priority:	Standard
Submission Date:	March 8, 2004
PDUFA Goal Date:	January 8, 2005
Primary Reviewer:	Nancy S. Scher, M.D.
Medical Team Leader:	Ramzi Dagher, M.D.
Project Manager:	Sheila Ryan, Pharm.D.

Table of Contents

Table of Tables

Table of Figures

The Executive Summary of the Primary Clinical Review

1 Recommendations

1.1 Recommendations on Approvability

The NDA for ABI-007 is filed under Section 505 (b)(2), referencing the label, efficacy and safety of Taxol (paclitaxel) Injection. We recommend approval of ABI-007 for the indication in the paclitaxel injection label based on clinical data from 460 patients in a randomized controlled comparative trial that provide evidence of safety and efficacy of ABI-007 compared to Taxol in metastatic breast cancer. The efficacy claim is supported by superiority for ABI-007 compared with Taxol for the primary response rate endpoint. Data from 106 patients accrued in two single arm open label studies provide additional support. ABI-007 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.

1.2 Recommendations on Postmarketing Studies and/or Risk Management Steps as Appropriate.

The appropriate dose of ABI-007 for patients with bilirubin greater than 1.5 mg/dL is not known. The effect of hepatic dysfunction on the disposition of ABI-007 has not been investigated. Since paclitaxel is metabolized by the liver, the applicant should study safety and pharmacokinetics in patients with hepatic impairment, in order to guide dosing.

The applicant has also agreed to fulfill a phase 4 commitment to provide survival data and analysis results from randomized study CA012-0 after 80% of patients have died.

2 Summary of Clinical Findings

2.1 Brief Overview of Clinical Program

A single randomized controlled, multi-center, phase 3 trial in 460 women with metastatic breast cancer demonstrated that ABI-007 260 mg/m2 IV over 30 minutes every 3 weeks was superior to Taxol 175 mg/m2 IV over 3 hours every 3 weeks for the primary response rate endpoint, with a similar safety profile. Data in two single arm trials from 103 patients with metastatic breast cancer were supportive of the efficacy and safety of ABI-007.

2.2 Efficacy

As a 505 (b)(2) application, referencing the label, efficacy and safety of Taxol (paclitaxel) Injection, the applicant was required to demonstrate non-inferiority (in response rate) to Taxol for the indication in metastatic breast cancer in a single, randomized, controlled, multi-center, open-label trial, with supportive data from single arm trials. In one single arm trial, 63 patients were treated with ABI-007 at a dose of 175 mg/m2 over 30 minutes every 3

weeks. The second trial treated 43 patients with ABI-007 at a dose of 300 mg/m^2 as a 30 minute infusion. Patients were treated without steroid premedication for ABI-007. Objective responses were observed in both studies.

The randomized controlled trial was conducted at 70 sites, located in Russia/Ukraine, Canada and the U.S., and the United Kingdom. A total of 460 patients were randomized in comparative trial CA012-0, 233 to the ABI-007 arm, and 227 patients to the Taxol arm. A total of 272 patients (58%) met the Taxol indication, of whom 129 were randomized to receive ABI-007 and 143 patients were randomized to receive Taxol. There were 189 patients (41%) who received study treatment as first-line therapy for metastatic breast cancer, 99 in the ABI-007 arm and 90 in the Taxol arm.

The primary efficacy endpoint was the confirmed reconciled Target Lesion Response Rate (*rec*TLRR). The response rate was based on independent, blinded radiologic assessment of digitized images through cycle 6, reconciled with investigator assessments (which also included clinical data). Lesions other than target lesions were considered in assessment of response only if progressive disease occurred in non-target lesions (nonTLs) or new lesions were identified. The confirmed *rec*TLRR was 21.5% (95% CI: 16.2%-26.7%) for ABI-007 patients and 11.1% (95% CI: 6.94-15.09) for Taxol patients (p=0.003). For the subgroup of 272 patients who met the Taxol indication, the responses were 15.5% and 8.4%, respectively. Although the difference was not statistically significant in this subgroup, the trend was in the same direction as for the overall study population. For the 189 first-line patients, the response rates were 31.3% and 17.8%, respectively, also favoring ABI-007.

Time to progression data from the randomized trial seemed to support the efficacy findings, but evaluation of this secondary endpoint was not rigorous enough to reach definite conclusions from a single, open-label trial. Survival data are not sufficiently mature to permit comparisons between the treatment arms.

2.3 Safety

The toxicity profile for ABI-007 was generally similar to that of Taxol, in spite of the 59% higher dose of paclitaxel delivered with each ABI-007 treatment. The substitution of albumin in ABI-007 for the Cremophor in Taxol as a solubilizing agent for paclitaxel has improved the safety profile and permitted the use of a more intense dosing regimen. Although routine corticosteroid premedication was not given with ABI-007, hypersensitivity reactions were significantly fewer in the ABI-007 arm compared with the Taxol treatment group (4% vs.12%). The percent of patients with neutropenia <0.5 X 10^9/L was less for ABI-007 (9%) than for Taxol (22%). The incidence of febrile neutropenia was low for both groups (2% and 1%, respectively).

No grade 4 sensory neuropathy occurred, but the percent of patients with any sensory neuropathy or grade 3 was higher for ABI-007 (71% and 10%, respectively) than for Taxol (56 % and 2%, respectively). The higher incidence of sensory neuropathy for ABI-007 patients compared with Taxol patients may reflect the much higher paclitaxel exposure per

dose. Of the 24 ABI-007 patients with grade 3 neuropathy, 14 improved after a median of 22 days; 10 patients resumed treatment at a reduced dose, and 2 discontinued due to peripheral neuropathy. Of the 10 patients without documented improvement, 4 discontinued the study due to peripheral neuropathy.

There were 6 deaths on study or within 30 days of study drug for patients in the ABI-007 treatment arm, and 8 deaths in the Taxol arm, all due to progression of cancer. Serious adverse events (SAEs) were reported in 28% of ABI-007 patients and 35% of Taxol patients, with neutropenia the most frequent SAE in both treatment groups. The most frequent toxicity leading to premature discontinuation was sensory neuropathy (ABI-007: 7 patients [3%] and Taxol: 2 patients [<1%]).

2.4 Dosing, Regimen, and Administration

The recommended dose of ABI-007 is 260 mg/m^2 administered intravenously over 30 minutes every 3 weeks. Routine premedication with corticosteroids to prevent hypersensitivity reactions is not required. Blood counts should be obtained before each treatment, and patients should not be treated unless the neutrophil count has recovered to 1500 cells/mm^3 and the platelet count to >100,000/mm^3. Dose reduction (to 220 mg/m^2) is recommended for neutropenia of < 500 cells/mm^3 lasting 7 days. Interruption of therapy is recommended for ≥ grade 3 sensory neuropathy until recovery to grade 1-2, with dose reduction for subsequent cycles of therapy. For recurrence of severe neutropenia or severe sensory neuropathy, additional dose reduction should be made to 180 mg/m^2.

2.5 Drug-Drug Interactions

Possible interactions of ABI-007 with concomitantly administered medications have not been formally investigated. Paclitaxel is metabolized primarily to 6-α-hydroxypaclitaxel by CYP2C8, and to two minor metabolites, 3'p-hydroxypaclitaxel and 6-α,3'-p-dihydroxypaclitaxel, by CYP3A4. Caution is required when ABI-007 therapy is given concomitantly with substrates or inhibitors of CYP2C8 and CYP3A4.
The proposed indication for ABI-007 is as a single agent in metastatic breast cancer. Since paclitaxel injection may have interactions, depending on the sequence of administration, with commonly used chemotherapy drugs such as doxorubicin and cis-platin, pharmacokinetic and drug-interaction studies should be done if ABI-007 is to be used or investigated in combination chemotherapy regimens.

2.6 Special Populations

ABI-007 should not be used in women who are pregnant or breast feeding infants, based on preclinical data for paclitaxel. The safety and effectiveness of ABI-007 has not been evaluated in children. ABI-007 has not been studied in patients with hepatic or renal dysfunction. The randomized controlled trial excluded patients for baseline serum bilirubin >1.5 mg/dL or baseline serum creatinine >2 mg/dL.

The ABI-007 breast cancer trials enrolled only females. In the randomized controlled trial, CA0120-0, there were 97% Caucasians in each arm of the trial; in the entire trial, 6 patients (1%) were black and 5 (1%) were Hispanic. Therefore, no evaluation could be made regarding the effect of gender, race or ethnicity on the safety and efficacy of ABI-007.

In the ABI-007 arm of trial CA0120-0, there were 199 (87%) patients younger than 65 years of age and 30 patients (13%) age 65 or older who were treated. In the Taxol arm, there were 193 patients (86%) younger than 65 years of age and 32 (14%) patients age 65 or older who were treated. For patients < age 65, the *rec*TLRR was 46/199 (23%) for the ABI-007 treatment group and 21/193 (11%) for the Taxol treatment group. For patients ≥ age 65, the *rec*TLRR was 9/30 (30%) for the ABI-007 treatment group and 4/32 (13%) for the Taxol treatment group. For both age groups, the *rec*TLRR is higher for ABI-007 patients than for Taxol patients. The number of patients ≥ age 65 is small, limiting the value of comparisons. In safety analysis by age, AEs did not appear more frequently for ABI-007 patients ≥ age 65 compared with younger patients. For Taxol patients, the percent of older patients with neutropenia, nausea and hyperglycemia was higher than for younger patients. For Taxol, 59% of patients ≥ age 65 and 47% of patients < age 65 experienced an adverse event of neutropenia. For Taxol, the incidence of patients with nausea was 38% for those age ≥ 65 and 18% for patients < age 65. The incidence of hyperglycemia was also higher for older Taxol patients than for younger patients < age 65, 19% and 5% respectively. The number of patients ≥ age 65 is too small for definite conclusions to be made.

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Clinical Review

1 Introduction and Background

1.1 Established and Proposed Trade Name of Drug, Drug Class, Sponsor's Proposed Indications(s), Dose, Regimens, Age Groups

1.1.1 Established Name: Paclitaxel protein-bound particles for injectable suspension (previously, *nab* paclitaxel for injectable suspension); Company Code Name ABI-007

1.1.2 Proposed Trade Name: Abraxane™

1.1.3 Drug Class: Cytotoxic antineoplastic; taxane

1.1.4 Applicant: American BioScience, Inc.
2730 Wilshire Boulevard, Suite 110,
Santa Monica, CA 90403

1.1.5 Applicant's Proposed Indication: "Abraxane™ (paclitaxel protein bound particles for injectable suspension) is indicated for —

1.1.6 Dosage and Administration: For metastatic breast cancer, the dosage is 260 mg/m2 administered intravenously over 30 minutes every 3 weeks. No premedication is advised. "Each mL of the reconstituted nanoparticle formulation will contain 5 mg/mL paclitaxel." The following instructions for preparation of ABI-007 for intravenous administration are taken from the proposed label:

1. Reconstitute each vial by injecting 20 mL of 0.9% Sodium Chloride Injection, USP.
2. Slowly inject the 20 mL of 0.9% Sodium Chloride Injection, USP, over a minimum of 1 minute, using the sterile syringe to direct the solution flow onto the inside wall of the vial.
3. DO NOT INJECT the 0.9% Sodium Chloride Injection, USP, directly onto the lyophilized cake as this will result in foaming.
4. Once the injection is complete, allow the vial to sit for a minimum of 5 minutes to ensure proper wetting of the lyophilized cake/powder.
5. Gently swirl and/or invert the vial slowly for at least 2 minutes until complete dissolution of any cake/powder occurs. Avoid generation of foam.
6. If foaming or clumping occurs, stand solution for at least 15 minutes until foam subsides.

1.1.7 How supplied: As a sterile lyophilized powder for reconstitution, "100 mg in a single use vial, individually packaged in a carton"

1.2 State of Armamentarium for the Indication

NDA 21660 is submitted as a 505(b)(2) application, referencing the label, efficacy and safety of Taxol (paclitaxel) Injection. In addition, the applicant has provided clinical trial data to support the indication "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." A number of chemotherapy drugs and drug combinations are approved or available in this clinical setting. For patients with metastatic breast cancer who are hormone receptor positive, hormonal therapy may be considered part of the armamentarium. For patients whose cancer over expresses HER-2, trastuzumab is an important part of the therapeutic armamentarium.

Several treatment choices are available at the present time for patients who have failed chemotherapy for metastatic disease or relapsed early after adjuvant therapy, and have previous exposure to or contraindication for anthracycline therapy. Approaches include combination chemotherapy, and or sequential single agent treatment. Single agents with reasonable response rates in second-line or greater therapy include the taxanes, paclitaxel injection (Taxol) and docetaxel injection concentrate, oral capecitabine, gemcitabine injection, and vinorelbine. Many patients will have already been exposed to cyclophosphamide as part of adjuvant or first-line therapy. An older combination regimen, mitomycin and vinblastine, is used less commonly since the development of newer combinations. In 2001, oral capecitabine was approved with docetaxel after failure of anthracyclines. Gemcitabine was approved in 2004 as first-line therapy in combination with paclitaxel after failure/contraindication of anthracyclines in the adjuvant setting, and is also available for use in second-line for patients who have not previously failed the components.

Among the unsettled issues in the therapy of advanced breast cancer with a taxane include the choice of taxane and the schedule (weekly or q 3 weekly). In an abstract (#10) presented at San Antonio in 2003, Jones et al reported a study of 449 women with doxorubicin resistant breast cancer who were randomized to treatment with paclitaxel 175 mg/m2 IV (3hours) q3week or docetaxel 100 mg/m2 (1 hour) q3week. Survival, TTP, and RR were higher for docetaxel than for paclitaxel, but the incidence of grade 3-4 hematologic and non-hematologic toxicity was higher for docetaxel. Several investigators have suggested that weekly administration of taxanes may be less toxic than conventional q3weekly dosing, possibly with greater efficacy. In an abstract (#512) at ASCO 2004, Seidman reported the results of CALGB trial #9840 in metastatic breast cancer in which 580 patients with metastatic breast cancer were randomized to receive either q3weekly dosing or "dose-dense" weekly dosing of paclitaxel. (There was a "patient sparing design," in that not all controls were concurrent.) For approximately 80% of subjects, study treatment was first-line. Weekly therapy was associated with improved TTP, less grade 3-4 neutropenia, but more grade 3-4 sensory neuropathy.

1.3 Important Milestones in Product Development

American BioScience, Inc. requests approval of their New Drug Application (NDA) for ABI-007 under section 505(b)(2) of the Food, Drug and Cosmetics Act (the Act), referencing the label, efficacy and safety of Taxol (paclitaxel) Injection (Bristol Myers Squibb Company). Taxol NDA 20-262 was approved December 29, 1992, for ovarian cancer and, subsequently, for additional indications, including, in April 1994, "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." ABI-007 was developed by American BioScience, Inc. (ABI) as a cremophor-free formulation of paclitaxel, with the proposed indication of "

The original Investigational New Drug Application (IND) #55974 was submitted by American BioScience, Inc., to the Food and Drug Administration (FDA) on May 12, 1998.

Table 1:Milestones in Drug Development (Reviewer Table)

5/12/1998	ABI submitted to Food and Drug Administration (FDA) original Investigational New Drug Application (IND) #55974
2/6/2001	End of Phase 2 Meeting. FDA agreed that filing under section 505(b)(2) would be acceptable, but clinical data from randomized controlled trials would be needed to support an indication for ABI-007 in a particular disease setting.
5/3/2001	End of Phase 2 follow-up meeting cancelled. FDA responses to submitted questions indicate acceptance of proposed phase 3 protocol (CA012-0), with changes to the statistical plan. Since ABI-007 and Taxol "have the same active ingredient...the Division would accept a single randomized, non-inferiority phase 3 study, maintaining at least 75% of the Taxol effect, with response rate as a primary endpoint. This phase 3 study, along with phase 2 data (study CA002) showing similar activity, would support approval of ABI-007 in a second-line metastatic breast cancer setting." FDA stated that ABI should "study a sufficient subset of patients (at least 100 treated with ABI-007) in Taxol's approved indication."
6/11/2001	Phase 3 protocol (CA012-0) submitted, entitled "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." (SN 070)
6/19/2001	Protocol amended to change treatment duration from a maximum of 3 cycles to 6 cycles and to change end of study from 9 weeks to 15 weeks. The design is for "210 evaluable patients (230 enrolled) per treatment arm with at least 100 patients per arm that have been previously treated with anthracyclines." (SN 071)

11/1/2001	First patient randomized in study CA012-0
11/30/2002	Enrollment closed for study CA012-0
1/16/2003	Fast Track status for ABI-007 for metastatic breast cancer granted under section 506 of the Food Drug and Cosmetics Act
3/19/2003	Pre-NDA meeting. FDA emphasized the importance, for a 505(b)(2) submission, of documenting that study patients had failed combination chemotherapy for metastatic breast cancer or relapsed within 6 months of adjuvant chemotherapy. "Previous chemotherapy should have included an anthracycline unless contraindicated," and the reason should be indicated. Randomization within each country was to be into two strata, anthracycline naïve and anthracycline treated.
4/7/2003	Data cut-off date (date of Cycle 4/Week 9 assessment for last patient entered); patients with ongoing benefit continued treatment beyond 6 cycles.
6/30/2003	Rolling NDA: Submission of pharmacology/toxicology portion
8/21/2003	Rolling NDA: Submission of chemistry/manufacturing/controls portion
11/21/2003	Meeting to discuss planned clinical submission. The statistical analysis plan (v3.0, submissions #275 and 279) defined 3 sets of response data (investigator, independent radiology group, and reconciled). The applicant specifies that "reconciled response" is the "primary response dataset."
3/8/2004	Rolling NDA: Submission of clinical portion
5/7/2004	NDA filed as a standard review
1/8/2005	User fee goal date

1.4 Other Relevant Information

ABI-007 has not been approved for use in any country.

1.5 Important Issues with Pharmacologically Related Agents

The two approved taxanes, paclitaxel (Taxol) and docetaxel (Taxotere), require premedication with corticosteroids to diminish the risk of hypersensitivity reactions and, for docetaxel, to diminish the risk of severe fluid retention. Both taxanes require the use of special intravenous tubing and containers formulated without plasticized polyvinyl chloride (PVC) to minimize leaching of the plasticizer into the intravenous infusion.

To achieve solubility, Taxol is formulated with 527 mg Cremophor-EL (polyoxyethylated castor oil) and 49.7% (v/v) dehydrated alcohol for each ml of solution containing 6 mg of paclitaxel. To reduce the incidence and severity of Cremophor-related acute hypersensitivity reactions, patients must be premedicated with corticosteroids and H1 and H2 blockers (antihistamines). Taxotere is formulated with polysorbate 80 to enhance solubility and requires a diluent consisting of 13% (w/w) ethanol in water. Premedication with corticosteroids is required , with 3 three days of oral dexamethasone in the labeled regimen, to reduce the incidence of acute hypersensitivity reactions and fluid retention with Taxotere.

ABI-007 is formulated without Cremophor (or polysorbate 80) and is solubilized with albumin to create a "nanoparticle formulation". The applicant states that the differences in formulation obviate the need to premedicate patients with corticosteroids and antihistamines to reduce the incidence of severe hypersensitivity reactions and the need to use specialized non-PVC drug delivery systems. The applicant also indicates that formulation with Cremophors may limit the dose of Taxol that can be administered and require "extended infusion times."

2 Significant Findings from Chemistry, Animal Pharmacology and Toxicology, and/or Microbiology

2.1 Chemistry

Paclitaxel is the active ingredient in ABI-007. The supplier of paclitaxel is which extracts paclitaxel from the roots of the yew tree, *Taxus media*. In the production of ABI-007, albumin is used to solubilize paclitaxel, resulting in an albumin-bound form of paclitaxel with a mean particle size of approximately 130 nanometers in diameter.

The source of albumin is — (USP). As a plasma-derived product, the J

Reviewer Comment: *Although the risk of transmission of viral or prion infection seems exceedingly low, with current knowledge, it cannot be guaranteed to be zero. The Abraxane label should include language similar to that required in other albumin-containing products.*

Slight variations were reported in batches of ABI-007 used for clinical trials, compared with the to-be marketed formulation, regarding the ratio of human albumin to paclitaxel (weight/weight) and pH of the product. The lot numbers of ABI-007 used in the phase 3 trial CA012-0 are: C101-001; C101-002; C101-003; C102-001; and C102-003. The ratio of

human albumin to paclitaxel (weight/weight) is 9:1 for all these lots, except for C101-002, for which it is 8:1. The pH range is — For lot number C102-004, used in the comparative pharmacokinetic (PK) study CA-008, the human albumin to paclitaxel ratio is — and pH is — The specifications for —stability lots of the to-be-marketed formulation are albumin:paclitaxel ratio of — and the pH range is —

Nomenclature

Following consultation with the CDER Labeling and Nomenclature Committee, it was recommended that the established name for the ABI-007 drug product should be "paclitaxel protein-bound particles for injectable suspension". To further differentiate Abraxane from currently marketed paclitaxel drug products, the applicant was given the option to add a parenthetical statement underneath the name of the drug product. The applicant chose the phrase "albumin-bound" to be placed parenthetically underneath the ABRAXANE name.

2.2 Animal Pharmacology and Toxicology

(See separate review of Dr. Margaret Brower, from which the following synopsis is abstracted.) The natural biosource formulation of ABI-007 utilized for phase 3 studies and to be marketed "exhibited a slightly higher systemic exposure, with an extended half-life compared to the — s" used in early studies. Acute toxicity and lethality of ABI-007 were "significantly reduced as compared to Taxol, based on comparative lethal doses and MTDs." Renal toxicity was observed in single-dose studies in rats with ABI-007 at doses > 540mg/m2, and lethality at doses > 720 mg/m2. Rats treated with ABI 540 mg/m2 had swollen nerve root axons, not observed in animals administered Taxol. Neurotoxicity of ABI-007 in dogs was enhanced compared to Taxol, although toxicology studies in this species "may have been complicated by the immunological reaction of the human albumin." ABI-007 is embryotoxic and fetotoxic to rats when administered during gestation days 7-17 at a dose approximately equivalent to "0.02 of the daily maximum recommended human dose on a mg/m2 basis."

The Pharmacology and Toxicology reviewer stated that "Preclinical studies demonstrated tumor accumulation of ABI-007 was higher than that of Taxol", and "The binding of the ABI-007 formulation to human serum albumin, microtubules and endothelial cells appeared to be superior to that of Taxol." Based on preclinical findings, the applicant hypothesizes that ABI-007 facilitates transport of paclitaxel across endothelial cells and into tumors via an albumin receptor.

2.3 Microbiology

The Microbiology consultant, Dr. Stephen Langille, recommended "approval from the standpoint of product quality microbiology."

3 Human Pharmacokinetics and Pharmacodynamics

3.1 Pharmacokinetics

Pharmacokinetic (PK) parameters were determined in phase 1, 2, and 3 trials after IV infusion over 30 and 180 minutes. Drug exposure for ABI-007 increased linearly with doses from 80 to 375 mg/m2. (The maximum tolerated dose of ABI-007 was 300 mg/m2.) PK parameters of paclitaxel for ABRAXANE were independent of the duration of administration. Although paclitaxel is highly protein-bound (89-98%), the applicant assayed concentration of total paclitaxel, rather than free paclitaxel, in the clinical studies.

Study CA008-0, a comparative pharmacokinetics study of ABI-007 and Taxol (paclitaxel injection), was conducted after the randomized phase 3 study (CA012-0) had completed enrollment. The subjects (n=12) were a non-randomized population of patients with metastatic solid tumors recruited from several of the Russian sites. ABI-007 was administered at a dose of 260 mg/m2 IV over 30 minutes, and paclitaxel injection 175 mg/m2 was administered IV over 3 hours. ABI-007 showed a higher total clearance (43%) and larger volume of distribution (53%) than paclitaxel injection. The terminal half life (approximately 21 hours) was the identical for both drugs. There was extensive non-renal clearance.

No drug-drug interaction studies were done for ABI-007. The applicant did not study ABI-007 in patients with either hepatic or renal impairment. Paclitaxel is metabolized primarily to 6-α-hydroxypaclitaxel by CYP2C8, and to two minor metabolites, 3'p-hydroxypaclitaxel and 6-α,3'-p-dihydroxypaclitaxel, by CYP3A4.

3.2 Pharmacodynamics

No special pharmacodynamic studies were performed. (See safety and efficacy sections for randomized trial CA0012-0 results.)

4 Description of Clinical Data and Sources

4.1 Sources of Clinical Data

ABI requests approval of ABI-007 under section 505(b)(2) of the Food, Drug and Cosmetics Act (the Act), referencing the label, efficacy and safety of Taxol (paclitaxel) Injection. In addition, the applicant provided clinical trial data to support the indication "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." NDA 21660 contains the clinical data as an electronic submission, with paper copies also of the text of study reports. Study CA012-0, the phase 3 trial, was conducted at 70 sites, located in Russia/Ukraine, the U.S. and Canada, and the United Kingdom (U.K.). Patients with metastatic breast cancer were randomized to receive either ABI-007 or Taxol. The trial included both first-line and ≥ second-line patients, and some patients had not received prior anthracycline therapy. A phase 2 trial, CA002, was performed in patients with metastatic breast cancer and was to provide support for the phase 3 data. CA-008, a comparative PK study, was performed at sites in Russia in patients with metastatic solid tumors treated either with ABI-007 or Taxol. Study CA-008 and PK data

from other studies are the subject of a separate Review by Dr. Angela Men. (Also, see above, section 3.1, for a brief synopsis of PK findings.)

4.2 Overview of Clinical Trials

The following table lists the clinical trials submitted to this NDA. In addition, Study Synopses were filed for ongoing studies: CA005-0, a phase 1 trial of weekly ABI-007 (3 weeks out of 4) in patients with non-hematologic malignancies; CA013-0, a phase 2 trial of ABI-007 weekly in taxane resistant patients with metastatic breast cancer; CA009-0, phase 2 trial of ABI-007 in non-hematologic malignancies; CVR-001-0, a phase 2 trial of ABI-007 for in-stent restenosis.

Table 2: Clinical Trials Submitted to NDA (Reviewer Table)

STUDY NUMBER	POPULATION	TREATMENT	NUMBER of PATIENTS	PRIMARY ENDPOINT
CA012-0 Phase 3	Metastatic breast cancer	ABI-007 260 mg/m2 IVq3wk Vs. Taxol 175 mg/m2 IVq3wk	ABI = 233 (plus PK sub study = 12) Taxol = 227	Reconciled Target Lesion Response Rate (*rec*TLRR)
CA002-0 Phase 2	Metastatic breast cancer	ABI-007 300 mg/m2 IVq3wk	63	Safety, tolerability, anti-tumor effect (TLRR)
CA002-0LD Phase 2	Metastatic breast cancer	ABI-007 175 mg/m2 IVq3wk	43	Safety, tolerability, anti-tumor effect (TLRR)
DM97-123 Phase 1-2	Solid tumors/ breast cancer	ABI-007 135, 200, 300 or 375 mg/m2 IVq3wk	19 (16 PK)	Dose ranging, safety, and PK

4.3 Postmarketing Experience

ABI-007 is not currently marketed in any country.

4.4 Literature Review

The applicant provided an extensive bibliography dealing with taxane and ABI-007-related preclinical and clinical issues. The clinical reviewer searched PubMed, using terms linking breast cancer with taxanes or paclitaxel or ABI-007 or nab paclitaxel. Several updated references were found and are among those listed in the Bibliography in the Appendix of this document. The ABI-007 phase 3 randomized trial data was presented by O'Shaughnessy at the San Antonio Breast Cancer Symposium (abstract #44) in 2003. In 2004 (ASCO abstract #543), Blum presented phase 2 single arm trial data from 66 evaluable patients (106 enrolled) with taxane-refractory, measurable metastatic breast cancer. Patients received ABI-007 100 mg/m2 IV over 30 minutes on day 1,8, and 15 of a 28-day cycle without pre-medication. Responses were observed in 13/66 (20%). The only grade 4 toxicity was neutropenia in 5

(8%) patients, and there was 1 case of febrile neutropenia. Grade 3 nausea was observed and grade 3 infection (3 patients). There were several grade 1-2 toxicities, including 1 patient with grade 1 neurotoxicity. Data from this trial using an escalated weekly dose of ABI-007 125 mg/m2 IV were presented at San Antonio in December 2004. Objective responses occurred in 9/75 (12%) patients. Dose modification for toxicity was required for approximately 25% of patients. The incidence of grade 3 neuropathy was 17%.

5 Clinical Review Methods

5.1 Describe How Review was Conducted

The NDA is filed under section 505 (b)(2), referencing the label, efficacy and safety of Taxol (paclitaxel) Injection (See Section 1.3). ABI performed a single, open label, randomized phase 3 trial to support the indication in metastatic 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". The phase 3 trial, (CA012-0) was the focus of the clinical review of efficacy and safety. FDA reviewed the original phase 3 protocol and amendments, study reports, case report forms (CRFs) and data. FDA employed a consultant radiologist, Dr. Erini Makariou, to review a subset of subjects' digitized radiographs to verify tumor response. Electronic data sets, raw and derived, were reviewed in detail to verify the applicant's claims for efficacy and safety. Study reports and summary data were reviewed for the phase 2 trial (CA-002-0) to provide additional support to the efficacy and safety of ABI-007. Study reports and summary data were also reviewed for (low dose) phase 2 trial CA- 002-0LD and comparative PK study (CA-008).

5.2 Overview of Materials Consulted in Review

The following materials were reviewed by the medical officer:

- The regulatory history of the application
- Submissions to IND #55974
- Correspondence between the applicant and FDA in Division Files
- Original submissions of protocol CA012-0 and amendments
- Digitized radiographs of selected patients for CA012-0
- NDA electronic submission, including raw and derived electronic datasets
- Study report and selected CRFs from trial CA012-0
- Study reports and summary data for CA-002-0LD, DM97-123, CA-008
- Relevant published literature
- Electronic labeling proposal and comparison to Taxol label
- Applicant presentation to FDA on April 22, 2004.

5.3 Overview of Methods Used to Evaluate Data Quality and Integrity

FDA's Division of Scientific Investigation (DSI) audited selected centers to assess data quality and integrity. David Gan, M.D. and other members of DSI inspected five sites in each of two cities in Russia, Moscow and St Petersburg. These sites were chosen because

they were high accrual sites. Of 460 patients enrolled in study CA012-0, 353 were from sites in Russia/Ukraine. The five Moscow and St. Petersburg sites inspected enrolled a combined total of 141 patients. Sites 308 and 313 were also chosen for inspection because they had an exceptionally high proportion of patients responding to ABI-007 (58% and 53%, respectively). The sites inspected were:

Table 3: DSI Audit Sites (Reviewer Table)

Site #	Site Location and Name of Principal Investigator	# of Subjects	Abraxane Response Rate (%)*	Taxol Response Rate (%)*
313	Russian Cancer Research Center n.a. Blokhin, Moscow, Prof S. Tjulandin	34	10/19 (53)	1/15 (7)
308	Russian Cancer Research Center n.a. Blokin, Moscow, Prof M. Lichinitser	29 (+ PK 5)	7/12 (58)	6/17 (35)
311	Petrov Research Institute of Oncology, St. Petersburg, Prof V. Moiseyenko	32 (+ PK 1)	5/12 (42)	4/20 (20)
312	Petrov Research Institute of Oncology, St. Petersburg, Prof V. Semiglazov	29 (+ PK 1)	3/13 (23)	4/16 (25)
305	Petrov Research Institute of Oncology, St. Petersburg, Prof M. Gershanovich	17	2/8 (25)	0/9 (0)

*Confirmed overall investigator response rate (per applicant)

Dr. Gan reported that there was "sufficient documentation to assure that all audited subjects did exist, fulfilled the eligibility criteria, and were available for the duration of the study, and that all enrolled subjects received the assigned study drug and had clinical and laboratory parameters recorded, completed the study, and had their primary efficacy endpoints (although very subjective) captured as specified in the protocols and amendments and correctly reported to the sponsor." He indicated that he "did not observe any wrong doing in deciding the primary endpoint", which is "very subjective".

FDA also assessed data quality and integrity by consulting an independent radiologist, Dr. Erini Makariou, to audit selected patient radiographs. The digitized images were provided remotely to FDA computers by WorldCare, the applicant's contract, blinded radiology group. Although there were infrequent discrepancies between the findings of Dr. Makariou and WorldCare, there was no evidence of a systemic problem with WorldCare's interpretations. (Also, see Efficacy section.)

5.4 Were Trials Conducted in Accordance with Accepted Ethical Standards?

The applicant indicates that clinical trials were conducted in compliance with Good Clinical Practice (GCP) Guidelines of the International Conference on Harmonization (ICH) and in compliance with the World Medical Association Declaration of Helsinki. The protocol, protocol amendments and "other appropriate related materials" were reviewed by the Institutional Review Boards (IRBs) before implementation. Written informed consent was obtained before enrollment of subjects in the trials in accordance with Title 21 CFR, Part 50, and in accordance with applicable regulatory bodies for sites outside the United States (U.S.).

5.5 Evaluation of Financial Disclosure

Bruce Clark, CPA, the Controller of American BioScience, Inc., signed the *Certification: Financial Interests and Arrangements of Clinical Investigators* (OMB Form No. 0910-0396). No investigator's compensation from the company would be affected by the outcome of the study. Each investigator was required to disclose proprietary interest in the product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) disclosed no such interests, *except* ABI was unable to obtain current contact information for one Sub investigator, [redacted]. This individual participated in study CA002-0LD, a phase 2 trial, for which the [redacted] recruited only 3 of 43 patients into the study. ABI reasonably states that "failure to obtain the necessary financial disclosure from this single sub investigator" would not likely impact the conclusions from this supportive study.

6 Integrated Review of Efficacy

6.1 Brief Statement of Conclusions

In a randomized controlled trial of women with metastatic breast cancer, ABI-007 260 mg/m2 IV over 30 minutes every 3 weeks was shown to be superior for the primary response rate endpoint compared with Taxol 175 mg/m2 IV over 3 hours every 3 weeks. A total of 460 patients were randomized in comparative trial CA012-0, 233 patients to the ABI-007 arm, and 227 patients to the Taxol arm. A total of 272 patients (58%) met the Taxol indication, of whom 129 were randomized to receive ABI-007 and 143 were randomized to receive Taxol. There were 189 patients (41%) who received study treatment as first-line therapy for metastatic breast cancer, 99 in the ABI-007 arm and 90 in the Taxol arm.

The applicant determined that 55 patients treated with ABI-007 (24%) and 25 patients treated with Taxol (11%) had CR or PR by the confirmed reconciled Target Lesion Response (*rec*TLR), the primary efficacy endpoint. The FDA clinical reviewer's adjudication of response excluded 5 ABI-007 patients, resulting in 50 and 25 responders in the ABI-007 and Taxol arms respectively. The *rec*TLR rate was 21.5% (95% CI: 16.2%-26.7%) for the ABI-007 patients and 11.1%, (95% CI: 6.94-15.09) for the Taxol patients (p=0.003). This suggests superiority for the primary endpoint for the entire study population. (See Table 33). For the 272 patients who met the Taxol indication, based on the FDA clinical reviewer's adjudication, there were 20 and 12 responders in the ABI-007 and Taxol arms, respectively. The response rates were 15.5% and 8.4%, for ABI-007 and Taxol groups, respectively. Although the difference was not statistically significant in this subgroup, the trend was in the same direction as for the overall study population. For the 189 first-line patients, the response rates were 31.3% and 17.8%, respectively, also favoring ABI-007.

The confirmed investigator overall response rate (*inv*ORR) was a secondary endpoint based on the investigator's assessment's over all treatment cycles (including > cycle 6), using TL and nonTL responses according to RECIST. The *inv*ORR also demonstrated superiority of ABI-007 over Taxol for the entire study population (33.2% vs. 18.7%). The observed median for Time to Progression (TTP), based on the reconciled response dataset, was 17.0

weeks for the ABI-007 patients and 15.6 weeks for the Taxol patients. The data are not sufficiently mature for comparisons for the additional secondary endpoints of duration of response and overall survival.

6.2 General Approach to Review of the Efficacy of the Drug

The NDA is filed under Section 505 (b)(2), referencing the label, efficacy and safety of Taxol (paclitaxel) Injection (See Section 1.3). The efficacy review is based primarily on the results of study CA012-0, a single phase 3, open label, multicenter, randomized trial performed to support the indication for ABI-007 in metastatic breast cancer. Study CA012-0 was conducted at 70 sites, located in Russia/Ukraine, the U.S. and Canada, and the U.K.. Patients with metastatic breast cancer were randomized to receive either ABI-007 or Taxol. The trial included both first-line and ≥second-line patients, and some patients had not received prior anthracycline therapy. The phase 2 trial, CA002-0, was performed in patients with metastatic breast cancer. The results of CA002-0 are summarized in Section 6.4. This single arm trial treated patients with a higher dose of ABI-007 (300 mg/m2 IV q3 week) than was used in the randomized phase 3 trial (260 mg/m2 IV q3 week). (See Section 4.2 for a table of clinical trials submitted to the NDA.)

6.3 Detailed Review of Randomized Trial CA012-0

The efficacy review is based primarily on a single, multicenter, open label, randomized trial of ABI-007 compared with Taxol in women with metastatic breast cancer. Study CA012-0 is entitled "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." The principal investigator was William Gradishar, MD, Northwestern University Medical School, Chicago, Illinois. The study was performed at 70 participating institutions, 28 in the United States and Canada, 22 in Russia and the Ukraine, and 20 in the United Kingdom.

6.3.1 Protocol Review

Table 4: Milestones for Study CA012-0 (Reviewer Table)

Milestone	Date	# Patients* Randomized	Highlights/Comments
First patient randomized	11/1/2001		
Amendment 1	1/28/2002	26	• Inclusion criteria changed to require prior chemotherapy to have included an anthracycline unless contraindicated • Dosing capped at surface area 2 m^2 • Changed definition of ITT population from exposure to ≥ 2

			cycles to ≥ 1 cycle of therapy • Added dose delay procedures • Only target lesions (TLs) to be evaluated for primary endpoint. • Imaging studies to assess response after cycles 2, 3 and 5, with confirmation of response at weeks 9 and 15 • Overall response to include TLs and non-TLs
Amendment 2	7/22/2002	294	• Inclusion criteria changed to remove requirement for prior anthracycline • WorldCare designated central image reader
Interim analysis by Data Monitoring Committee	10/8/2002	401	After response assessed for 105 pts treated for ≥ 2 cycles in each arm. No excess toxicity. No change in sample size.
Last patient accrued	11/29/2002	472*	
Data cut-off date	4/7/2003		Date of 9-week assessment for last patient entered
Amendment 3	5/23/2003		PK patients not to be included in analyses of randomized patients
Data lock date	9/3/2003		
NDA submission (clinical portion)	3/8/2004		

*Source for # patients randomized by date: Dataset "survival"; includes 12 PK patients

Study Synopsis/Design

Protocol CA012-0 is a multicenter (70 sites), international (22 sites in North America, 20 sites in U.K., 28 sites in Russia/Ukraine), controlled, randomized, open label, phase 3 trial comparing safety/tolerability and anti-tumor effect of ABI-007 to Taxol in women with metastatic breast cancer. Within each country, patients were randomized separately according to whether they had or had not previous anthracycline therapy. The requirement for patients to have had previous chemotherapy in the metastatic setting (or progression within 6 months of adjuvant chemotherapy) and previous anthracycline exposure was waived after accrual of > 100 patients in each arm of the trial.

The randomization ratio was 1:1, for patients to be treated intravenously every 3 weeks with either ABI-007 260 mg/m2 IV over 30 minutes or Taxol 175 mg/m2 IV over 3 hours. Patients were to be treated for up to 6 cycles and patients without progression could be treated for a longer period, at the discretion of the investigator. Patients were to be assessed

with imaging studies for response after cycles 2, 3, and 5, with confirmation of response at weeks 9 and 15.

The protocol defines the primary efficacy endpoint as the target lesion response rate achieved after a minimum of two cycles of treatment, using Response Evaluation Criteria in Solid Tumors (RECIST). The trial was designed as a non-inferiority trial, with a goal of enrolling 210 evaluable patients per arm, with at least 100 patients per arm who had previously been treated with anthracycline-based chemotherapy. Interim analysis was prespecified in order to re-estimate sample size after 105 patients in each arm were treated and evaluated for 2 cycles.

Reviewer comment: *In fact, the specified primary efficacy endpoint is a modification of RECIST. RECIST requires designation of an overall response taking into consideration both target and non-target lesion responses, and development of new disease. Although amendment 1 to the protocol specified only target lesions would be assessed for the primary endpoint, subsequently, the applicant specified that patients would not be considered to have a target lesion response if there were progression of non-target lesions or any new disease. In the study report, the applicant further defines the primary efficacy endpoint as the* "reconciled *Target Lesion response"* (rec*TLRR)." This endpoint was chosen to decrease bias, since it incorporates the blinded assessment of response performed by the WorldCare radiologist. An algorithm prespecifies how to reconcile disagreements between the independent radiologist and investigator assessments of response(which could include clinical data) . Since WorldCare only reviewed images for the first 6 cycles of therapy, the primary endpoint requires confirmation of response by cycle 6*

In the study report, the "investigator *Overall Response Rate"* (inv*ORR) is described as a secondary endpoint, based on the investigator's assessment of best confirmed response through all cycles, including evaluation of TLs and nonTLs, including disease which could be evaluated by physical examination and sonogram, not accessible to WorldCare.*

Study Objectives

The study objectives are taken directly from section 2.1 of the protocol.
Primary:

- To compare antitumor activity of ABI-007 with that of Taxol in metastatic breast cancer patients
- To evaluate safety/tolerability of ABI-007 compared to Taxol

Secondary:

- To evaluate time to disease progression and survival
- To evaluate changes from baseline in Quality of Life (QOL)
- To determine PK of ABI-007

Eligibility Criteria

The eligibility criteria are taken directly from section 3.3.1 and 3.3.2 of the protocol.

Inclusion criteria:

1. Patient is female, non-pregnant and not lactating, and ≥ 18 years of age. If patient is of chil bearing potential, as evidenced by regular menstrual periods, she must have a negative seru pregnancy test (β-hCG) within 72-hours prior to first study drug administration and, if sexual active, agrees to utilize contraception considered adequate and appropriate by the investigato
2. Patient has histologically or cytologically confirmed measurable metastatic breast cancer wh is a candidate for paclitaxel therapy in accordance with standard of care;
3. If patient has received TAXOL or docetaxel as adjuvant therapy, the patient must not hav relapsed with breast cancer within one year of completing adjuvant TAXOL or docetaxel;
4. Patient has no other malignancy within the past five years, except non-melanoma skin cance cervical intraepithelial neoplasia (CIN), or in-situ cervical cancer (CIS);
5. Patient is a suitable candidate for single agent paclitaxel treatment;
6. Patient has hematology levels at Baseline of:
   - ANC ≥ 1.5 x 10^9 cells/L (1500 cells/mm^3);
   - Platelets ≥ 100 x 10^9 cells/L (100,000 cells/mm^3);
   - Hgb ≥ 90 g/L (9 g/dL);
7. Patient has the following chemistry levels at Baseline:
   - AST (SGOT), ALT (SGPT) ≤ 2.5 x upper limit of normal range (ULN) if no evidence of liv metastases;
   - AST (SGOT), ALT (SGPT) ≤ 5.0 x upper limit of normal range (ULN), total bilirubin ≤ 2 µmol/L (1.5 mg/dL) if liver metastases are present;
   - Total bilirubin ≤ 26 µmol/L (1.5 mg/dL);
   - Creatinine ≤ 177 µmol/L (2 mg/dL);
   - Alkaline phosphatase ≤ 5x ULN (unless bone metastasis is present in the absence of liver metastasis);
8. Patient has an expected survival of > 12 weeks;
9. Patient or his/her legally authorized representative or guardian has been informed about the nature of the study, and has agreed to participate in the study, and signed the Informed Consent form prior to participation in any study-related activities.

Reviewer comment: *During part of the trial, patients were recruited to meet criteria similar to the Taxol indication, specifying that patients should have failed prior chemotherapy either in the adjuvant or metastatic setting and prior therapy should have included an anthracycline unless contraindicated. After enrolling more than 100 patients in each arm of the trial who had previous anthracycline exposure, the requirement for prior therapy was waived, so that patients could be treated with study drug as first-line therapy in the metastatic setting.*

Exclusion criteria:

1. Patient has clinical evidence of active brain metastases, including leptomeningeal involvement, requiring steroid or radiation therapy;
2. The only evidence of metastasis is lytic or blastic bone metastases or pleural effusion or ascites;
3. The patient has a clinically significant concurrent illness (as determined by the Principal Investigator);
4. The patient has an ECOG (Zubrod) performance status of > 2 (see Appendix F);
5. The patient, is, in the investigator's opinion, unlikely to be able to complete the study through the End of Study (EOS) visit;
6. The patient receives treatment with any:
   -hormonal therapy 2 weeks prior to first dose;
   -chemotherapy (except for palliative bisphosphonate therapy for bone pain which can be administered as clinically indicated) 4 weeks prior to first dose;
   -investigational drug or immunotherapy within 4 weeks prior to first dose;
   -concurrent radiation therapy (except for palliative radiotherapy for bone pain which can be administered as clinically indicated);
7. Patient has received paclitaxel or docetaxel because of **metastatic carcinoma;**
8. Patient has pre-existing peripheral neuropathy of NCI Toxicity Criteria Scale of Grade ≥ 1;
9. Patient has a history of allergy or hypersensitivity to the study drugs or any of its excipients;
10. Investigator considers the patient unsuitable to receive an experimental drug.

Treatment

Patients were treated intravenously every 3 weeks with either ABI-007 260 mg/m2 IV over 30 minutes or Taxol 175 mg/m2 IV over 3 hours. Patients were to be treated for a minimum of 2 cycles to assess response and a maximum of 6 cycles. However, patients without progression could be treated for a longer period, at the discretion of the investigator. Steroid premedication was *not* to be given to ABI-007 patients "unless the Principal Investigator or designee deems it necessary". Prior to administration of Taxol, patients were to be pre-medicated with corticosteroids, H1 and H2 blockers.

Dose Adjustments

Dose adjustments for Taxol were to be made in accordance with the package insert authorized in the country in which the study was conducted. For ABI-007, a maximum of 2 dose reduction levels was specified, to 220 mg/m2 and then to 180 mg/m2. No action was to be taken for the first incidence of acute neutrophil count (ANC) $< 0.5 \times 10^9$ /L without fever, but dose reduction was to be instituted for recurrence or for the first instance of neutropenic fever/sepsis. For subsequent cycles, either the dose could be maintained if G-CSF were given prophylactically or, in the absence of growth factor therapy, dose-reduction would be required. For grade 3 or 4 thrombocytopenia, dose reduction was required. Dosing was not to be resumed until ANC was $\geq 1.5 \times 10^9$ cells/L and platelets $\geq 10^9$ cells/L. For any non-hematological toxicity ≥ grade 2, dose delay was permitted, but was *not mandated* except for

neurotoxicity. For any grade 3 or 4 non-hematological toxicity, dose reduction was required, up to a maximum of 2 dose reduction levels (see above).

Patients were considered to have failed therapy and were to be discontinued from study for progressive disease after a minimum of 2 cycles of study drug.

Concomitant Medications

Since paclitaxel is metabolized through CYP2C8 and CYP3A4 isoenzymes, the protocol recommended "caution" in the administration of substrates or inhibitors of CYP2C8 and CYP3A4. Patients in both arms of the protocol were excluded from taking "ritonavir, saquinavir, indinavir, nelfinavir, doxorubicin, any taxane, anthracycline, anti-cancer drug or other investigational study drug." (See above section , "Treatment," regarding premedication for chemotherapy, and see "Dose Reductions," regarding growth factor therapy.)

Pharmacokinetic Evaluations

Twelve patients from multiple sites were to be assigned directly to ABI-007 and "not be included in the analyses of randomized patients." Nineteen samples were to be collected at time points from time zero to 72 hours post dose. Eight urine samples were to be collected from pre-dose to 96-120 hours post dose.

Schedule of Assessments

The following schedule is taken directly from section 5.2 of the protocol.

Table 5: Schedule of Assessments (Applicant Table)

ASSESSMENT	BL	WK0 C1	W1	W2	W3 C2	W4	W5	W6 C3	W7	W8	W9 C4	W10	W11	W12 C5	W13	W14	W15 C6 (EOS[a])	W16	W17	W18 (if no further trt)	W 18 and q3 wks if further trt[b]	F/U[c]	Phone F/U
Informed Consent	X																						
Medical History[d]	X																						
Conc. Medication Evaluation	X	X			X			X			X			X			X				X	X	
Conc. Procedure Evaluation		X			X			X			X			X			X				X	X	
Physical Examination/Vital Signs	X	X			X			X			X			X			X				X	X	
ECOG (Zubrod) Scale	X	X			X			X			X			X			X					X	
EORTC QLQ-C30	X							X			X						X					X	
Peripheral Neuropathy Assessment[e]	X	X			X			X			X			X			X					X	
Adverse Event Evaluation		X			X			X			X			X			X				X	X	
Assessment of Toxicities		X			X			X			X			X			X				X	X	
EKG	X																					X	
Echocardiogram/MUGA[f]	X										X						X					X	
Chest X-ray[g]	X						X				X						X				X		
Bone Scan[h]	X																				X		
X-Ray (of positive bone scans)[h]	X						X				X						X				X		
Imaging Studies of tumor[i]	X						X				X						X				X		
CBC, diff., platelet count[j]	X	X		X	X		X	X		X	X		X	X		X	X		X		X	X	
Clinical Chemistry Panel	X	X			X			X			X			X			X		X		X	X	
Serum ß-hCG[k]	X																X						
Telephone Follow-Up[l]																							X

a EOS = End of Study. Although the final study assessments (with the exception of the safety lab monitoring) will be performed at Week 15 (Cycle 6), the primary efficacy endpoint (PEE) may be established as early as week 9. If a patient discontinues prematurely from the study EOS should be completed as soon as feasible. Patients who are found to have progressive disease during the study will be discontinued from the study and EOS evaluations should be performed.

b Patients who complete 6 cycles of therapy who do not have PD will be able to continue their arm of treatment (ABI-007 or TAXOL) at the Investigator's Discretion, provided the withdrawal criteria in section 3.3.4 have not been met. Patients who receive continued therapy will have assessments every three weeks, as noted, prior to study dosing, in addition to further assessments deemed necessary by the PI. Imaging studies to be performed at PI discretion. When the patient is withdrawn from continued therapy, the F/U assessments and Phone F/U will be performed as specified.

c F/U=Follow-up evaluations should be performed 30 days (± 2 days) of final study drug administration.

d Medical history should include the assessment of whether patient has any evidence of anthracycline-related cardiac abnormality.

e The occurrence of peripheral neuropathy will be reported by the investigator as an adverse event or SAE. Patient self-evaluation of peripheral neuropathy events will be performed at Baseline, at each treatment cycle and at Follow-up visit.

f A baseline Echocardiogram or MUGA will be performed only for patients who exhibit congestive heart failure symptoms or if otherwise clinically indicated (for example, in patients who have received extended high cumulative doses of anthracycline).

g If the Baseline chest x-ray results are positive, a CT of the thorax must be performed. If Baseline CT of the thorax is performed, this assessment must be repeated at Weeks 5, 9, and 15. If the Baseline chest x-ray is negative, repeat assessment is optional at Weeks 5 and 9, unless clinically indicated, but must be repeated at **Week 15, regardless of Baseline result.**

h At Baseline, only patients with positive bone scans will undergo X-rays to confirm bone metastases. Repeat X-rays of all positive bone metastases will be performed at Week 5, Week 9 and Week 15.

i If the Baseline CT of the Liver/Abdomen is positive, this assessment must be repeated at Weeks 5, 9 and 15. If the Baseline CT of the Liver/Abdomen is negative, repeat assessment is optional at Weeks 5and 9, unless clinically indicated, but must be repeated at **Week 15, regardless of Baseline result.** Imaging studies will be conducted for all patients but will be limited to sites of pre-existing metastasis or to new sites suspected to contain metastasis based on patient symptoms. The mode of imaging at Baseline must be used throughout the study.

j Study drug must not be administered until the absolute neutrophil counts have returned to ≥1.5 x 10^9 cells/L and platelets have returned to ≥100 x 10^9 cells/L. In the event of any other toxicity that is grade 2 or greater (excluding alopecia) which in the opinion of the principal investigator is probably or definitely related to ABI-007, a dose delay will be permitted but is not mandated. Weekly monitoring of lab values will be conducted if the neutrophil and/or platelet counts drop below this criteria. The lab tests must be performed and evaluated within 72 hours prior to each dosing and at 14 days (+/- 2 days) after each course, and at EOS visit. All samples taken at scheduled visits will be analyzed by a central laboratory. At weeks 3, 6, 9, 12, and 15 duplicate samples will be collected for CBC, differential, platelet count, and clinical chemistry for analysis at local laboratories, so that dosing decisions may occur prior to result receipt from Central Lab. Exceptions: For Cycle 1 only, the labs may be performed and evaluated up to seven days prior to the dose. Results should be obtained from the central laboratory prior to initial dosing.

k Pregnancy test required for women of child-bearing potential only. Serum β-hCG pregnancy test to be performed within 72-hours of dosing, with negative results available prior to study drug administration.

l Phone Follow-Up will be performed every month for the first three months after completion/withdrawal from this study and every three months thereafter and will include time to disease progression, and survival data.

Section 5.2.5 of the protocol specifies that patients are "to be evaluated post-study, via telephone, every month for the first three months and every three months thereafter in order to obtain post-study *survival* data and *time to disease progression*."

Reviewer comment: *Although survival data can be obtained by telephone, it does not seem that time to disease progression data can reliably be obtained in this manner since radiographic data might be required for confirmation of progression.*

Efficacy Criteria and Study Endpoints

The protocol defines the primary efficacy endpoint as percentages of patients who achieve "complete or partial response for target lesions after a minimum of two cycles of treatment." Response was to be determined according to the RECIST guidelines. Patients were to be assessed with imaging studies for response after cycles 2, 3, and 5, with confirmation of response to cycle 2 at week 9 and to cycle 3 at week 15. Secondary analyses were specified to "include time to disease progression and patient survival during treatment and post study." Changes from baseline in Quality of Life (QOL) were to be assessed by scores on the Eastern Cooperative Oncologic Group (ECOG) performance status scale, EORTC QLQ-C30 and weight.

Reviewer comment: *The eligibility criteria do not explicitly require measurable disease as defined by RECIST (target lesions ≥ 20 mm by conventional measurement or 10 mm by spiral CT). The protocol requires "measurable metastatic breast cancer" and excludes patients if "the only evidence of metastasis is lytic or blastic bone metastases or pleural effusion or ascites." This accounts for some of the differences in assessments by investigators vs. "blinded" independent radiologists(see below). Other differences are attributable to the evolving definition of "Target lesion response" in the protocol compared with more explicit instructions given independent radiologists for assessment of response.*

The protocol defines target lesion response by the RECIST criteria. Complete response (CR) is defined as "disappearance of all clinical evidence (confirmed radiologically or by physical examination) of visible tumor. Partial response (PR) is defined as a ≥ 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameters. Duration of complete or partial response is ≥ 4 weeks." RECIST criteria define progressive disease (PD) as "at least a 20% increase in the sum of the longest diameter of target lesions," with reference to the "smallest sum longest diameter since the treatment started" ***or*** "the *appearance of one or more new lesions*".

Reviewer comment: *The applicant modified the RECIST criteria, selecting the "Target Lesion Response" (TLR) as the protocol-specified primary endpoint. The protocol indicated that an "Overall Response Rate" (ORR) would be determined "secondarily", "using the response from the target and non-target lesions." However, when FDA requested clarification of how the primary endpoint (TLR) was determined, the applicant replied (July 30, 2004),"... since a new lesion resulted in [scoring] a target lesion response as PD [Progressive Disease], we felt it was most consistent to also* ***code the target lesion response as PD (regardless of the target lesion measurements) if there was non-target lesion progression****". This reinterpretation of the definition of TLR, instead of simply using OR as defined by RECIST as the primary endpoint, led to additional confusion for investigators attempting to categorize the response.*

A central image reader, blinded to treatment, was specified in the protocol. The reader was to evaluate images "archived in a centralized database." WorldCare was designated the central image reader by Amendment 2, in July 2002. The Radiologist Guidelines are defined in a separate document. This document (revision 3, effective 3/24/03) was forwarded by the

applicant to FDA at the request of FDA on July 28, 2004. Ultrasound and mammographic images were "not part of the Radiologist assessment protocol."

The procedures for reconciling differences between investigator assessments (*invTLR)* and independent radiologist assessments of response are defined in the study report, and result in additional study endpoints being defined and redefinition of the primary efficacy endpoint as the "reconciled Target Lesion response" (*rec*TLRR). This endpoint was chosen with the goal of minimizing bias, since the blinded radiographic assessment of response by WorldCare takes precedence, *unless there is additional clinical data unavailable to WorldCare. RecTLRR* requires confirmation of best response by cycle 6, since WorldCare only reviewed images for the first 6 cycles of therapy. In the study report, the *"investigator* Overall Response Rate" (*inv*ORR) is described as a secondary endpoint, based on the *investigator's* assessment of best confirmed response through all cycles, including evaluation of TLs and nonTLs, including disease which could be evaluated by physical examination and sonogram, and, therefore not assessed by WorldCare.

Statistical Considerations/Sample Size

The initial protocol submission provided for a non-inferiority design. The null hypothesis is "ABI-007 patients have a response percentage that is no larger than 75% of the response percentage of Taxol." Response is defined as "complete or partial response for target lesions after at least two cycles of treatment." If non-inferiority were established, the plan was for 3 nested tests, conducted sequentially. Superiority analysis would be done for all patients and then for patients receiving study drug as first-line therapy for metastatic cancer.

Reviewer Comment: *The sub- population of particular interest is not the first-line population but the Taxol-labeled population for this 505(b)(2) NDA.. This population includes patients who failed previous combination chemotherapy for metastatic disease (or relapsed within 6 months of adjuvant therapy) and had anthracycline exposure, unless contraindicated.*

The initial planned sample size was 210 evaluable patients per treatment arm (230 enrolled) with at least 100 patients per arm with previous anthracycline therapy. This was estimated "to provide at least 80% power with a one-side Type 1 error of level of 0.025 to reject the null hypothesis that ABI-007 has a response percentage that is no larger than 75% of the response rate of Taxol." The Taxol response rate was assumed to be 28-30% and the ABI-007 response rate was assumed to be 33.6-38.4% (a relative improvement of 20%).

An interim analysis to re-estimate sample size was performed after approximately 105 patients had been treated for a minimum of two cycles in each arm, and had undergone assessment of response. Sample size did not have to be changed from the initial estimate.

The protocol defined the following analysis populations:

- Intention to Treat (ITT): Patients randomized and received ≥ 1 cycle of therapy
- All Randomized (AR): Includes all patients randomized, even if not treated
- Per Protocol (PP): Patients from the ITT population who were evaluated for response after 2 cycles and have no major protocol violations.

The applicant performed the primary analysis on the ITT population, as well as secondary and safety analyses. An additional 12 patients were enrolled into the PK sub-study at 4 sites in Russia. These patients were assigned directly to treatment with ABI-007 and are not part of the ITT, Safety, or PP populations.

Reviewer comment: *The applicant's AR population (n=460) conforms to the FDA's ITT population. The applicant's ITT population (n=454) conforms to the FDA's (and the applicant's) safety population. There were 6 pts (4ABI-007, 2 Taxol) who were randomized but not treated. FDA considers these patients part of the ITT population.*

6.3.2 Trial Results

STUDY PATIENTS, DEMOGRAPHIC and BASELINE CHARACTERISTICS

Enrollment and Disposition

A total of 472 patients were enrolled in the trial and 460 were randomized to receive treatment with either ABI-004 (n=233) or Taxol (n=227). The randomized patients were recruited from 28 sites in Russia/Ukraine (n=353, 77% of patients), 20 sites in U.K. (n=67, 15%) and 22 sites in U.S./Canada (n=40, 9%). The 12 patients who were the subject of PK studies were not randomized, but were assigned directly to treatment with ABI-007. These patients were recruited from 4 of the Russian sites and are not included in any of the analysis populations. The largest centers for study enrollment were in Russia (n=34, each of 2 sites). Many sites, particularly in North America and U.K., enrolled only 1 (n=15) or 2 (n=17) patients per site.

A total number of 233 randomized patients were treated with at least one cycle of ABI-007 and 227 with at least one cycle of Taxol. The following table shows the proportion of randomized patients who received >= 6 cycles or < 6 cycles of study treatment compared by treatment arm and geographic location of study sites.

Table 6: Cycles of Therapy by Region and Treatment Arm

Country (No. of Study Centers)	Variable	Number of Patients		
		ABI-007 [N = 233]	Taxol [N = 227]	Total [N = 460]
US and Canada (22)	Randomized	21	19	40
	Received ≥ 6 cycles	9 (43%)	6 (32%)	15 (38%)
	Received < 6 cycles	12 (57%)	13 (68%)	25 (63%)
UK (20)	Randomized	34	33	67
	Received ≥ 6 cycles	15 (44%)	17 (52%)	32 (48%)
	Received < 6 cycles	19 (56%)	16 (48%)	35 (52%)
Russia (28)	Randomized	178	175	353
	Received ≥ 6 cycles	105 (59%)	89 (51%)	194 (55%)
	Received < 6 cycles	73 (41%)	86 (49%)	159 (45%)

(Source: Abstracted from Sponsor's Summary Table 3.1 by Statistical Reviewer)

The following table lists the number of patients in each arm of the study who were treated with <= 6 cycles or > 6 cycles of study therapy, overall.

Table 7: Treatment Exposure by Treatment Arm (Reviewer Table)

Number of Cycles Delivered Per Patient	ABI-007 N=229 (%)	Taxol N=225 (%)
≤ 6	168 (73%)	182 (81%)
> 6	65 (28%)	45 (20%)

Source: Dataset "patient"; all randomized patients

A slightly higher percent of ABI-007 patients was treated with > 6 cycles of chemotherapy compared with the percentage of Taxol patients who received > 6 cycles of therapy. However, approximately three quarters of patients from both treatment arms were discontinued after receiving ≤ 6 cycles of therapy. (For more detail as to the specific number of cycles delivered to patients by treatment arm, see Table 37 in section 7.3 [safety].) The mean/median number of cycles administered for randomized patients was 5.6/6 for the ABI-007 treatment arm and 5.2/5 for the Taxol treatment arm.

Reviewer comment: *It should be noted that the primary endpoint, recTLRR, which included blinded radiology review, required confirmation of response during the first 6 cycles of treatment. The secondary endpoint, invORR could include the best confirmed response observed over all treatment cycles.*

The following applicant table lists the reasons that all randomized patients came off therapy.

Table 8: Reasons for Withdrawal from Therapy (Applicant Table)

Reason Patient Came Off Therapy	Number (%) of Patients		
	ABI-007 (N = 233)	Taxol (N = 227)	All (N = 460)
Patients Who Have Come Off Therapy	230 (100%)	225 (100%)	455 (100%)
Progressive Disease Only	100 (43%)	114 (50%)	214 (47%)
Progressive Disease With Treatment-related Toxicity	4 (2%)	3 (1%)	7 (2%)
Progressive Disease With Non-treatment-related Toxicity	3 (1%)	7 (3%)	10 (2%)
Treatment Related Toxicity Only	11 (5%)	6 (3%)	17 (4%)
Non-treatment Related Toxicity Only	5 (2%)	4 (2%)	9 (2%)
Death	1 (<1%)	0	1 (<1%)
Withdrew Consent	11 (5%)	9 (4%)	20 (4%)
Protocol Violation	0	1 (<1%)	1 (<1%)
Investigator Discretion	15 (6%)	19 (8%)	34 (7%)
Other	5 (2%)	1 (<1%)	6 (1%)
Received ≥ 6 cycles of therapy	75 (32%)	61 (27%)	136 (30%)

Source: In-Text Table 18; data from Summary Table 3.0 and Listing 1.0

The largest category of patients was discontinued from therapy due to progressive disease. The reported incidence of withdrawal for treatment related toxicity was slightly higher for ABI-007 (5%) compared with Taxol patients (3%).

Patent Populations for Analysis

The applicant defined the following analysis populations:

- All Randomized (AR): Includes all patients randomized, even if not treated
- Intention to Treat (ITT): Patients randomized and received ≥ 1 cycle of therapy
- Per Protocol (PP): Patients from the ITT population who were evaluated for response after 2 cycles and have no major protocol violations.

The applicant described patient disposition for the AR population (n=460). The applicant performed the primary efficacy analysis on the ITT population (n=454) as well as secondary and safety analyses. The applicant also performed the primary efficacy analysis on the AR and PP (n=429) populations. The ITT population excluded 6 patients (4 ABI-007 and 2 Taxol) who were randomized, but not treated. The PP population consisted of 211 patients in the ABI-007 arm and 218 in the Taxol arm, excluding from the ITT population 9 patients with protocol deviations (8 ABI-007, 1 Taxol) and 16 patients (10 ABI-007, 6 Taxol) who

received only 1 dose of study drug. An additional 12 patients were enrolled in the PK sub-study at 4 sites in Russia. These patients were assigned directly to treatment with ABI-007 and are not part of the ITT, Safety, or PP populations. The PP population consisted of 429 patients, 211 in the ABI-007 arm and 218 in the Taxol arm.

The following applicant table demonstrates the patient populations for analysis, including the applicant's breakdown of the ITT population by arm of treatment and prior chemotherapy, including line of treatment and anthracycline exposure.

Table 9: Patient Populations for Analysis (Applicant Table)

	Number (%) of Patients		
Study Population	**ABI-007**	**Taxol**	**All**
All Randomized (AR)	233	227	460
Intent-to-Treat (ITT)	229 (100%)	225 (100%)	454 (100%)
Receiving study drug as 1st-line therapy	97 (42%)	89 (40%)	186 (41%)
Receiving study drug as > 1st-line therapy	132 (58%)	136 (60%)	268 (59%)
Anthracycline-exposed (adjuvant or metastatic)	176 (77%)	175 (78%)	351 (77%)
Anthracycline-exposed (metastatic only)	115 (50%)	130 (58%)	245 (54%)
Per Protocol (PP)[a]	211	218	429
Safety	229	225	454

Source: In-Text Table 20 (from Summary Tables 1 and 13, and Listing 1.1)

The table demonstrates that a similar percent of patients in each treatment arm received study drug as first-line metastatic therapy (42% of ABI-007 patients and 40% of Taxol patients). Some of these patients had previous anthracycline exposure in the adjuvant setting, since 77% of ABI-007 patients and 78% of Taxol patients in the overall population were exposed to anthracycline in adjuvant or metastatic settings. For the overall study population, more patients in the Taxol treatment arm (58%) had received anthracycline in the metastatic setting compared with patients in the ABI-007 arm (50%)

Protocol Deviations

Six patients were randomized, but not treated (4 ABI-007, 2 Taxol). One patient in each group withdrew consent. One Taxol patient (enrolled under Amendment 1) was deemed ineligible because of no prior exposure to chemotherapy. One ABI-007 patient was ineligible because of no prior chemotherapy. The two remaining ABI-007 patients (#171 and #504) were said to be "randomized in error", one patient a "screen failure" and one patient had no baseline laboratory studies to confirm eligibility.

Applicant table 2.0 lists ten ABI-007 and two Taxol patients whom they considered to have "important, predefined protocol deviations." Eight of these patients (7 ABI-007, 1 Taxol) had "violations of inclusion/exclusion criteria that were not approved by the sponsor" and 4 of these patients, #111, 507, 350 (all ABI-007) and #545 (Taxol) had "dosing delays of more than 5 weeks." Three of the patients who "did not meet eligibility criteria" (2 ABI-007 and 1 Taxol), patients #171, 504, 109, are among the 6 patients who were randomized, but not treated. These 3 patients were discontinued from the study, but the Applicant believed the remaining 9 (of 12) patients with "important" protocol deviations were evaluable for efficacy and safety. Patients #138, 422, and 428 were treated with aromatase inhibitors while on study for *4 months*, 1 week, and 2 weeks, respectively.

Reviewer comment: *I reviewed dataset "elig" to evaluate the nature of violations of eligibility criteria not deemed to be "serious". Many of these patients were considered ineligible because of no prior anthracycline exposure. This was minor, since the requirement for previous anthracycline was only operative until approximately 100 such patients were randomized per arm. The violation of patient #437, who was treated with ABI-007, was that she had not completed a 2-week washout of hormonal therapy. Regarding the 3 patients treated with aromatase inhibitors while on study, none of these 3 patients responded to therapy and only one patient was treated for sufficient duration to confound the outcome. The applicant indicates that other protocol deviations are contained in Listing 32.0, "none of which were considered important." I reviewed this listing , and many of the deviations pertained to limited baseline abdominal CT studies.*

Baseline Demographics

There were no significant differences in baseline demographic factors between the treatment arms. All patients were female; 97% were Caucasian. The mean age was approximately 53 years for both treatment groups. The menopausal status was similar for both groups, 17% premenopausal and 83% postmenopausal in both treatment groups. For each geographic area, the number of patients treated in each arm of the study was balanced (see Table 5, above). Approximately 77% of all patients were enrolled from Russia/Ukraine, 15% from the U.K. and 9% from the U.S./Canada.

The next table (applicant's In-Text Table 21) summarizes the sponsor's determination of baseline demographic factors (not including geographic site).

Table 10: Baseline Demographics (Applicant Table)

Variable	ABI-007 (N = 233)	*P-value*[a]	Taxol (N = 227)	All (N = 460)
Age (yr)				
n	229		225	454
mean (S.D.)	53.1 (10.18)	*0.798*	53.3 (10.05)	53.2 (10.10)
min, max	26, 79		30, 83	26, 83
Age Category, n (%)				
n	229		225	454
< 65 yr	199 (87%)	*0.669*	193 (86%)	392 (86%)
≥ 65 yr	30 (13%)		32 (14%)	62 (14%)
Race, n (%)				
n	229		225	
Caucasian	221 (97%)	*0.186*	218 (97%)	439 (97%)
Black	1 (< 1%)		5 (2%)	6 (1%)
Asian	1 (< 1%)		0	1 (< 1%)
Indian - Eastern	2 (< 1%)		0	2 (< 1%)
Hispanic	3 (1%)		2 (< 1%)	5 (1%)
Other	1 (< 1%)		0	1 (< 1%)
Weight (kg)				
n	225		223	448
mean (S.D.)	70.6 (14.09)	*0.344*	69.4 (12.38)	70.0 (13.26)
min, max	42, 125		40, 105	40, 125
Height (cm)				
n	229		225	454
mean (S.D.)	161.7 (6.27)	*0.952*	161.7 (5.86)	161.7 (6.06)
min, max	147, 182		145, 178	145, 182
Menopausal Status, n (%)				
n	229		225	454
Premenopausal	40 (17%)	*0.855*	38 (17%)	78 (17%)
Postmenopausal	189 (83%)		187 (83%)	376 (83%)

[a] P-value for age, weight, and height are from a 2-way ANOVA model with effects for country and treatment group; P-value for age category is from the Cochran-Mantel-Haenszel test stratified by country using modified ridit scores; P-value for menopausal status is from the Cochran-Mantel-Haenszel test for general associated stratified by country; P-value for race is from Fisher's exact test.

Applicant's In-Text Table 21; (data source Summary Table 5.0 and Listing 3.0)

Baseline Disease Characteristics

For the applicant-defined ITT population, there were no significant differences between the treatment groups for time from initial diagnosis to study entry, initial cancer stage at diagnosis, or initial estrogen receptor (ER) status. There was a small difference between the groups for positive progesterone receptor (PR) status, 17% for ABI-007 patients compared with 10% for Taxol patients (p=.040). This information is displayed in the following table, applicant's In-Text Table 22.

Table 11: Patient Characteristics at Diagnosis (Applicant Table)

Variable Category/Statistic	ABI-007 (N = 229)	*P-value*[a]	Taxol (N = 225)	All (N = 454)
Time from Initial Diagnosis to Study Entry (yr)				
Mean (S.D.)	3.89 (4.020)	*0.132*	3.33 (3.585)	3.61 (3.816)
Min, Max	0.0, 20.8		0.0, 20.4	0.0, 20.8
Initial AJCC Cancer Stage, n (%)				
Stage 0	1 (< 1%)	*0.787*	0	1 (< 1%)
Stage I	18 (8%)		14 (6%)	32 (7%)
Stage II	73 (32%)		74 (33%)	147 (32%)
Stage III	58 (25%)		61 (27%)	119 (26%)
Stage IV	46 (20%)		50 (22%)	96 (21%)
Unknown	33 (14%)		26 (12%)	59 (13%)
Initial ER Status, n (%)				
Positive	53 (23%)	*0.358*	42 (19%)	95 (21%)
Negative	49 (21%)		59 (26%)	108 (24%)
Unknown	127 (55%)		124 (55%)	251 (55%)
Initial PgR Status, n (%)				
Positive	39 (17%)	*0.040**	23 (10%)	62 (14%)
Negative	36 (16%)		51 (23%)	87 (19%)
Unknown	154 (67%)		151 (67%)	305 (67%)

[a] P-value for time from initial diagnosis to study entry is from a 2-way ANOVA model with effects for country and treatment group; P-values for other variables are from the Cochran-Mantel-Haenszel test for general association stratified by country; * $P < 0.05$.

Applicant In-Text Table 22; data source Summary Table 6.0 and Listing 4.0

There were no significant differences between treatment groups for initial histology type, the marked preponderance being ductal (scirrhous) carcinoma in 54% of ABI-007 patients and 50% of Taxol patients. There were no imbalances for the groups regarding the choice of initial treatment modality for breast cancer, *i.e.* surgery, radiotherapy, hormonal or chemotherapy. This information is displayed (for the applicant-defined ITT population) in the following table, which is applicant In-Text Table 24.

Table 12: Initial Treatment of Breast Cancer (Applicant Table)

Variable Category	ABI-007 (N = 229)	*P-value*[a]	Taxol (N = 225)	All (N = 454)
Initial treatment, n (%)				
Surgery	165 (72%)	*0.239*	150 (67%)	315 (69%)
Radiotherapy	137 (60%)	*0.954*	134 (60%)	271 (60%)
Hormonal therapy	111 (48%)	*0.717*	105 (47%)	216 (48%)
Chemotherapy	180 (79%)	*0.151*	164 (73%)	344 (76%)

[a] P-values are from the Cochran-Mantel-Haenszel test for general association stratified by country.

Applicant In-Text Table 24; source Summary table 7.0 and listings 4.0

For approximately three-quarters of patients, initial therapy of breast cancer included chemotherapy, 79% of ABI-007 patients and 73% of Taxol patients. The following table demonstrates that most patients had ECOG performance status at baseline of 1 (60%) or 0 (36%) for applicant's ITT population

Table 13: ECOG Performance Status at Baseline (Applicant Table)

Variable Category	ABI-007 (N = 229)	*P-value*[a]	Taxol (N = 225)	All (N = 454)
ECOG Performance Status, n (%)				
0 (Fully Active)	81 (35%)	*0.493*	82 (36%)	163 (36%)
1 (Restricted But Ambulatory)	134 (59%)		138 (61%)	272 (60%)
2 (Ambulatory but Unable to Work)	13 (6%)		5 (2%)	18 (4%)
3 (Limited Self-Care)	1 (< 1%)		0	1 (< 1%)
ECOG Performance Status				
Mean (S.D.)	0.7 (0.59)	–	0.7 (0.52)	0.7 (0.56)
Min, Max	0, 3		0, 2	0, 3

[a] P-value is from the Cochran-Mantel-Haenszel test stratified by country using modified ridit scores.

Applicant In-Text Table 25; source summary table 9.0 and listing 15.0

There were no significant differences between the treatment groups for baseline number of lesions and dominant lesion sites for the applicant defined ITT (n=454). The dominant lesion site was liver in 41% of the ABI-007 patients and 43% of the Taxol patients, and lung in 33% and 35%, respectively. This information is displayed in the next table, which is applicant In-Text Table 26.

Table 14: Baseline Number of Lesions and Dominant Sites (Applicant Table)

Variable Category	ABI-007 (N = 229)	*P-value*[a]	Taxol (N = 225)	All (N = 454)
Number of Lesions, n (%)				
1	7 (3%)	*0.119*	9 (4%)	16 (4%)
2 – 3	42 (18%)		53 (24%)	95 (21%)
> 3	180 (79%)		163 (72%)	343 (76%)
Dominant Lesion Site, n (%)[b]				
Liver	92 (41%)	*0.731*	97 (43%)	189 (42%)
Abdominal	10 (4%)		6 (3%)	16 (4%)
Lung	74 (33%)		79 (35%)	153 (34%)
Bone	13 (6%)		13 (6%)	26 (6%)
Only Lymph Node, Soft Tissue, and/or Breast	37 (16%)		30 (13%)	67 (15%)

[a] P-values are from Cochran-Mantel-Haenszel test stratified by country using modified ridit scores.

[b] Includes target and nontarget lesions.

Applicant In-Text Table 26; data source Summary Table 10.0 and Listing 12.0

At baseline, 88% of ABI-007 patients and 85% of Taxol patients had had prior chemotherapy. Seventy-seven percent and 78%, respectively had been exposed to anthracycline in either the adjuvant or metastatic setting. Fifty percent of ABI-007 patients and 58% of Taxol patients had previous exposure to anthracycline in the metastatic setting. Only 1% of patients in either treatment arm had prior exposure to taxane. The previous chemotherapy exposures at baseline appear balanced for the treatment groups, although a higher percent of patients in the Taxol arm (58%) had previous anthracycline in the metastatic setting compared with the ABI-007 arm (50%). The next table displays this information for the applicant-defined ITT population.

Table 15: Prior Therapies at Baseline (Applicant Table)

Therapy	Number (%) of Patients		
	ABI-007 (N = 229)	Taxol (N = 225)	All (N = 454)
Chemotherapy-naive	28 (12%)	34 (15%)	62 (14%)
Chemotherapy-exposed	201 (88%)	191 (85%)	392 (86%)
Anthracycline-naive	53 (23%)	50 (22%)	103 (23%)
Anthracycline-exposed (adjuvant or metastatic)	176 (77%)	175 (78%)	351 (77%)
Anthracycline treatment for metastatic disease	115 (50%)	130 (58%)	245 (54%)
Taxane-naive	226 (99%)	222 (99%)	448 (99%)
Taxane-exposed	3 (1%)	3 (1%)	6 (1%)
Hormonal therapy-naive	96 (42%)	103 (46%)	199 (44%)
Hormonal therapy-exposed	133 (58%)	122 (54%)	255 (56%)

Applicant In-Test Table 27; source summary table 13.0 and listings 8.0, 8.1 and 8.2

The next applicant table displays the number of prior therapies for metastatic breast cancer. The percent of patients that received study drug as first-line therapy for metastatic disease was 42% for the ABI-007 group and 40% for the Taxol group.

Table 16: Prior Treatment for Metastatic Breast Cancer (Applicant Table)

Number of Prior Metastatic Treatments	Number (%) of Patients		
	ABI-007 (N = 229)	Taxol (N = 225)	All (N = 454)
0 (study drug as 1st-line therapy)	97 (42%)	89 (40%)	186 (41%)
≥ 1 (study drug as > 1st-line therapy)	132 (58%)	136 (60%)	268 (59%)
1	94 (41%)	96 (43%)	190 (42%)
2	23 (10%)	35 (16%)	58 (13%)
≥ 3	15 (7%)	5 (2%)	20 (4%)

Applicant In-Text Table 28; source Summary table 13.0 and listings 8.0, 8.1 and 8.2

CONCOMITANT MEDICATIONS

Corticosteroids and Antihistamines

The applicant provided an analysis of the incidence of concomitant therapy with the 3 classes of drugs commonly used as prophylaxis against hypersensitivity reactions to Taxol. These drugs include corticosteroids, H_2 receptor antagonists and aminoalkyl ethers (e.g. diphenhydramine). In the following applicant table, the latter 2 categories are combined as "antihistamines", and the incidence of antihistamine and corticosteroid use is displayed for each treatment arm in the applicant-defined ITT population

Table 17: Use of Corticosteroids and Antihistamines (Applicant Table)

	ABI-007		Taxol	
Therapeutic Drug Class	**Patients (N = 229)**	**Cycles (N = 1293)**	**Patients (N = 225)**	**Cycles (N = 1174)**
Any Corticosteroids or Antihistamines	71 (31%)	147 (11%)	224 (>99%)	1150 (98%)
Any Corticosteroids	50 (22%)	109 (8%)	224 (>99%)	1146 (98%)
Any Antihistamines	33 (14%)	55 (4%)	224 (>99%)	1144 (97%)

Note: Concomitant medications were any medications taken on or after the date of the first dose of study drug. Patients taking multiple concomitant medications with the same generic name or multiple concomitant medications in the same drug class were counted only once for each generic name and drug class.

Applicant In-Text Table 29; source summary table 13.3.3, listing 9.0

As expected, virtually all of the Taxol patients were treated with corticosteroids and antihistamines, consistent with the package label requiring triple premedication to prevent hypersensitivity reactions. Premedication with corticosteroids and antihistamine is not prespecified for ABI-007. The applicant indicated that "the most common reasons for administering corticosteroids to the ABI-007 patients were anti-emesis, myalgia/arthralgia, and anorexia. The applicant provided additional analysis in an attempt to show the incidence of these drugs used for prophylaxis by tabulating corticosteroid and antihistamine use initiated only on the day of or the day before study drug administration. This information is displayed in the following applicant table for the applicant-defined ITT population.

Table 18: "Predosing" Use of Corticosteroids and Antihistamines (Applicant Table)

Therapeutic Drug Class	ABI-007		Taxol	
	Patients (N = 229)	Cycles (N = 1293)	Patients (N = 225)	Cycles (N = 1174)
Any Predosing Corticosteroids or Antihistamines[a]	18 (8%)	31 (2%)	224 (>99%)	1121 (95%)
Any Predosing Corticosteroids	13 (6%)	23 (2%)	224 (>99%)	1113 (95%)
Any Predosing Antihistamines	6 (3%)	9 (<1%)	223 (>99%)	1111 (95%)

[a] Corticosteroids and antihistamines that were initiated the day of or the day before study drug administration were considered as "predosing," ie, they were conservatively assumed to function as premedications administered as prophylaxis against hypersensitivity reactions, regardless of the actual indication.

Applicant In-Text Table 30; source summary table 13.3, listing 9.0

As expected, corticosteroids and antihistamines were prescribed as premedication for Taxol for > 99% of the patients, and for 95% of cycles. For ABI-007 patients, only 6% were premedicated with corticosteroids, which occurred during 2% of treatment cycles. The incidence of premedication with antihistamines for ABI-007 patients was 3%, employed during < 1% of cycles.

Reviewer comment: *The lack of requirement for premedication with corticosteroids, H_2 blockers and diphenhydramine for ABI-007 due to formulation without Cremophor has been specified by the applicant as an advantage of ABI-007 over the currently-marketed taxanes. The data suggests that ABI-007 patients are* not *requiring triple premedication.*

Growth Factors

Eight ABI-007 patients (3%) and 14 (6%) of Taxol patients were treated with G-CSF (granulocyte colony stimulating factor) or GM-CSF (granulocyte macrophage colony stimulating factor) for neutropenia during the study. For the ABI-007 and Taxol groups, 5 (2%) and 8 (4%) of patients, respectively, were treated with recombinant erythropoietin for anemia.

Bisphosphonates

The incidence of concomitant therapy with bisphosphonates was 10% for ABI-007 patients and 12% for Taxol patients.

Aromatase Inhibitors

Three patients in the ABI-007 group (#138, #422, #428) were treated with aromatase inhibitors during the study, in violation of the protocol, for 4 months, 1 week and 2 weeks respectively. (The patients received letrozole, exemestane and anastrozole.)

Reviewer comment: *None of these 3 patients was classified as a responder and it appears that only one patient was treated for sufficient duration to confound the outcome, had the patient been a responder.*

TREATMENT COMPLIANCE

The following applicant table shows the cumulative dose and average dose intensity for the applicant-defined ITT population, which is the same population as the safety population. (This includes the 460 randomized patients, less 4 ABI-007 and 2 Taxol patients who received no study drug.)

Table 19: Cumulative Dose & Mean Dose Intensity (Safety Population) (Applicant Table)

Variable	ABI-007 (N = 229)	Taxol (N = 225)
Cumulative Dose During Study (mg/m^2)		
Mean	1459.3	909.0
S.D.	787.85	494.88
Median	1560.0	875.0
min, max	260, 4680	175, 3150
Cumulative Dose During Study (mg)		
Mean	2567.6	1578.8
S.D.	1420.64	887.20
Median	2540.0	1644.0
min, max	390, 8424	10, 5760
Average Dose Intensity (mg/m^2/week)		
Mean	85.13	57.02
S.D.	3.118	3.008
Median	86.43	58.07
min, max	69.8, 92.0	31.7, 70.2
Percentage of Protocol Dose (%)		
Mean	98.2	97.8
S.D.	3.60	5.16
Median	99.7	99.5
min, max	81, 106	54, 120

Applicant In-Text Table 32; data source summary table 24.2 and listing 10.0

Approximately 98% of the protocol-specified study dose was delivered both for ABI-007 and Taxol patient groups. At least 90% of the protocol-specified dose was delivered to 96% and 94% of the groups, respectively. Since the specified dose was ABI-007 260 mg/m2 per cycle compared with 175 mg/m2 per cycle of Taxol, as expected, the mean cumulative dose for ABI-007 (1459 mg/m2) was significantly higher than for Taxol (909 mg/m2). (Also see Section 7.3 below, "Patient Exposure.")

EFFICACY RESULTS: APPLICANT ASSESSMENT

Primary Efficacy Endpoint (*rec*TLRR) - Applicant

The primary efficacy endpoint was the confirmed *rec*TLRR. This response rate was derived by reconciling differences between the IRL (Independent Radiology Lab) determined Target Lesion Response and Investigator Response Assessment Datasets according to a predefined algorithm. The applicant also analyzed efficacy for a secondary endpoint, the confirmed overall response rate as determined by the investigator over all cycles of therapy (*inv*ORR). The *rec*TLRR required confirmation of response within the first 6 treatment cycles and only considered nontarget lesions (nonTLs) if there were new lesions or progressive disease in nonTLs. The *inv*ORR was based on the assessment of response by the investigator only, using TL and nonTL responses according to RECIST. The investigators had access to data from clinical exam, sonograms and radiographic images throughout the evaluation period. The IRL could only evaluate response in lesions that were assessed by radiographic images obtained during the first 6 months of study. As a result, the IRL was unable to evaluate 25 patients; 15 patients had lesions only detected clinically and 10 patients had inadequate or absent radiographic images.

The applicant determined that 55 patients treated with ABI-007 (24%) and 25 patients treated with Taxol (11%) had CR or PR by the *rec*TLR, the primary efficacy endpoint. The following applicant table compares, by treatment arm, the response rates for *rec*TLR as well as for *irl*TLR (independent radiology lab) and *inv*TLR, based on patients who received at least one study treatment. (See FDA Assessment, below.)

Table 20: Target Lesion Response Rates and Superiority Test (Applicant Table)

Category	ABI-007 (N = 229)	Taxol (N = 225)	Ratio[a] *(P-value)*[c]
Reconciled Response Assessment Dataset			
Patients in Dataset, n	229	225	–
Patients With Target Lesion Response, n	55	25	–
*rec*TLRR, %	24.0	11.1	2.110 *(<0.001*)*
Confidence Interval[b]	18.48, 29.55	7.00, 15.22	1.376, 3.236
Investigator Response Assessment Dataset			
Patients in Dataset, n	229	225	–
Patients With Target Lesion Response, n	72	37	–
*inv*TLRR, %	31.4	16.4	1.876 *(<0.001*)*
Confidence Interval[b]	25.43, 37.45	11.60, 21.29	1.329, 2.649
IRL Response Assessment Dataset[d]			
Patients in Dataset, n	176	171	–
Patients With Target Lesion Response, n	37	13	–
*irl*TLRR, %	21.0	7.6	2.650 *(0.001*)*
Confidence Interval[b]	15.00, 27.04	3.63, 11.57	1.472, 4.769

[a] Ratio = (ABI-007 response rate) / (Taxol response rate). Ratio and 95% CI were adjusted for 1st line versus >1st line therapy.

[b] 95% binomial confidence interval of response rate.

[c] P-value from CMH test stratified by 1st line vs > 1st line therapy; * P < 0.05.

[d] See above for explanation of exclusion of patients from IRL dataset

Applicant In-Text Table 40; source summary tables 14.1, 14.4, 14.7, listings 13.0 & 14.0

For each of the datasets, the two primary and the reconciled, the response rates were higher for ABI-007 patients than for Taxol patients. The applicant sequentially tested for non-inferiority and then for superiority on the applicant-defined ITT population, and then for superiority on the subset of patients who received study treatment as first-line for metastatic disease. (See separate Statistical Review for details.)

Reviewer comment: *As expected, since the invTLR dataset incorporated all clinical observations, the absolute response rates were highest for both treatment arms compared with* invTLR *and* irlTLR *datasets. The FDA statistical reviewer confirmed the superiority of ABI-007 for the primary endpoint, even using the adjudicated results based on the FDA review of the primary data. (See below-"FDA Assessment.") As part of the applicant's pre-*

specified analysis, they demonstrated superiority for ABI-007 for the study and for the subset of patients who were treated first-line in the metastatic setting. However, first-line therapy of breast cancer is not an approved indication for Taxol, which is the reference drug for this 505(b)(2) application.

Primary Efficacy Endpoint (*rec*TLRR) in Patients Meeting Taxol Indication - Applicant

The following table shows the incidence of confirmed TL responses in patients who failed anthracycline-containing chemotherapy for metastatic disease or relapsed within 6 months of anthracycline-containing adjuvant chemotherapy. In the applicant-defined ITT (454 patients who received study drug), 127 patients treated with ABI-007 and 142 patients treated with Taxol met the Taxol indication for metastatic breast cancer. Therefore, in study CA012-0 55.5% (127/229) of the ABI-007 patients and 63.1% of the Taxol patients (142/225) met the Taxol indication.

Table 21: *Rec*TLRR for Patients Who Met Taxol Indication

	ABI-007 N=127	Taxol N=142	Ratio ABI-007 TLR/Taxol TLR
# of Patients with TLR	23	12	
Confirmed TLR Rate	18.1%	8.5%	2.143
Confidence Interval 95%	11.41, 24.81	3.88, 13.03	1.113, 4.128
P-value from chi-square			0.019

Source: Analysis provided by applicant 10/19/04 in response to FDA request

Secondary Efficacy Endpoints - Applicant

***Inv*ORR (Investigator Overall Response Rate)**

The *inv*ORR is the confirmed investigator overall response rate as determined by the investigator over all cycles of therapy (as opposed to over 6 cycles only for the TLRR). For all patients treated (454 of 460 randomized patients), the applicant ITT population, the *inv*ORR was 33.2% (76/229) for the ABI-007 group and 18.7% (42/225) for the Taxol group. The p-value determined by the applicant from the CMH test stratified by first-line vs. > first-line of therapy was 0.001). The applicant stated that 2 ABI-007 responses and 3 Taxol responses were complete responses (CRs).

The following applicant table shows the *inv*ORR by line of therapy for the applicant-defined ITT population. ABI-007 appears superior compared to Taxol for the subgroups.

Table 22: *inv*ORR by Line of Therapy (Applicant Table)

Category	ABI-007 (N = 229)	Taxol (N = 225)	Ratio[a] *(P-value)*[c]
Patients Receiving 1st-line Therapy, n	97	89	–
Patients With Overall Response, n	41	24	–
*inv*ORR, %	42.3	27.0	1.567 *(0.029*)*
Confidence Interval[b]	32.44, 52.10	17.75, 36.19	1.037, 2.370
Patients Receiving > 1st-line Therapy, n	132	136	–
Patients With Overall Response, n	35	18	–
*inv*ORR, %	26.5	13.2	2.003 *(0.006*)*
Confidence Interval[b]	18.98, 34.05	7.54, 18.93	1.196, 3.355

[a] Ratio = (ABI-007 response rate) / (Taxol response rate).

[b] 95% binomial confidence interval of response rate.

[c] P-value from chi-square test; * $P < 0.05$.

Applicant In-Text Table 36: source Summary table 15.9.0, 15.9.0.1, listing 13.0

Reviewer comment: *The findings are consistent with the results for the primary endpoint. However,* invORR *is a relatively subjective endpoint in an open-label trial. The analysis showing superiority of* invORR *ABI-007 for the subset of patients who were treated first-line in the metastatic setting must be considered exploratory. Furthermore, first-line therapy of breast cancer is not an approved indication for Taxol, which is the reference drug for this 505(b)(2) application.*

The following applicant figure displays the *inv*ORR results for all treated patients (the applicant's ITT population) and by line of therapy.

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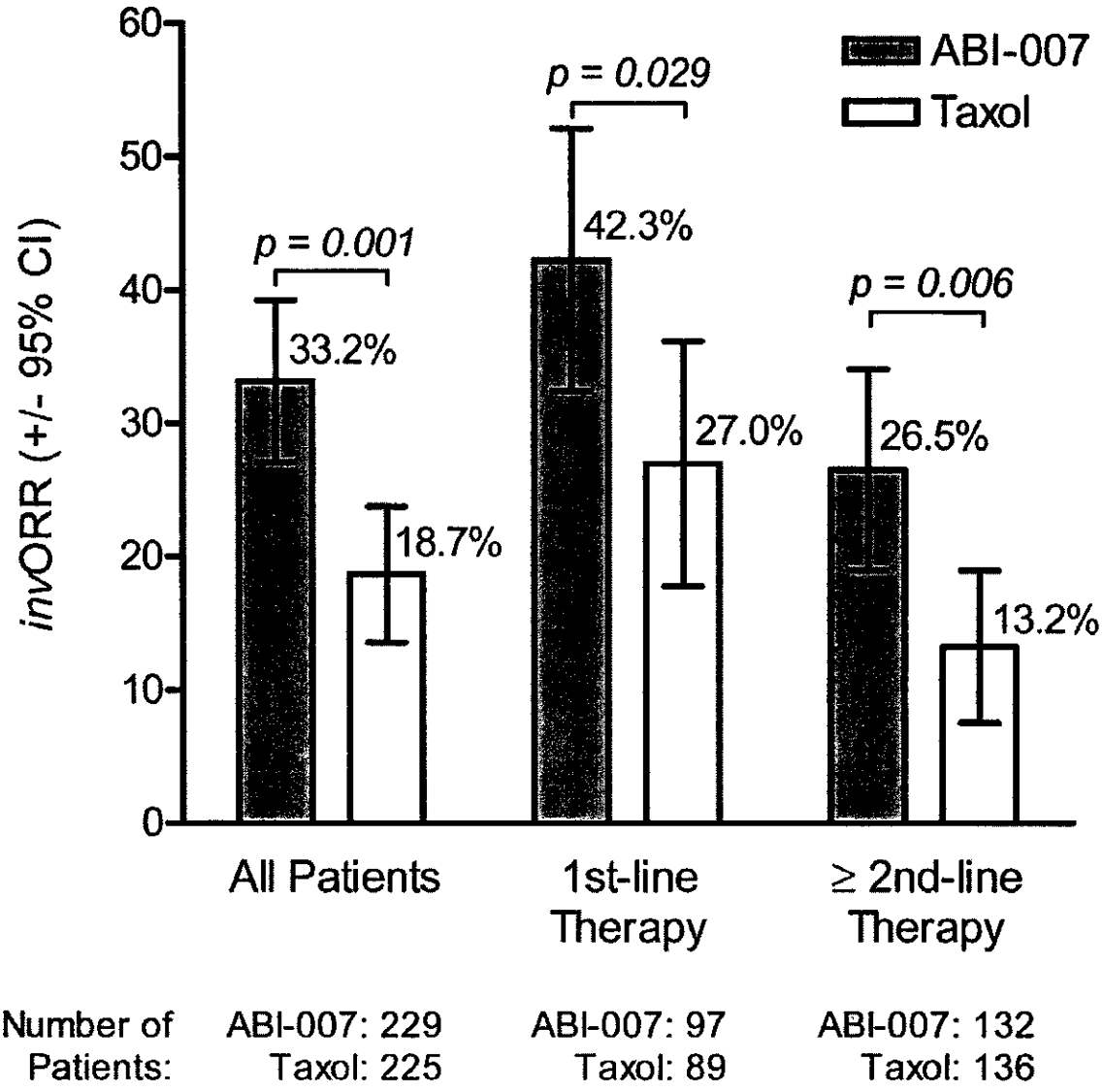
Figure 1: InvORR for All Treated Patients and by Line of Therapy (Applicant Figure)



Applicant In-Text Figure 2; source summary tables 15.8.3, 15.9.0, 15.9.0.1

In another subset analysis, the applicant determined that, for *inv*ORR, the response rate was significantly higher for ABI-007 than Taxol for patients who had prior anthracycline in the adjuvant or metastatic setting, or only in the metastatic setting. The following applicant table displays this information for the applicant-defined ITT population.

Table 23: InvORR by Prior Anthracycline Therapy (Applicant Table)

Category	ABI-007 (N = 229)	Taxol (N = 225)	Ratio[a] *(P-value)*
Patients with Prior Anthracycline Therapy (Adjuvant or Metastatic), n	176	175	–
Patients With Overall Response, n	60	32	–
*inv*ORR, %	34.1	18.3	1.738 *(0.002*)*[c]
Confidence Interval[b]	27.09, 41.09	12.56, 24.01	1.208, 2.500
Patients with Prior Metastatic Anthracycline Therapy, n	115	130	–
Patients With Overall Response, n	31	18	–
*inv*ORR, %	27.0	13.8	1.947 *(0.010*)*[d]
Confidence Interval[b]	18.85, 35.07	7.91, 19.78	1.153, 3.287

[a] Ratio = (ABI-007 response rate) / (Taxol response rate). For "Patients with Prior Anthracycline Therapy (Adjuvant or Metastatic)", ratio and 95% CI were adjusted for 1st line versus >1st line therapy.

[b] 95% binomial confidence interval of response rate.

[c] P-value from CMH test stratified by 1st line vs >1st line therapy; * P < 0.05.

[d] P-value from chi-square test.

Applicant In-Text Table 37; source summary tables 15.9.2, 15.9.3 and listing 13.0

Reviewer comment: *Again, the subset analysis using a secondary, more subjective endpoint is consistent with the findings for the primary endpoint and ABI-007 appears to show superiority over Taxol for patients with previous anthracycline exposure. It should be noted that neither of the anthracycline-exposed populations in the table conforms to the Taxol-approved indication population precisely. The Taxol-approved breast cancer population is defined by patients who have failed previous combination chemotherapy (which should have included an anthracycline if not contraindicated) or who progressed within 6 months of adjuvant chemotherapy (which should have included an anthracycline if not contraindicated).*

The applicant did additional analyses for the *inv*ORR endpoint to evaluate the potential influence of prognostic factors on response. "Using a logistic regression model with effects for country, treatment group, prognostic factor, and treatment group-by-prognostic factor interaction", no significant interaction was shown for 24 prognostic factors assessed, showing consistency of the differences in drug treatment effect across most baseline prognostic factors. The applicant states that analyses for patients enrolled at the 3 major geographic sites (Russia/Ukraine, US/Canada, and UK) showed "no significant interactions of *inv*ORR with prognostic factors." The following table, from applicant in-text table 44,

displays *inv*ORR by treatment arm for the three geographic regions from which patients were accrued.

Table 24: InvORR by Country and Treatment arm

Country	ABI-007 Patients N=229	Taxol Patients N=225
US/Canada	7/20 (35%)	3/17 (18%)
United Kingdom	6/34 (18%)	2/33 (6%)
Russia/Ukraine	63/175 (35%)	37/175 (21%)

Source: Applicant in-Text Table 44; summary table 15.10

The p-value was 0.862 for country from the logistic regression model with "effects for country, treatment group, prognostic factor and treatment group-by-prognostic factor interaction." The *inv*ORR was similar in both treatment arms for US/Canada and Russia/Ukraine. The lower response rates for U.K. for both treatment arms could be due to relatively small numbers of patients entered from the U.K..

The next applicant table summarizes the response results, based in *inv*ORR for all patients, by line of therapy, and by prior anthracycline therapy for the applicant-defined ITT population (454 treated patients of 460 randomized).

Table 25: Applicant's Summary of *inv*ORR by Line of Therapy and Prior Anthracycline

Category	ABI-007	Taxol	*P-value*	Cross-reference
All Patients	33.2%	18.7%	*0.001*	In-Text Table 34 In-Text Figure 2
Patients Receiving 1st-line Therapy	42.3%	27.0%	*0.029*	In-Text Table 36 In-Text Figure 2
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*	In-Text Table 37 In-Text Figure 3
Patients with Prior Metastatic Anthracycline Therapy	27.0%	13.8%	*0.010*	

Source: Applicant In-Text Table 57

Reviewer comment: *For the overall population and for important subgroups, using the investigator-determined secondary endpoint, ABI-007 appears to show superiority over Taxol. It should be noted that none of these populations in the table conforms to the Taxol-approved indication population precisely. The Taxol-approved breast cancer population is defined by patients who have failed previous combination chemotherapy or who progressed within 6 months of adjuvant chemotherapy, and therapy should have included an anthracycline if not contraindicated. The FDA analysis of response, using* recTLRR, *showed*

marginal statistically significant superiority for ABI-007 with p=0.05 for the patients who conformed to the Taxol indication. See below

Duration of Response – Applicant

There was no statistically significant difference between treatment groups for Kaplan-Meier median duration of response based on responders who achieved *rec*TLRR. The data was immature, since *rec*TLRR only included data for patients during the first 6 cycles of therapy. Even if the *inv*ORR was used to determine duration of response, the data was immature to make meaningful comparisons.

Time to Disease Progression (TTP) – Applicant

The applicant defined TTP as "the number of weeks from the *first dose* of study drug to the start of disease progression. Patients who did not have disease progression are censored at the last known time the patient was evaluated for response." The applicant performed this secondary analysis in two ways. The analysis using the Investigator Response Assessment demonstrated a significantly longer (p=0.030) TTP for ABI-007 (21.9 weeks) than for Taxol (16.1 weeks). An additional applicant assessment using the Reconciled Response Assessment Dataset also demonstrated a longer TTP for the ABI-007 patients than for the Taxol patients (16.6 vs. 15.4 weeks, p=0.016). The following applicant table shows this data for both analyses for the applicant-define ITT population (454 of 460 randomized patients who received study drug).

Table 26: Time to Disease Progression (Applicant Table)

Category	ABI-007 (N = 229)	Taxol (N = 225)	*P-value*[a]
Investigator Response Assessment Dataset			
Patients Evaluated for Disease Progression During Study, n	220	215	
Patients With Disease Progression, n (%)	107 (49%)	124 (58%)	
Median Time to Disease Progression (weeks)	21.9	16.1	*0.030**
Confidence Interval (weeks)[b]	18.3, 28.4	15.1, 21.0	
Median Time to Disease Progression (months)[c]	5.0	3.7	*0.030**
Confidence Interval (months)[b, c]	4.2, 6.5	3.5, 4.8	
Reconciled Response Assessment Dataset			
Patients Evaluated for Disease Progression During Study, n	222	219	
Patients With Disease Progression, n (%)	92 (41%)	118 (54%)	
Median Time to Disease Progression (weeks)	16.6	15.4	*0.016**
Confidence Interval (weeks)[b]	15.6, >21.4	14.9, 16.1	
Median Time to Disease Progression (months)[c]	3.8	3.5	*0.016**
Confidence Interval (months)[b, c]	3.6, >4.9	3.4, 3.7	

Note: Time to disease progression is defined as the number of weeks from the first dose of study drug to the start of disease progression. Patients who did not have disease progression are censored at the last known time the patient was evaluated for response.

[a] P-value from log-rank test. * $P < 0.050$.

[b] 95% confidence interval for median time to disease progression.

[c] Conversion assumes 30.5 days/month or 4.3571 weeks/month.

Applicant In-Text Table 48; source summary tables 19.3, 19.0 and listings 13.0 and 14.0

Reviewer comment: *The applicant chose to use baseline as the time from the first dose of study drug, rather than the more conventional "time from randomization". The findings appear consistent whether the primary or secondary response endpoints were used to calculate the TTP. We did not agree to include TTP information in the label because the data could not be adjudicated objectively in this open-label, single trial. In addition, the only provision for follow-up after completion of the study was by telephone every 3 months, which could not provide accurate TTP information for patients who progressed after trial completion . In many cases, assessment of progression might require radiologic confirmation.*

The following applicant table shows TTP by line of therapy for the applicant-defined ITT population. For both subgroups, the TTP is shorter for Taxol-treated patients than for ABI-007 patients, although the differences are not statistically significant.

Table 27: TTP by Line of Therapy (Applicant Table)

Category	ABI-007	Taxol	*P-value*[a]
Patients Receiving Study Drug as 1st-line Therapy, n	97	89	
Patients Evaluated for Disease Progression During Study, n	92	87	
Patients With Disease Progression, n (%)	37 (40%)	48 (55%)	
Median Time to Disease Progression (weeks)	28.4	21.1	*0.056*
Confidence Interval (weeks)[b]	21.0, 50.3	15.0, 25.9	
Median Time to Disease Progression (months)[c]	6.5	4.8	*0.056*
Confidence Interval (months)[b, c]	4.8, 11.5	3.4, 5.9	
Patients Receiving Study Drug as > 1st-line Therapy, n	132	136	
Patients Evaluated for Disease Progression During Study, n	128	128	
Patients With Disease Progression, n (%)	70 (55%)	76 (59%)	
Median Time to Disease Progression (weeks)	19.4	16.1	*0.199*
Confidence Interval (weeks)[b]	15.6, 24.1	15.0, 18.3	
Median Time to Disease Progression (months)[c]	4.5	3.7	*0.199*
Confidence Interval (months)[b, c]	3.6, 5.5	3.4, 4.2	

Note: Time to disease progression is defined as the number of weeks from the first dose of study drug to the start of disease progression. Patients who did not have disease progression are censored at the last known time the patient was evaluated for response.

[a] P-value from log-rank test.

[b] 95% confidence interval for median time to disease progression.

[c] Conversion assumes 30.5 days/month or 4.3571 weeks/month.

Applicant In-Text Table 49; source summary tables 19.3 and 19.3.2

Reviewer comment: *The subgroup analysis shows a trend toward significance for patients receiving study drug as first-line therapy. There is a lesser trend toward improvement of TTP for ABI-007 over Taxol for patients receiving study drug as > first-line.*

Survival - Applicant

The next table shows the applicant's analysis of survival based on the applicant-defined ITT population. Only 35% of patients had died at the time of analysis. The median time to death was not statistically different for the treatment groups.

Table 28: Patient Survival (Applicant Table)

	ABI-007 (N = 229)	Taxol (N = 225)	*P-value*[a]
Patients Who Died, n (%)	73 (32%)	84 (37%)	
Median Time to Death (weeks)	39.9	37.9	*0.636*
Confidence Interval (weeks)[b]	34.7, 44.7	34.4, 40.7	
Median Time to Death (months)[c]	9.2	8.7	*0.636*
Confidence Interval (months)[b,c]	8.0, 10.3	7.9, 9.3	

Note: Analysis includes patient survival information during study follow-up.

Note: Patients who did not die are censored at the last known time the patient was alive.

[a] P-value from log-rank test. * $P < 0.050$.

[b] 95% confidence interval for median time to death.

[c] Conversion assumes 30.5 days/month or 4.3571 weeks/month.

Applicant In-Text Table 50; source summary table 20.0 and listing 30.0

Reviewer comment: *The survival data are not mature, with only 32% of ABI-007 patients and 37% of Taxol patients having died by the date of data cut-off.*

Quality of Life – Applicant

The applicant noted no differences between the treatment groups for "measures of quality of life (ECOG status, EORTC-QLQ, and weight)."

EFFICACY RESULTS: FDA ASSESSMENT

FDA Radiology Audit

FDA attempted to assess quality and integrity of the radiographic study data by employing an independent, consultant radiologist, Dr. Erini Makariou, to audit a subset of study patient radiographs. The digitized images were provided remotely to FDA computers by WorldCare, the applicant's contract, blinded radiology group.

Initially, Dr. Makariou was given a list of patients from both treatment groups and various geographic sites, the patients chosen at random by the medical and statistical reviewer. Dr. Makariou was blinded as to treatment group and investigator assessment of response. The digitized images contained markings of target lesions identified by WorldCare, but these

markings were subsequently removed by Dr. Makariou, who made her own determination and measurements of most appropriate target and non-target lesions. We were able to verify that the quality of radiographs, including those from various geographic sites, and the methodology, in general, were acceptable to allow assessment of responses.

While Dr. Makariou remained blinded to treatment arm, the medical reviewer provided her with a list of patient ID numbers for review, enriched with a subset of patients who were identified by the applicant as responders from both arms of the trial and a subset of Taxol patients with stable disease. The medical reviewer also requested (blinded) review by Dr. Makariou of a subset of patients that the medical reviewer identified as problematic, based on apparent discrepancies in review of raw data and/or discrepancies in response designation between the investigator and WorldCare. Some of the patients Dr. Makariou was asked to review also included a subset of Taxol arm patients said to have stable disease.

There were occasional problems identified with the quality of radiographic images, the completeness of studies (eg. abdominal CT limited to liver evaluation only), the complete absence of measurable disease, the absence of lesions $\geq$ 20 mm required for WorldCare to define target lesions (but assessed as target lesions by some investigators). These limitations to adequate assessment were equally distributed between the two arms of the trial. There were infrequent discrepancies between the findings of Dr. Makariou and WorldCare, and there was no evidence of a systemic problem with WorldCare's interpretations.

Reviewer comment: *The limitations of some of the images provided to the remote radiologists, the inability to verify clinical and ultrasound data, and the availability of only the first 6 months of radiographs for review accounted for many cases where the* ***rec****TLRR was really based only on investigator assessments without independent radiologist input.*

FDA Review of Raw Data, Radiology Audit and Adjudication of Response

The FDA clinical reviewer evaluated all the tabulated raw data (tumor measurements) that provided the basis for assessment of response from datasets "INVLESN" and "WCLESN" for all patients identified by the applicant in both arms of the study as having partial or complete confirmed TLR. The clinical reviewer also evaluated the data from a subset of Taxol patients who were identified by the applicant to have stable disease (SD). FDA agreed that none of those Taxol patients designated as SD had evidence of response. Therefore, their designation as SD was appropriate. FDA agreed that all Taxol patients designated as responders had adequate evidence of response and the designation was appropriate. The applicant reported that for the ABI-007 arm and the Taxol arm of the randomized trial, there were 55 and 25 patients, respectively, who could be scored as having a confirmed *rec*TLR.. The clinical reviewer, based on the audit of tumor measurements in the electronic database and the radiology audit, suggested adjudication to remove 5 ABI-007 patients from the category of confirmed *rec*TL responder. The following table lists the adjudicated patients and the FDA justification.

Table 29: ABI-007 Treatment Arm Patients with Discrepancy in Response Status between FDA and Applicant (Reviewer Table)

Site #	Pt ID	*Rec*TLR (6 cycles)	*Inv*TLR (6 cycles)	WC TLR (6 cycles)	FDA TLR	FDA Comment
309	**342**	CR	CR	--	Not evaluable	We could not verify measurable disease at baseline to assess response. WC did not assess response. Investigator cited 17mm axillary lesion on CT resolved.
302	**303**	PR	PR	--	PD	We identified a response in the sum of measurable lesions on CT, apparently confirmed — Baseline liver CT (limited study) showed no lesions, but no repeat until — when apparently new disease seen.
335	**430**	PR	SD	PR	PD	Although sum of TLs decreased from baseline through week 12, there appear to be new nonTLs in liver, suspicious week 5, confirmed week 9.
308	**161**	PR	PR	--	SD	Multiple small lung nodules, probably no change over time. Investigator lung lesions 11mm + 18mm, decreased to 8+8 mm
318	**225**	PR	PR	--	SD	Poor quality films. We saw one stable left lung lesion. WC reported nonTL left lung decreased. Investigator says 1 TL on CT chest 27mm, decreased to 8mm

TLR = Target Lesion Response
Rec = Reconciled
Inv = Investigator
WC = WorldCare

Reviewer comment: *The patients for whom we rejected the designation of recTL responder, with the exception of patient #430, were all designated not evaluable or non-responders by WorldCare, based on radiographic criteria. By the algorithm, WorldCare takes precedence over the investigator when it is a matter of radiographic interpretation. We disagreed with the assessment of WorldCare for patient #430, because there were new non-Target lesions in the liver, which precludes designating the patient a responder (by applicant's definition), even if the Target lesions were smaller.*

The following table lists additional information regarding prior therapy for these 5 adjudicated patients, all of whom were in the ABI-007 treatment arm.

Table 30: Line of Therapy Data for Disputed Patients (Reviewer Table)

Pt ID	# of Prior Lines of Chemotherapy in Metastatic Setting	Prior Adjuvant chemotherapy	Prior Anthracycline?
342	2 (CMF, CAF)	No	Yes
303	3 (CMF Tam, CA, CAF, provera)	No	Yes
430	0 (First-line metastatic)	Yes (CMF)	No
161	1 (FAC Tam)	Yes (CMF)	Yes
225	0 (First-line metastatic)	Yes (CMF)	No (1 dose only adjuvant setting)

CMF = cyclophosphamide, methotrexate, 5-fluorouracil
CAF = cyclophosphamide, doxorubicin, 5-fluorouracil
CA = cyclophosphamide, doxorubicin
Tam = tamoxifen

The next table reflects the applicant's response to adjudication of the 5 ABI-007 patients (their comments added to the last column of our table above). They have also provided brief narrative explanations for each case.

Table 31: Applicant's Response Regarding FDA-Adjudicated Patients

Pt #	*Rec*TLR (6 cycles)	*Inv*TLR (6 cycles)	WCTLR (6 cycles)	FDA TLR	Radiology FDA Review	Response in Accordance with Predefined Algorithm (See Attachment 6)
342	CR	CR	-	Not evaluable	We could not verify measurable disease at baseline to assess response. WC did not assess response. Investigator cited 17mm auxiliary lesion on CT resolved.	**Criterion 2: Not interpretable by WorldCare based on film quality. Investigator response used.**
303	PR	PR	-	PD	We identified a response in the sum of measurable lesions on CT, apparently confirmed — Baseline liver CT (limited study) showed no lesions, but no repeat until — when apparently new disease seen.	**Criterion 2: Not measurable by WorldCare based on film quality (but decrease in size noted). Therefore investigator response used.**
430	PR	SD	PR	PD	Although sum of TLs decreased from baseline through week 12, there appear to be new nonTLs in liver, suspicious week 5, confirmed week 9.	**Criteria 4 and 5: Discrepancy between investigator and WorldCare due to different measurements of same lesion (criterion 4) or selection of different target lesions by WorldCare (criterion 5). Therefore WorldCare response used.**
161	PR	PR	-	SD	Multiple small lung nodules, probably no change over time. Investigator lung lesions 11mm + 18mm, decreased to 8 + 8mm.	**Criteria 2 and 3: No measurable target lesions by WorldCare-lung lesions less than 20mm (criterion 2). Absence of reading of progressive disease by WorldCare and investigator (criterion 3). Therefore investigator assessment used.**
225	PR	PR	-	SD	Poor quality films. We saw one stable left lung lesion. WC reported nonTL left lung decreased. Investigator says 1 TL on CT chest 27mm, decreased to 8mm.	**Criterion 2: No measurable lesions by WorldCare (scale missing from films) therefore investigator assessment used.**

Reviewer comment: *The applicant has not refuted the radiographic findings satisfactorily. We do not accept the determination of the investigator for these cases. By the algorithm, if there is a difference in interpretation of radiographic findings between WorldCare and the Investigator, the resolution is in favor of the blinded radiologist. The investigator's view is primary if it is a matter of interpretation of clinical data not accessible to radiology review, which was not the case in these patients.*

Complete Responders (CRs)

The applicant identified 7 ABI-007 patients and a single Taxol patient as complete responders by *rec*TLR. Information regarding these patients is displayed in table 32 below. Most of these patients were not assessed by WorldCare for response. Several patients were called CRs by the investigators because target lesions resolved, but patients had residual non target lesion disease.

Table 32: List of Patients Designated as Reconciled Complete Target Lesion Response by Applicant (Reviewer Table)

Site #	Pt #	*Rec*TLR (6 cycles)	*Inv*TLR (6 cycles)	*WC* TLR (6 cycles)	FDA Comment
ABI-007 Treated Patients					
309	342	CR	CR	--	FDA and WC could not verify measurable disease at baseline to assess response. Investigator: 17 mm axillary lesion on CT, resolved.
311	446	CR	CR	--	TL resolved but only PR for nonTLs. WC: TL=93mm, then 0 but did not designate response. FDA: CR TL; PR nonTL.
310	288	CR	CR	CR	Inv: CR . WC: TLR, but unclear if 1 nTL remained; 1 resolved; close to CR? FDA: TL CR; overall PR
308	901	CR	PR	CR	WC: 4 TLs =135 mm, then 0. Inv: 3 TL=105 mm, then 17mm. Smaller but not resolved nonTL Close to CR.
137	325	CR	CR	--	
313	318	CR	CR	--	Inv: Multiple lesions resolved on ultrasound; probably true CR
318	250	CR	CR	--	Inv: "TL" liver lesion 15mm resolved. WC: There is no TL, but several non TL are smaller. This would be PR, but not designated.
Taxol-Treated Patient					
314	902	CR	CR	--	Investigator: TL in chest wall, 40mm on CT, decreased to 0; residual pleural effusion. WC: No TL; nonTL pleural effusion decreased. Probably not CR due to residual effusion.

TLR = Target Lesion Response
Rec = Reconciled
Inv = Investigator
WC = WorldCare

Reviewer comment: *From review of the data for the patients designed CR, it appears misleading to distinguish "complete" from partial response for the primary study endpoint.*

Primary Efficacy Endpoint (*rec*TLRR) – FDA

The FDA's analysis was performed on all randomized patients (460), whereas the applicant's analyses were base on 454 patients, the number of patients actually *treated* with study drug. As discussed above, the applicant determined that 55 ABI-007 patients and 25 Taxol patients met criteria for the reconciled target lesion response, the primary efficacy endpoint. FDA excluded 5 ABI-007 patients from designation as responders (see above), but excluded no Taxol patients. The data in next table is from the FDA statistical reviewer's analysis. The confirmed Reconciled Target Lesion Response Rate for all randomized patients treated with ABI-007 was 21.5% (95% CI: 16.19-26.73%) and for Taxol was 11.1% (95% CI: 6.94-

15.09%). The difference was statistically significant (p=0.003), demonstrating superiority for ABI-007.

Table 33: FDA Evaluation of Response and TTP (All Randomized Patients) (Reviewer Table)

		ABI-007 260 mg/m^2	Taxol 175 mg/m^2
Reconciled Target Lesion Response Rate			
All randomized patients	Response Rate [95% CI]	50/233 (21.5%) [16.19% – 26.73%]	25/227 (11.1%) [6.94% – 15.09%]
	P-value [a]	0.003	
Patients who failed combination chemotherapy or relapsed within 6 months of adjuvant chemotherapy†	Response Rate [95% CI]	20/129 (15.5%) [9.26% – 21.75%]	12/143 (8.4%) [3.85% – 12.94%]
Time to Disease Progression (Reconciled Response Assessment Dataset Through Cycle 6)			
All randomized patients	% of Patients with Disease Progression	92/233 (39.4%)	118/227 (52.0%)
	Median [b] [95% CI]	17.0 [15.9 – 19.3]	15.6 [15.1 – 16.4]
	Hazard Ratio [c] [95% CI]	0.749 [0.570 – 0.984]	

[a] from Cochran-Mantel-Haenszel test stratified by 1st line vs. > 1st line therapy.
[b] Kaplan-Meier estimates of median time to disease progression in weeks.
[c] hazard ratio of ABI-007/Taxol from the Cox regression model without any covariate.
†Prior therapy should have included an anthracycline unless clinically contraindicated
Source: FDA Statistical Reviewer

The above table also demonstrates efficacy data for the subset of patients who meet the Taxol indication in metastatic breast cancer, patients who " failed combination chemotherapy or relapsed within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated." For the 272 patients who met the Taxol indication, based on the FDA clinical reviewer's adjudication, there were 20 and 12 responders in the ABI-007 and Taxol arms, respectively. The response rates were 15.5% and 8.4%, for ABI-007 and Taxol groups, respectively. The P-value from Chi-Square Test calculated by the FDA statistical reviewer was 0.069. Although the difference was not statistically significant in this subgroup, the trend was in the same direction as for the overall study population.

For the 189 first-line patients, the response rates were 31.3% and 17.8%, respectively, also favoring ABI-007. The next table, prepared by the FDA statistical reviewer displays the efficacy data and analysis for the sub-group.

Table 34: FDA Evaluation of Response for First-Line Therapy Patients (All Randomized) (Statistical Reviewer Table)

Reconciled Target Lesion Response Assessment Dataset	ABI-007 [N = 99]	Taxol [N = 90]
No. of FDA-Confirmed Responders	31	16
Response Rate (95% Binomial Confidence Interval)	31.3% (22.18% – 40.45%)	17.8% (9.88% – 25.68%)
Ratio of Response Rates (ABI-007/Taxol) (95% Confidence Interval)	1.761 (1.035 – 2.997)	
P-value from Chi-Square Test	0.032	

Source: Statistical Reviewer Table 15 (Statistical Review)

Selected Secondary Efficacy Endpoints – FDA

Duration of Response – FDA

The following table summarizes an exploratory analysis performed by the FDA statistical reviewer.

Table 35: Duration of Response on FDA-Confirmed Responders (Based on Reconciled Assessment through Cycle 6) (Statistical Reviewer Table)

Category	**ABI-007 [N = 50]**	**Taxol [N = 25]**
No. of FDA-Confirmed Responders Who Subsequently Had Progressive Disease	6 (12%)	5 (20%)
Kaplan-Meier Median Duration of Response	Not available	Not available
P-value from (two-sided) Logrank Test	0.300	

Note: Duration of confirmed complete or partial target response is based on patients with a confirmed complete or partial target response. Duration of confirmed complete or partial target response is defined as the number of weeks from first confirmed complete or partial target response to the start of disease progression. Patients that did not have disease progression are censored at the last known time the patient was evaluated for response.

Source: FDA Statistical Reviewer Table 24 (Statistical Review)

FDA Reviewer comment: *No meaningful comparisons can be made because the data is not mature. Alternate calculations of Response Duration have been made by the applicant, but the applicant's analysis is based on the confirmed* invORR, *a secondary endpoint based solely on investigator's assessment of response for all cycles of therapy.*

Time to Disease Progression (TTP) – FDA

Table 33, above displays the FDA statistician's determination of TTP, based on the time from randomization, including all randomized patients, with evaluation through cycle 6 based on *rec*TLRR. There was progression for 92 (39.4%) ABI-007 patients and for 118 (52.0%) Taxol patients. The Kaplan-Meier median time to disease progression in weeks was 17 (95% CI: 15.9-19.3) for ABI-007 patients and 15.6 (95% CI: 15.1-16.4) for Taxol patients. The p-value from the 2-sided logrank Test was 0.036 and hazard ratio was 0.749 (95% CI: 0.570-0.984).

Reviewer comment: *There was a statistically significant difference in TTP between the 2 treatment arms. FDA did not allow inclusion in the label of the secondary endpoints of invORR (investigator Overall Response Rate) or TTP. In a single, open-label trial, these secondary endpoints were felt to be open to subjective bias, not objectively verifiable, and, therefore, not sufficiently reliable to be placed in the label.*

Survival – FDA

The next table shows the FDA statistical reviewer's exploratory analysis for overall survival, for all-randomized patients and calculated from the randomization date.

Table 36: FDA Results for Overall Survival (All Randomized) (Statistical Reviewer Table)

Category		ABI-007 [N = 233]	Taxol [N = 227]
No. of Deaths		73 (31.3%)	84 (37.0%)
Kaplan-Meier Median Time to Death in weeks	in weeks	39.9 (34.7 – 44.7)	37.9 (34.4 – 40.7)
(95% Confidence Interval)	in months	9.15 (5.44 – 7.54)	8.79 (8.03 – 9.51)
P-value from Logrank Test		0.774	
Hazard Ratio (ABI-007/Taxol)[a] (95% Confidence Interval)		0.955 (0.696, 1.310)	

Note: Analysis includes patient survival information during study follow-up. Patients that did not die are censored at the last known time the patient was alive.

[a] Hazard ratio of ABI-007/Taxol, based on Cox model with treatment being the only factor.

Source: Statistical Reviewer Table 29 (Statistical Review)

Reviewer comment: *The data are not sufficiently mature for meaningful comparisons between treatment arms for survival, as < 40% of events had occurred. As a phase 4 post-marketing commitment, the applicant will be required to submit survival data when 80% of deaths have occurred.*

6.4 Summary of Single Arm Trials

Table 1 (section 4.2) displays the study numbers, patient populations, treatment, number of patients and primary endpoints for the phase 1-2 trial and two phase 2 trials submitted to the NDA, and also displays this information for the randomized trial discussed in section 6.3.

DM97-123

In this single arm phase 1-2 trial in patients with solid tumors including breast cancer, 19 patients (16 PK) were treated with ABI-007 at doses of 135 mg/m2, 200 mg/m2, 300 mg/m2 or 375 mg/m2 IV q3weeks. No steroid or anti-histamine premedications were given, and no hypersensitivity reactions to ABI-007 were observed. The maximum tolerated dose (MTD) of ABI-007 was 300 mg/m2 IV over 30 minutes every 3 weeks. This dose was delivered to 9 patients in a total of 32 treatment cycles. Dose limiting toxicities (DLT) observed at 375 mg/m2 were keratitis, blurred vision, sensory neuropathy, stomatitis, and grade 4 neutropenia. The most commonly reported treatment-related toxicities were fatigue (84% of patients), nausea (63%), alopecia (58%), sensory neuropathy (53%), stomatitis (53%), diarrhea (42%), skin (42%), vomiting (37%), blurred vision (37%), fever (32%), and anorexia (32%).

CA002-0

In this single arm phase 2 trial, performed from October 29, 1999, until September 29, 2001, 63 patients with metastatic breast cancer were treated with ABI-007 300 mg/m2 IV over 30 minutes every 3 weeks. The applicant reported that the confirmed TLRR was 47.6% overall; 57.7% for 26 anthracycline-naïve patients; 40.5% for 37 anthracycline-exposed patients, and 66.7% for the 15 first-line patients.

There were no severe hypersensitivity reactions reported, even though steroid premedication was not given routinely. The most common treatment-related toxicities were alopecia (94% of patients), sensory neuropathy (65%), neutropenia (63%), fatigue (40%), nausea (38%), myalgia (25%), infections and vomiting (22% each), and anemia and stomatitis/pharyngitis (21% each). Grade 4 neutropenia was reported for 24% of patients, usually occurring during cycle one and, requiring 25% dose reduction for subsequent cycles. Neutropenic fever was "uncommon" and there were no deaths due to infection. Reasons for dose reductions for > 1 patient were "uncomplicated" neutropenia (7 patients), sensory neuropathy (4), febrile neutropenia (3), and myalgia and fatigue (2 patients each). Grade 4 hematologic toxicity occurred in $\leq$ 5% of patients; grade 3 leukopenia occurred in 19% of patients, grade 3 thrombocytopenia in 5%. Grade 3 myalgia occurred in 8% of patients. Sensory neuropathy required discontinuation in 8% of patients before 6 cycles and 3% of patients after 6 cycles of therapy. Ocular toxicities were "uncommon and not severe."

CA002-0LD

In this single arm phase 2 trial, performed from July 21, 2000, until September 6, 2001, 43 patients with metastatic breast cancer were treated with ABI-007 175 mg/m2 IV over 30

minutes every 3 weeks. The confirmed TLRR was 39.5% for all 43 patients dosed; 42.9% for 21 anthracycline-naïve patients; 44.8% for 29 first-line patients.

There were no severe hypersensitivity reactions reported, even though steroid premedication was not given. The most commonly reported adverse events included alopecia (100% of patients), fatigue (37%), neutropenia (33%), myalgia (33%), nausea (28%), fever (28%), anorexia (28%), pigmentation changes (26%), sensory neuropathy (26%), extremity pain (23%), pain other (23%), vomiting (23%), infections (21%) and pruritus (19%). The most common severe treatment-related toxicities were neutropenia, infections, vomiting, fatigue, and myalgias. One septic death occurred, without neutropenia. Grade 4 neutropenia was reported for 3 (7%) patients. There was no grade 3 or 4 neurologic toxicity. No significant ocular toxicity was reported (grade 1 tearing in 2 patients).

6.5 Efficacy Conclusions

This NDA was filed under Section 505(b)(2), referencing the label, efficacy and safety of Taxol Injection. For approval, the applicant was required to demonstrate non-inferiority in objective response rate to Taxol in a single randomized trial in metastatic breast cancer. At least 100 patients in each arm were to match the Taxol indication which is "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." Phase 2 data in two single arm trials in metastatic breast cancer were to be supportive.

In a randomized controlled trial of women with metastatic breast cancer, ABI-007 260 mg/m2 IV over 30 minutes every 3 weeks was shown to be superior for the primary response rate endpoint compared with Taxol 175 mg/m2 IV over 3 hours every 3 weeks. A total of 460 patients were randomized in comparative trial CA012-0, 233 to the ABI-007 arm, and 227 patients to the Taxol arm. A total of 272 patients (58%) met the Taxol indication, of whom 129 were randomized to receive ABI-007 and 143 patients were randomized to receive Taxol. There were 189 patients (41%) who received study treatment as first-line therapy for metastatic breast cancer, 99 in the ABI-007 arm and 90 in the Taxol arm.

The primary efficacy endpoint was the confirmed reconciled Target Lesion Response Rate (*rec*TLRR). According to a predefined algorithm, differences in assessment between a blinded radiology group and the investigators were reconciled. The *rec*TLR required confirmation of response within the first 6 treatment cycles and only considered nontarget lesions (nonTLs) if there were new lesions or progressive disease in nonTLs. The applicant determined that 55 patients treated with ABI-007 (24%) and 25 patients treated with Taxol (11%) had CR or PR by the *rec*TLR, the primary efficacy endpoint. The FDA clinical reviewer's adjudication of response excluded 5 ABI-007 patients, resulting in 50 and 25 responders in the ABI-007 and Taxol arms respectively, for a *rec*TLRR of 21.5% and 11.1%, respectively. (95% CI: 16.19-26.73% for ABI-007; 6.94-15.09% for Taxol) The difference was statistically significant (p=0.003), demonstrating superiority for ABI-007 for the primary endpoint for the entire study population. (See Table 33.) For the 272 patients who met the Taxol indication, based on the FDA clinical reviewer's adjudication, there were 20 and 12 responders in the ABI-007 and Taxol arms, respectively. The response rates were 15.5% and

8.4%, for ABI-007 and Taxol groups, respectively. Although the difference was not statistically significant in this subgroup, the trend was in the same direction as for the overall study population. For the 189 first-line patients, the response rates were 31.3% and 17.8%, respectively, also favoring ABI-007.

The confirmed investigator overall response rate (*inv*ORR) was a secondary endpoint based on the investigator's assessment's over all treatment cycles (including > cycle 6), using TL and nonTL responses according to RECIST. The investigators had access to data from clinical exam and sonograms for all cycles, and radiographic images after cycle 6, not accessible to the blinded radiology group. The *inv*ORR also demonstrated superiority of ABI-007 over Taxol for the overall study population (33.2% vs. 18.7%). Based on the applicant's analysis, about 33% of responders from each arm had progressed by the data cut-off date.

When Time to Progression (TTP), based on the reconciled response dataset, was calculated from the date of randomization (rather than date of first study dose as per applicant), the observed median was 17.0 weeks for the ABI-007 patients and 15.6 weeks for the Taxol patients. For patients who did not progress until they were off study, TTP was not adequately evaluated, since only telephone follow-up every 3 months was required for patients off study. The data are not sufficiently mature to permit comparison between treatment arms for the additional secondary endpoints of duration of response and overall survival.

7 Integrated Review of Safety

7.1 Brief Statement of Findings

ABI-007 260 mg/m2 administered IV over 30 minutes every 3 weeks has an acceptable safety profile compared to Taxol 175 mg/m2 administered IV over 3 hours every 3 weeks for the treatment of patients with metastatic breast cancer. The toxicity profile for ABI-007 was generally similar compared with Taxol, in spite of the higher dose of paclitaxel delivered with each ABI-007 treatment. Although routine steroid premedication was not given with ABI-007, hypersensitivity reactions were significantly fewer in the ABI-007 arm compared with the Taxol treatment group (4% vs.12%). The percent of patients with neutropenia <0.5 X 10^9/L was less for ABI-007 (9%) than for Taxol (22%). The incidence of febrile neutropenia was low for both groups (2% and 1%, respectively). No grade 4 sensory neuropathy occurred, but the percent of patients with any sensory neuropathy or grade 3 was higher for ABI-007 (71% and 10%, respectively) than for Taxol (56 % and 2%, respectively), possibly reflecting the higher doses of paclitaxel delivered. However, the applicant indicated that, of the 24 ABI-007 patients with grade 3 neuropathy, 14 improved after a median of 22 days; 10 patients resumed treatment at a reduced dose, and 2 discontinued due to peripheral neuropathy. Of the 10 patients without documented improvement, 4 discontinued the study due to peripheral neuropathy. The applicant indicated that the time to improvement from grade 3 neuropathy for Taxol patients was longer (median 79 days). However, in view of the small number of patients in the Taxol group who experienced grade 3 neuropathy (n=5), comparisons between the treatment arms of the time to improvement to grade 1 or 2 neuropathy do not appear meaningful.

The number of deaths on study or within 30 days of study drug was 6 in the ABI-007 arm and 8 in the Taxol arm, all deaths said to be due to progression of cancer. SAEs were reported in 28% of ABI-007 patients and 35% of Taxol patients, with neutropenia the most frequent SAE in both treatment groups. No sensory neuropathy SAEs were reported in either group. The most frequent toxicity leading to premature discontinuation was sensory neuropathy (ABI-007: 7 patients [3%] and Taxol: 2 patients [<1%], p=0.175).

7.2 Materials Utilized in the Review

The following materials were utilized in the safety review by the medical officer:

- NDA electronic submission, including raw and derived electronic datasets
- Study report and selected CRFs from trial CA012-0
- Study reports and summary data for CA002-0, CA002-0LD, DM97-123
- 120-Day Safety Update submitted July 7, 2004
- Relevant published literature
- Electronic labeling proposal for Abraxane
- Taxol label (Bristol-Myers Squibb Co)
- Applicant presentation to FDA on April 22, 2004.

7.3 Description of Patient Exposure

The primary safety population consists of 454 patients with metastatic breast cancer treated in randomized trial CA012-0, 229 patients who were treated with at least one cycle of ABI-007 260 mg/m2 IV every 3 weeks and 225 patients who were treated with at least one cycle of Taxol 175 mg/m2 IV every 3 weeks. There were two single arm trials, which provide supportive data for efficacy and safety. Patients were treated with a higher dose of ABI-007 in one trial, and with a lower dose in the other single arm trial compared with the dose of ABI-007 chosen for the randomized trial. In the single arm trial CA002-0LD, 43 patients with metastatic breast cancer were treated with at least one cycle of ABI-007 175 mg/m2 every 3 weeks; 31 patients completed at least 6 cycles of therapy. In the single arm study CA002-0, 63 patients with metastatic breast cancer were treated with at least one cycle of ABI-007 300 mg/m2 every 3 weeks; 37 patients completed at least 6 cycles of therapy. (See section 6.4 above for a summary of safety findings from single-arm trials.)
The following applicant table, from the integrated summary of safety (ISS), displays the cumulative dose of drug, average dose intensity and number of cycles administered in phase 2 and 3 trials of ABI-007.

Table 37: Cumulative Dose, Dose Intensity, Cycles Administered in phase 2 and 3 Studies (Applicant Table)

	Phase II: CA002-0LD ABI-007 175 mg/m^2 (n = 43)	Phase III: CA012-0 (controlled study) Taxol 175 mg/m^2 (n = 225)	Phase III: CA012-0 (controlled study) ABI-007 260 mg/m^2 (n = 229)	Phase II: CA002-0 ABI-007 300 mg/m^2 (n = 63)
Cumulative Dose During Study (mg/m^2)				
Mean	1021.5	909.0	1459.3	1431.9
S.D.	319.35	494.88	787.85	709.72
Median	1050.0	875.0	1560.0	1725.0
min, max	175, 1750	175, 3150	260, 4680	300, 3000
Average Dose Intensity (mg/m^2/week)				
Mean	57.58	57.02	85.13	93.50
S.D.	1.765	3.008	3.118	10.732
Median	58.33	58.07	86.43	99.24
min, max	49.9, 59.5	31.7, 70.2	69.8, 92.0	53.3, 102.6
Cumulative Dose During Study (mg)				
Mean	1610.0	1578.8	2567.6	2293.4
S.D.	568.74	887.20	1420.64	1182.66
Median	1625.2	1644.0	2540.0	2471.0
min, max	307, 2925	10, 5760	390, 8424	463, 5078
Cycles administered				
Mean per patient (S.D.)	5.8	5.2	5.6	5.1
S.D.	1.82	2.85	3.04	2.62
Min, Max	1, 10	1, 18	1, 18	1, 13
Median	6.0	5.0	6.0	6.0

Source: Table 9 ISS (CA012-0 date from summary tables 24.0 and 24.2 study report)

In trial CA012-0, the mean/median number of cycles administered for randomized patients was 5.6/6 for ABI-007 and 5.2/5 for Taxol. The minimum and maximum numbers of cycles were 1 and 18 for both treatment groups. The average dose intensity (paclitaxel exposure) in the phase 3 trial was approximately 85 mg/m2/week for ABI-007 compared with 57 mg/m2/week for Taxol. Similarly the mean cumulative dose during the phase 3 study was higher for ABI-007 (approximately 2568 mg) than for Taxol (1579 mg), due to the protocol specified higher dose of drug delivered per cycle. This resulted in the ABI-007 patients receiving approximately 61% more paclitaxel than the Taxol patients.

A slightly higher percent of ABI-007 patients was treated with > 6 cycles of chemotherapy (28%) compared with the percentage of Taxol patients who received > 6 cycles of therapy (20%) in study CA012-0. However, approximately three quarters of patients from each

treatment arm were discontinued after receiving ≤ 6 cycles of therapy. (See table 6 above and table 29 below.) The following applicant table displays treatment exposure by cycle for the safety population of the randomized trial.

Table 38: Treatment Exposure by Cycle (Applicant Table)

Category		ABI-007 (N = 229)	Taxol (N = 225)
Number of cycles administered	Mean per patient (S.D.)	5.6 (3.04)	5.2 (2.85)
	Min, Max	1, 18	1, 18
	Median	6	5
Number of cycles administered, n (%)	1	10 (4%)	6 (3%)
	2	33 (14%)	41 (18%)
	3	22 (10%)	26 (12%)
	4	14 (6%)	16 (7%)
	5	21 (9%)	24 (11%)
	6	64 (28%)	67 (30%)
	> 6	65 (28%)	45 (20%)
	7	11 (5%)	14 (6%)
	8	22 (10%)	9 (4%)
	9	9 (4%)	5 (2%)
	10	10 (4%)	5 (2%)
	11	3 (1%)	2 (<1%)
	12	4 (2%)	4 (2%)
	13	1 (<1%)	3 (1%)
	14	2 (<1%)	1 (<1%)
	15	0	0
	16	2 (<1%)	1 (<1%)
	17	0	0
	18	1 (<1%)	1 (<1%)

Applicant In-Text Table 64; source: summary table 24.0 and Listing 10.0.

The following applicant table displays treatment exposure by cycle and dose for the safety population of the randomized trial.

Table 39: Treatment Exposure by Cycle and Dose (Applicant Table)

	Number (% at each cycle) of Patients					
	ABI-007 Dose (mg/m^2)			Taxol Dose (mg/m^2)		
Cycle	208	220	260	112	140	175
1	–	–	229 (100%)	–	–	225 (100%)
2	–	3 (1%)	216 (99%)	–	1 (<1%)	218 (>99%)
3	1 (<1%)	5 (3%)	180 (97%)	–	6 (3%)	172 (97%)
4	2 (1%)	6 (4%)	156 (95%)	–	5 (3%)	147 (97%)
5	2 (1%)	7 (5%)	141 (94%)	–	4 (3%)	132 (97%)
6	3 (2%)[a]	7 (5%)	119 (92%)	–	3 (3%)	109 (97%)
7	–	3 (5%)	62 (95%)	1 (2%)	2 (4%)	42 (93%)
8	–	3 (6%)	51 (94%)	1 (3%)	1 (3%)	29 (94%)
9	–	1 (3%)	31 (97%)	1 (5%)	1 (5%)	20 (91%)
10	–	–	23 (100%)	–	1 (6%)	16 (94%)
11	–	1 (8%)	12 (92%)	–	–	12 (100%)
12	–	1 (10%)	9 (90%)	–	–	10 (100%)
13	–	1 (17%)	5 (83%)	–	–	6 (100%)
14	–	–	5 (100%)	–	–	3 (100%)
15	–	–	3 (100%)	–	–	2 (100%)
16	–	–	3 (100%)	–	–	2 (100%)
17	–	–	1 (100%)	–	–	1 (100%)
18	–	–	1 (100%)	–	–	1 (100%)
Total cycles	8 (<1%)	38 (3%)	1247 (96%)	3 (<1%)	24 (2%)	1147 (98%)

[a] Cycle 6 for ABI-007 includes 1 dose each at 175 and 180 mg/m^2.

In-Text Table 65; source: Listing 10.0

Greater than 90% of the protocol-specified dose of drug was delivered to 96% of the ABI-007 patients and 94% of the Taxol patients, with 4% receiving 80-< 90% of the dose of ABI-007 and 5% receiving 80-< 90% of the dose of Taxol. Only 2 Taxol patients received less than 80% of the protocol-specified dose.

7.4 Safety Findings from Clinical Studies

See section 6.4 for a summary of safety findings from single-arm trials. The focus of this safety review is the comparative safety findings from the controlled trial, CA012-0, the only study in which the specified dose of ABI-007 was 260 mg/m2 IV every 3 weeks.

APPLICANT SAFETY FINDINGS FROM RANDOMIZED TRIAL CA-012-0

Dose Delays

The mean interval between treatment cycles was 21.4 and 21.5 days for ABI-007 and Taxol, respectively. There was delay in 4% of ABI-007 treatment cycles and 6% of Taxol treatment cycles, usually for 4-8 days. Dose reductions and delays due to adverse events (AEs) occurred in $\leq 7\%$ of patients in each treatment arm.

Adverse Events

AEs "were reported by the investigator by the toxicity term that the investigator felt best described the event (i.e., the 'verbatim' term) and graded using the NCI CTC grading definitions. The 'verbatim' terms for toxicities/ AEs were coded to the closest (lower level) MedDRA term and then mapped into the appropriate NCI CTC toxicity category." All treatment-emergent and treatment-related events were summarized and analyzed. Treatment-emergent events were defined as AEs that started or worsened after beginning study drug, through 30 days after the last dose. Treatment-related events were defined as treatment-emergent events that the investigator assessed as "possibly, probably, or definitely related to study drug." AEs were summarized by NCI-CTC term, as well as by body system and Med DRA preferred term.

Virtually all patients experienced at least one treatment-emergent AE. The following applicant table displays the most commonly reported treatment-emergent toxicities for all cycles. The most common AEs were alopecia and sensory neuropathy. The latter was reported in 71% of patients with ABI-007 and 56% of patients with Taxol. The incidence of neutrophil toxicity was significantly higher for Taxol patients (49%) than for ABI-007 patients (34%). Gastrointestinal (GI) toxicity was reported for more ABI-007 than Taxol patients, and was significantly higher for each of the symptoms nausea, diarrhea and vomiting. The incidence of hepatic enzyme elevation (GGT) was only slightly higher for ABI-007 patients (14%) than for Taxol patients (11%), and not significantly higher. The incidence of skin flushing was reported as 14% for Taxol patients and 3% for ABI-007 patients, which was significantly higher ($p<0.001$)

Table 40: Most Commonly Reported (>= 10% Patients per either Arm) Treatment-Emergent Adverse Events for All Cycles (Applicant Table)

NCI CTC Term	Number (%) of Patients		*P-value*[a]
	ABI-007 (N = 229)	Taxol (N = 225)	
Patients with at least one Toxicity	227 (>99%)	225 (100%)	*0.499*
Dermatology/Skin: Alopecia	207 (90%)	211 (94%)	*0.224*
Neurology: Neuropathy-sensory	163 (71%)	125 (56%)	*0.001**
Constitutional Symptoms: Fatigue	108 (47%)	86 (38%)	*0.058*
Blood/Bone Marrow: Neutrophils	78 (34%)	110 (49%)	*0.002**
Pain: Arthralgia	80 (35%)	75 (33%)	*0.767*
Pain: Myalgia	65 (28%)	71 (32%)	*0.475*
Gastrointestinal: Nausea	69 (30%)	48 (21%)	*0.041**
Infection/Febrile Neutropenia: Infection with unknown ANC	54 (24%)	44 (20%)	*0.307*
Gastrointestinal: Diarrhea	60 (26%)	33 (15%)	*0.002**
Gastrointestinal: Stomatitis/pharyngitis	38 (17%)	31 (14%)	*0.434*
Blood/Bone Marrow: Leukocytes	30 (13%)	38 (17%)	*0.293*
Gastrointestinal: Vomiting	42 (18%)	22 (10%)	*0.010**
Pain: Other-Extremity	34 (15%)	28 (12%)	*0.496*
Hepatic: GGT	33 (14%)	25 (11%)	*0.326*
Constitutional Symptoms: Fever	32 (14%)	24 (11%)	*0.319*
Pain: Other	27 (12%)	29 (13%)	*0.776*
Pulmonary: Dyspnea	27 (12%)	21 (9%)	*0.447*
Pain: Bone Pain	25 (11%)	19 (8%)	*0.429*
CV (General): Edema	22 (10%)	18 (8%)	*0.620*
Gastrointestinal: Constipation	26 (11%)	14 (6%)	*0.068*
Dermatology/Skin: Flushing	6 (3%)	32 (14%)	*<0.001**

Note: If a patient reports the same toxicity more than once, then that patient is only counted once for the summary of that toxicity, using the most severe intensity.

CV = cardiovascular

[a] P-values are from Fisher's exact test. * P-values < 0.05.

Applicant In-Text Table 67; source summary table 25.2 and listing 17.0

Reviewer Comment: *The significantly greater number of ABI-007 patients experiencing neurotoxicity and GI symptoms compared with Taxol patients could be explained by the higher exposure to paclitaxel for each dose of ABI-007 compared with each dose of Taxol.*

The significant increase in percent of Taxol patients with flushing compared with ABI-007 patients is likely due to hypersensitivity to Cremophor with which Taxol is formulated. An increased incidence of flushing was observed with Taxol in spite of routine premedication including corticosteroids for patients in that treatment arm.

The applicant suggests that the explanation for the significantly greater number of Taxol patients experiencing neutrophil AEs compared with ABI-007 patients may relate to toxicity from the Cremophor excipient contained in Taxol. However, the number of patients with infections, without reference to WBC, was slightly higher for the ABI-007 group (24%) compared with the Taxol group (20%). When this reviewer searched dataset ADEX for the MedDRA term "febrile neutropenia", there were only 2 ABI-007 patients found, both grade 4, and 1 Taxol patient, grade 3.

The most frequently reported treatment-emergent Grade 3 or 4 AEs (occurring in > 5% of all patients) were neutropenia (ABI- 007 = 30%, Taxol = 46%), increased GGT (14%, 10%), leukopenia (6%, 9%), sensory neuropathy (10%, 2%), fatigue (8%, 3%), arthralgia (7%, 4%), and myalgia (7%, 2%). The number of patients experiencing Grade 3 and 4 infection was similar for both treatment groups, although the incidence of grade 3 plus 4 neutropenia was significantly higher for the Taxol treatment arm.

Table 41: Number (%) of Patients with Treatment-Emergent Grade 3 and 4 Adverse Events (≥ 5% Either Treatment Arm)

NCI CTC Term	ABI-007 (n=229)		Taxol (n=225)	
	Grade 3	Grade 4	Grade 3	Grade 4
Neurology: Neuropathy-Sensory	24 (10%)	0	5 (2%)	0
Constitutional: Fatigue	18 (8%)	1 (<1%)	6 (3%)	1 (<1%)
Blood/Marrow: Neutrophils	46 (20%)	24 (10%)	56 (25%)	48 (21%)
Pain: Arthralgia	15 (7%)	0	8 (4%)	0
Pain: Myalgia	17 (7%)	0	4 (2%)	0
Infection/febrile neutropenia: Infection + unknown ANC	10 (4%)	1 (<1%)	7 (3%)	0
Blood/Marrow: Leukocytes	14 (6%)	0	17 (8%)	3 (1%)
Hepatic: GGT	22 (10%)	10 (4%)	16 (7%)	7 (3%)

Source: Applicant In-Text Table 69; summary table 25.5 and Listing 17.0

Reviewer comment: *See additional analyses below ("FDA Analysis") for discussion of the sub-categories of GI toxicity and listing of incidence of "any symptoms" vs." severe symptoms" (grade 3 and 4).*

Blood and Bone Marrow Adverse Events: Neutropenia

The following applicant table displays the incidence of grade 3 or 4 neutropenia, based on (central) laboratory values and the time to recovery for the safety population.

Table 42: Incidence of Grade 3 or 4 Neutropenia and Time to Recovery (Applicant Table)

	ABI-007 (N = 229)	Taxol (N = 225)	*P-value*[a]
Patients with Grade 3 or 4 Neutropenia	77 (34%)	118 (52%)	
Median Time to Recovery (days)	8.0	8.0	*0.227*
95% Confidence Interval[b]	–	–	
Patients With Colony-Stimulating Factor Treatment	2 (<1%)	10 (4%)	
Median Time to Recovery (days)	14.5	8.0	*0.972*
95% Confidence Interval[b]	7.0, 22.0	7.0, 10.0	
Patients Without Colony-Stimulating Factor Treatment	75 (33%)	108 (48%)	
Median Time to Recovery (days)	8.0	8.0	*0.160*
95% Confidence Interval	–	–	

[a] P-value from log-rank test.

[b] 95% confidence interval from median time to recovery.

Note: Grade 3 or 4 neutropenia is defined as ANC < 1.0 x 10^9/L, and recovery is defined as ANC ≥ 1.5 x 10^9/L.

Note: Time to recovery is based on patients with Grade 3 or 4 neutropenia after the start of treatment. Time to recovery is defined as the number of days from the first occurrence of Grade 3 or 4 neutropenia to the first occurrence of recovery. Patients with Grade 3 or 4 neutropenia who did not recover are censored at the last known time ANC was evaluated.

Source: Applicant In-Text Table 75; summary table 27.4.1.

Grade 4 neutropenia occurred in 20 (9%) and 48 (22%) patients in the ABI-007 and Taxol groups, respectively, but the difference was not significant. The median time to recovery from Grade 3 or 4 neutropenia was 8.0 days for both treatment groups. Few patients were treated with granulocyte or granulocyte-macrophage colony-stimulating factor (CSF). The time to neutrophil recovery (ANC ≥1.5 x 10^9/L) was similar (median 8 days) for patients in both treatment arms who were not treated with CSF. For the few patients treated with CSF, recovery was longer for Abraxane patients.

Neutrophil nadir counts were statistically significantly higher for the ABI-007 group overall. The mean (S.D.) nadirs were 1.67 (2.28) and 1.31 (1.52) x 10^9/ L for the ABI- 007 and Taxol groups, respectively. The difference was statistically significant (P = 0.046).

There were no patients discontinued prematurely from the study for grade 4 neutropenia. Dose reductions were required for one ABI-007 patient and two Taxol patients.

Overall, in the ABI-007 group, 8 (3%) of patients were treated with G-CSF and/or GM-CSF for neutropenia or leukopenia of all grades, as were 14 (6%) Taxol patients.

Blood and Bone Marrow Adverse Events: Anemia

The incidence and severity of anemia (assessed by laboratory values) was similar for the treatment groups. Grade 3 or 4 anemia occurred in 3 (1%) and 1 (<1%) of ABI-007 and Taxol groups. The mean (S.D.) hemoglobin nadirs were 11.35 (1.30) and 11.48 (1.23) g/dL) for the respective treatment groups. For the ABI-007 patients, 5 (2%) were treated with erythropoietin and/or 4 (2%) transfusion; 8 (4%) of Taxol patients were treated with erythropoietin and 3 (1%) with transfusion.

Blood and Bone Marrow Adverse Events: Thrombocytopenia

The incidence and severity of thrombocytopenia (assessed by laboratory values) was similar for the treatment groups. There was no grade 4 thrombocytopenia. Grade 3 occurred in 1 ABI-007 patient, reported as a serious adverse event (patient #275) and 2 Taxol patients. Platelet nadirs were similar for the treatment groups. The mean (S.D.) nadirs were 220 (64) and 224 (75) x 10^9/ L for the ABI-007 and Taxol groups, respectively. No patients were discontinued from the study nor required dose reduction for thrombocytopenia. A single Taxol patient required dose delay.

Neurology Adverse Events: Sensory

Motor neuropathy was observed in one patient in the study, a patient in the ABI-007 arm. Treatment emergent-sensory neuropathy was observed in 71% of ABI-007 patients and in 55% of Taxol patients. No grade 4 neuropathy was reported. Treatment-related grade 3 neuropathy was seen in 10% of patients in the ABI-007 treatment arm and 2% of Taxol patients.

The following two paragraphs are taken directly from the applicant's study report (section 12.2.2.2):

> "Of the 24 patients in the ABI- 007 group with a maximum of Grade 3 sensory neuropathy, 10 patients continued on ABI- 007, all at a reduced dose (220 mg/ m2 [n = 8] or 208 mg/m2 [n = 2]). The 14 patients who did not restart therapy discontinued from the study for the following reasons: treatment- related toxicity only (6), progressive disease only (4), received = 6 cycles of therapy (2), withdrew consent (1), and investigator discretion (1). Of the patients who reported a maximum Grade 3 sensory neuropathy, almost all did so by Cycle 6 (ABI- 007: 23/ 24, Taxol: 5/ 5)."

> "Of the 45 patients in the ABI- 007 group with a maximum of Grade 2 sensory neuropathy, 40 (89%) continued without dose reduction for a median of 3 additional cycles (range: 1- 17), 4 had their dose reduced, and 1 stopped treatment. Of the patients who reported a maximum Grade 2 sensory neuropathy, most did so by Cycle 6 (ABI-007: 35/ 45, Taxol: 22/ 23)."

The applicant reported that, for ABI-007 patients, grade 3 sensory neuropathy "improved rapidly to grade 2 or 1 by a median of 22 days (n=24)," whereas, for Taxol patients, "the median time to improvement was 79 days (n=5)." At 28 days after first occurrence, 4 of 14 patients (17%) of ABI-007 patients with grade 3 neuropathy were unchanged, compared with 4 of 5 (80%) of Taxol patients who had persistent grade 3 neuropathy. The following applicant table displays this information.

Table 43: Incidence of Grade 3 Sensory Neuropathy and Time to Improvement to Gradel or 2 (Applicant Table)

Incidence of Grade 3 Sensory Neuropathy and Time to Improvement to Grade 1 or 2 (Based on AE Data)

Variable	ABI-007 (N=229)	Taxol (N=225)	P-value
Number of Patients with Grade 3 Sensory Neuropathy	24 (10%)	5 (2%)	
Median Time to Improvement (days)	22.0	79.0	0.028*
Confidence Interval [1]	17.0, 22.0	22.0, 129.0	

Note: Time to improvement is based on patients with grade 3 sensory neuropathy anytime after the start of treatment. Time to improvement is defined as the number of days from the first occurrence of grade 3 sensory neuropathy to the first occurrence of improvement. Patients with grade 3 sensory neuropathy that did not improve are censored at the last known occurrence of grade 3 sensory neuropathy.
Note: P-value from log-rank test.
[1] 95% confidence interval for median time to improvement.

Source: Applicant summary table 30.2

Reviewer comment: *In view of the small number of patients in the Taxol group who experienced grade 3 neuropathy, comparisons between the two treatment arms of the time to improvement to grade 1 or 2 neuropathy do not appear meaningful. Furthermore, determination of grade of neurotoxicity (e.g. 2 vs. 3) and time to improvement is subjective and open to bias in an open-label trial. There are also influences due to intrinsic cultural differences in an international trial. The incidence of dose reduction and dose discontinuation (see below) are better indicators of the rapidity of improvement, since dosing was scheduled to occur every 21 days.*

There were no serious adverse events (SAEs) reported for sensory neuropathy.

Dose reductions were required for sensory neuropathy for 13 ABI-007 patients (10 grade 3; 2 grade 2) and for 5 Taxol patients (3 with grade 3; 2 with grade 2). The dose reductions for ABI-007 patients were from 260 mg/m2 to 220 mg/m2. A single patient required a second dose reduction for grade 3, from 220 to 180 mg/m2. The 5 Taxol patients were dose-reduced from 175 mg/m2 to 140 mg/m2.

Seven patients in the ABI-007 group were prematurely discontinued from study for sensory neuropathy, as were 2 patients in the Taxol group.

The applicant performed an exploratory analysis of the physician and patient-reported assessments of sensory neuropathy as related to cumulative paclitaxel dose. They found no statistically significant difference between treatment groups when the incidence and severity of sensory neuropathy was adjusted to cumulative dose of paclitaxel.

Reviewer comment: *Although it is customary to evaluate comparative toxicity of therapies over unit of time or by number of treatment cycles, there seems to be some justification for an approach related to cumulative paclitaxel dose, since the exposure per dose was higher for Abraxane than Taxol. The applicant's analysis of the patient-reported symptom data was difficult to interpret, partly due to missing data.*

DEATHS, OTHER SERIOUS ADVERSE EVENTS, AND OTHER SIGNIFICANT ADVERSE EVENTS

Deaths

Six patients (3%) treated with ABI-007 died while on study, as did 8 patients (4%) in the Taxol group. The applicant indicates that death, in all cases, was due to progression of cancer. Only one death in the study was listed as "possibly related to study drug" and that was said to be due to multi-organ failure, for a patient in the Taxol group Two ABI-007 deaths were listed as "not related to study drug" but were said to be due to liver dysfunction/failure. No additional deaths occurred within 30 days of the last dose of study drug in either arm of the trial.

Serious Adverse Events

SAEs were reported in 63 (28%) of ABI-007 patients and 78 (35%) of Taxol patients. Neutropenia was the SAE with the highest incidence in both treatment groups. The number of patients affected was significantly lower for the Abraxane treatment arm (10%) than for the Taxol treatment arm (21%). Cancer related SAEs were the second most prevalent, 3% of ABI-007 patients, and 4% of Taxol patients. Next in frequency were SAEs of elevated GGT, involving 9 ABI-007 patients (4%) and 6 Taxol patients (3%). SAE "Infection with unknown ANC" was reported for 4 (2%) of ABI-007 patients and 6 (3%) Taxol patients. Febrile neutropenia was reported for 2% and 1% of patients, respectively. SAE hyperuricemia was reported for 1% of patients in each group. SAE fracture was reported in 2% of ABI-007 and <1% of Taxol patients. SAE "leukocytes" was reported in zero ABI-007 patients and in 1% of Taxol patients. All other SAEs were reported <1% in each treatment

group. Of particular interest, among the low frequency SAEs, there was only a single patient with SAE "platelets" for ABI-007 and zero for Taxol. No SAE "cardiac arrhythmia" was reported for ABI-007 and <1% for Taxol (1 patient). SAE "hypersensitivity" was reported for 1 ABI-007 patient (#313, but reported also as grade 2, not severe), and for 2 Taxol patients.

Sensory neuropathy was not reported as an SAE for patients in either treatment group.

Treatment-Emergent, Treatment-Related Adverse Events Leading to Premature Discontinuation from Study

Treatment-emergent, treatment related AEs leading to premature discontinuation occurred in 15 (7%) ABI-007 patients and in 9 (4%) Taxol patients (p=0.295). The most frequent toxicity leading to premature discontinuation was sensory neuropathy (ABI-007: 7 patients [3%] and Taxol: 2 patients [<1%], p=0.175). All other AEs leading to premature discontinuation occurred with an incidence of <1% for patients in each arm.

Treatment-Emergent, Treatment-Related Adverse Events Leading to Dose Reductions

Treatment-related AEs leading to dose reductions occurred in 14 (6%) ABI-007 patients and 8 (4%) Taxol patients (p=0.157). Sensory neuropathy resulted in dose reductions for 11 of 14 ABI-007 patients and 4 of 8 Taxol patients (p=0.090). Neutropenia was responsible for dose reduction in 1 ABI-007 patient and 2 Taxol patients. Febrile neutropenia was the cause of dose reduction in 1 ABI-007 patient and 2 Taxol patients.

Treatment-Emergent, Treatment-Related Adverse Events Leading to Dose Delays

Treatment-related AEs lead to dose delays in 3% (8 patients) for the ABI-007 arm and in 7% (16 patients) for the Taxol arm. For ABI-007 patients, the most common cause for dose delay due to treatment-related toxicity was sensory neuropathy (3 of 8). For Taxol patients, the most common cause for dose delays due to treatment-related toxicity was neutropenia (4 of 16). In the Taxol group there were dose delays for 3 patients due to cardiac-ischemia/infarction and for 2 patients with fever. Other treatment-related toxicities resulted in dose delay in ≤ 1% of patients in each arm.

CLINICAL LABORATORY EVALUATIONS

Hematology Parameters

See above for discussion of blood/bone marrow AEs: Neutropenia, anemia, and thrombocytopenia, which were based on central laboratory assessed data.

Clinical Chemistry Parameters

For the treatment groups, there were similar percents of patients with shifts for chemistry parameters from normal at baseline to high at final evaluation for alkaline phosphatase (ABI-

007: 13%; Taxol: 10%), ALT (12%; 16%), AST (12%; 9%), total bilirubin (3%; 1%), and creatinine (2%; 2%) (In-Text Table 106).

VITAL SIGNS, PHYSICAL FINDINGS, AND OTHER OBSERVATIONS RELATED TO SAFETY

Vital Signs

There were no clinically significant differences between treatment groups for minimum and maximum values of vital signs during study drug administration. Neither were there significant differences for treatment groups as assessed at baseline and at follow-up.

Electrocardiogram (ECG) Results

When ECG data was compared with baseline at 30-day follow-up for (78%) ABI-007 patients and (74%) Taxol patients, results had worsened in 9% of ABI-007 patients and 11% of Taxol patients.

Safety Results from Patients Receiving First-Line Therapy

Tolerability and toxicity profiles were similar for patients receiving study drug as first-line therapy compared with the overall study population. The following applicant table provides tolerability information for the first-line population.

Table 44: Tolerability in Patients Receiving First-Line Therapy (Applicant Table)

Category	Number (%) of Patients	
	ABI-007 (N = 97)	Taxol (N = 89)
Percentage of Protocol Dose, mean (S.D.)	98.1% (3.83%)	97.9% (6.56%)
Patients Receiving ≥ 90% of Protocol Dose, %	94%	93%
Treatment Cycles Administered per Patient, mean (S.D.)	5.7 (2.92)	5.4 (2.71)
Interval Between Cycles (days), mean (S.D.)	21.5 (2.09)	21.4 (1.91)
Dose Intensity (mg/m^2/week), mean (S.D.)	84.99 (3.315)	57.11 (3.827)

Source: Applicant In-Text Table 109 (from summary tables 24.1.1, 24.0.1, 24.2.1)

FDA ANALYSIS OF SAFETY FINDINGS

The FDA safety analysis was conducted using raw and derived data sets provided electronically by the applicant. Patient narratives were also reviewed. The main adverse event data set was "ADEX." The dataset "toxy" contained AE data for six parameters,

nausea, vomiting, diarrhea, mucositis, alopecia and infection. Neurotoxicity data was also captured in datasets "fact" (subjective assessment of peripheral neuropathy), "fact-TAX," "PSPN," and "PHY-PN".

The clinical reviewer attempted to audit the applicant's assessment of the safety data by verifying the incidence of those toxicities with statistically significant differences between the treatment arms and those toxicities with the highest percent of patient's reporting grade 3 or 4 toxicity. This reviewer also searched the database for certain potentially serious toxicities that were not identified by the applicant as occurring frequently in the ABI-007 data base, including hypersensitivity reactions and cardiac arrhythmias.

The following table lists AEs for which there were statistically significant differences in incidence for the treatment arms (See Table 32 above). We were able to verify these data.

Table 45: Toxicities with Significant Differences between Treatment Arms

NCI CTC Term	ABI-007	Taxol
Neutrophil AE	34%	49%
GI nausea	30%	21%
GI Diarrhea	26%	15%
GI Vomiting	18%	10%
Dermatology: Flushing	3%	14%

Source: Applicant In-Text Table 67

For GI AEs, the next table demonstrates the incidence of any events and severe (grade 3 or 4) events.

Table 46: GI Adverse Events by Subcategory and Severity (Reviewer Table)

	ABI-007 (Paclitaxel 260 mg/m2) Percent of Patients	Taxol (Paclitaxel 175 mg/m2) Percent of Patients
Nausea		
Any symptoms	30	21
Severe symptoms	3	<1
Vomiting		
Any symptoms	18	9
Severe symptoms	4	1
Diarrhea		
Any symptoms	26	15
Severe symptoms	<1	1
Mucositis		
Any symptoms	7	7
Severe symptoms	<1	0

Source: Applicant supplemental analysis and "toxy" database

Reviewer comment: *Although the percent of patients with GI AEs, overall and by sub-category, is higher for ABI-007 than for Taxol treatment groups, the proportion of grade 3 or 4 AEs is low for each group. The sub-categories with the highest percent of severe AEs for ABI-007 are nausea and vomiting. This is not unexpected, given the substantially higher exposure to paclitaxel with each dose of Abraxane compared with Taxol. Furthermore, steroid premedication was required for Taxol to prevent hypersensitivity reactions but discouraged for ABI-007. It is possible that more liberal use of steroids in the ABI-007 arm would have diminished the incidence and severity of chemotherapy related nausea and vomiting.*

The following table displays the most frequent treatment emergent grade 3 or 4 AEs. (Also, see Table 41.)

Table 47:Most Frequent Treatment-Emergent Grade 3-4 Adverse Events (Reviewer Table)

NCI CTC Term	ABI-007 (Paclitaxel 260 mg/m2) Percent of Patients	Taxol (Paclitaxel 175 mg/m2) Percent of Patients
Neutropenia	30%	46%
Increased GGT	14%	10%
Leukopenia	6%	9%
Sensory Neuropathy	10%	2%
Fatigue	8%	3%
Arthralgia	7%	4%

Source: Applicant In-Text Table 69; also database "ADEX"

Although the percent of patients with grade 3-4 neutropenia was higher for Taxol than for ABI-007, the incidence of febrile neutropenia was low for both groups, 2% for ABI-007 and 1%for Taxol, respectively. The percent of patients who experienced infections overall was 24% and 20 % respectively. There were no patients in the trial with grade 4 sensory neuropathy in either arm, but the percent of patients with grade 3 sensory neuropathy was higher for ABI-007 than for Taxol, just as the overall incidence was higher for ABI-007 (71%) than for Taxol (56%).

Reviewer comment: *It is unclear if the higher incidence of sensory neuropathy for ABI-007 is simply a dose effect. One might speculate that there could be increased bioavailability of ABI-007 to peripheral nerves, since the drug is not "trapped" in Cremophor micelles. The applicant claims that ABI-007 neuropathy is much more rapidly reversed than for Taxol patients, but only 5 Taxol patients with grade 3 sensory neuropathy were available for comparison to the 24 ABI-007 patients with grade 3 neuropathy in the randomized trial.*

The applicant's analysis of GGT liver function elevations showed a non-statistically significant difference for ABI-007 and Taxol patients. However, most of the GGT elevations were grade 3-4 in both arms of the randomized trial ("ADEX" dataset). This is in contrast to the data for alkaline phosphatase and AST where most elevations were grade 1-2 for both treatment groups, per the analysis provided by the applicant.

Table 48: Liver Function Test Elevations by Severity and Treatment (Reviewer Table)

	ABI-007 (Paclitaxel 260 mg/m2) Percent of Patients	Taxol (Paclitaxel 175 mg/m2) Percent of Patients
Bilirubin Elevation		
Any	7	7
Grade 3-4	1	1
Alkaline Phosphatase Elevation		
Any	36	31
Grade 3-4	1	0
AST Elevation		
Any	38	32
Grade 3-4	2	2
GGT Elevation*		
Any	14 (33/229)	12 (27/225)
Grade 3-4	14 (32/229)	11 (25/225)

*Source: "ADEX" dataset;

Reviewer comment: *The reason for the high incidence of grade 3-4 elevations of GGT in both treatment arms, compared with the pattern of elevation of alkaline phosphatase and AST, predominantly grade 1-2, is uncertain.*

This reviewer analyzed the "ADEX" database by NCI CTC, MedDRA and "verbatim" terms in an attempt to explore the incidence of significant, but low frequency, cardiac events in the 2 treatment arms. There were 5 ABI-007 patients and 1 Taxol patient who experienced "hypotension"; all were coded as "not serious" and required no intervention; only 1 for ABI-007 and 2 episodes for Taxol were felt to be "possibly treatment-related". For the term "cardiac", there were 15 ABI-007 patients and 16 Taxol patients. Many of these AEs were chest wall or breast pain (ABI-007: 8;Taxol: 8), some were cardiac ischemia (ABI-007: 4;Taxol: 6), a few were "decreased LV function" (ABI-007: 2;Taxol: 1). A single ABI-007 patient had "pericarditis." A single Taxol patient experienced "cardiorespiratory arrest," said to be unrelated to study drug (patient #313). For the term arrhythmia, there were 17 ABI-007 patients and 9 Taxol patients. Most of these in both treatment arm were "tachycardia", and not serious. Four of the arrhythmia AEs were "conduction" abnormality in the ABI-007 arm and 3 in the Taxol arm. All were thought to be "not serious" except patient #311, in the Taxol arm, who had "AV block", which was felt to be "possibly drug-related."

Reviewer comment: *From the data base, serious treatment-emergent cardiac events were unusual in both treatment arms of the randomized trial.*

7.5 Miscellaneous Studies

See section 6.4 for a summary of safety findings from single arm trials.

7.6 Literature Review for Safety

Review of the literature for safety did not reveal any unanticipated safety issues. The applicant provided an extensive bibliography, including references dealing with toxicity of the Cremophor excipient found in Taxol, but not in ABI-007.

7.7 Postmarketing Surveillance

Not applicable

7.8 Safety Update 120 Day

The applicant's safety update provides an update of safety information after the April 7, 2003, data cut-off date for the NDA. The data cut-off date for the Safety Update is March 29, 2004. For randomized trial CA012-0, the applicant has provided updated data for "patient disposition", SAEs, and AEs leading to discontinuations, dose reductions, and dose delays. There are updated listings and tables of deaths on study and within 30 days of study drug and of treatment-emergent toxicities with outcome of death within 30 days. Case report forms and narrative summaries are provided for patients who experienced deaths or withdrawals due to toxicity after the NDA data cut-off date. Safety information is also provided for additional on-going trials in several different diseases and dosage schedules.

At the time of initial NDA submission, data was complete for the dose-seeking phase 1 trial and for the two single arm phase 2 trials. For the randomized trial CA012-0, six of 460 enrolled patients were still receiving study drug at the time of the initial data cut-off date in April 2003. There were 3 ABI-007 patients (#524, #250, #520), 2 Taxol patients (#496. #519) and 1 ABI-007 PK patient (#P07). Five patients discontinued at the data cut-off date and one patient discontinued subsequently. The applicant indicates that the updated data from this trial "do not alter the conclusions of the study, nor do they suggest additional safety concerns..." Similarly, the applicant states that data from the supportive studies, some of which included weekly dosing (CA005-0 and CA013-0), "do not suggest additional safety concerns."

Reviewer comment: *The applicant's conclusion appears accurate, that follow-up data from the 5 randomized patients who were still receiving study drug at the time of the initial data cut-off date did not impact the earlier safety conclusions.*

7.9 Drug Withdrawal, Abuse, and Overdose Experience

There seems to be no potential for dependence or abuse. The expected complications of overdosage would include bone marrow suppression, sensory neurotoxicity and mucositis.

7.10 Adequacy of Safety Testing

Data from the randomized phase 3 trial and two supportive single arm trials in metastatic breast cancer demonstrate reasonable safety of ABI-007 in this setting when given IV as a 30-minute infusion every 3 weeks, without corticosteroid premedication or G-CSF support.

The primary safety population consists of 454 patients with metastatic breast cancer treated in randomized trial CA012-0, 229 patients who were treated with at least one cycle of ABI-007 260 mg/m2 IV every 3 weeks and 225 patients who were treated with at least one cycle of Taxol 175 mg/m2 IV every 3 weeks. In a dose-seeking trial (DM97-123) in patients with advanced solid tumors, including breast cancer, the MTD had been established as 300 mg/m2 IV every 3 weeks. In single arm trial CA002-0LD, 43 patients with metastatic breast cancer were treated with at least one cycle of ABI-007 175 mg/m2 every 3 weeks. In single arm study CA002-0, 63 patients with metastatic breast cancer were treated with at least one cycle of ABI-007 300 mg/m2 every 3 weeks. (See Section 7.3, Patient Exposure).

The toxicity profile for ABI-007 (paclitaxel dose 260 mg/m2) was generally similar compared with Taxol (paclitaxel dose 175 mg/m2), in spite of the higher dose of paclitaxel delivered with each ABI-007 treatment. Although routine steroid premedication was not given with ABI-007, hypersensitivity reactions were significantly reduced in the ABI-007 arm (4% vs. 12%). The percent of patients with neutropenia $<0.5 \times 10^9$/L was less for ABI-007 (9%) than for Taxol (22%). No grade 4 sensory neuropathy occurred, but the percent of patients with any sensory neuropathy or grade 3 was higher for ABI-007 (71% and 10%, respectively) than for Taxol (56 % and 2%, respectively). However, the applicant indicated that, of the 24 ABI-007 patients with grade 3 neuropathy, 14 improved after a median of 22 days; 10 patients resumed treatment at a reduced dose... and 2 discontinued due to peripheral neuropathy. Of the 10 patients without documented improvement, 4 discontinued the study due to peripheral neuropathy."

7.11 Labeling Safety Issues and Postmarketing Commitments

See Section 10.3 (Labeling) which includes discussion of labeling safety issues.

The applicant will be asked to fulfill the following phase 4 commitments and submit expected timelines for the submissions:

- ABI-007 should be evaluated for safety and pharmacokinetics in subjects with hepatic impairment to determine the appropriate dosing adjustment for such patients
- Survival data and analysis results should be submitted from randomized study CA012-0 after 80% of patients have died.

8 Dosing, Regimen, and Administration Issues

The recommended dose of ABI-007 is 260 mg/m^2 administered intravenously over 30 minutes every 3 weeks. Routine premedication to prevent hypersensitivity reactions is not required. Even though the recommended dose is approximately 49% higher than the recommended dose of Taxol, routine use of G-CSF is not required with ABI-007 therapy. Blood counts should be

obtained before each treatment, and patients should not be treated unless the neutrophil count has recovered to 1500 cells/mm^3 and the platelet count to >100,000/mm^3. Dose reduction (to 220 mg/m^2) is recommended for neutropenia of < 500 cells/mm^3 lasting 7 days. Interruption of therapy is recommended for ≥ grade 3 sensory neuropathy until recovery to grade 1-2, with dose reduction for subsequent cycles of therapy. For recurrence of severe neutropenia or severe sensory neuropathy, additional dose reduction should be made to 180 mg/m^2.

The appropriate dose of ABI-007 for patients with bilirubin greater than 1.5 mg/dL is not known. The effect of renal or hepatic dysfunction on the disposition of ABRAXANE has not been investigated. Since paclitaxel is metabolized by the liver, a phase 4 commitment has been requested to study safety and pharmacokinetics in patients with hepatic impairment, in order to guide dosing.

Possible interactions of ABI-007 with concomitantly administered medications have not been formally investigated. Paclitaxel is metabolized primarily to 6-α-hydroxypaclitaxel by CYP2C8, and to two minor metabolites, 3'p-hydroxypaclitaxel and 6-α,3'-p-dihydroxypaclitaxel, by CYP3A4. Caution is required when ABI-007 therapy is given concomitantly with substrates or inhibitors of CYP2C8 and CYP3A4. When used in combination, paclitaxel injection is known to have interactions with commonly used chemotherapy drugs such as doxorubicin and cis-platin, with a sequence of administration dependent effect on clearance.

[redacted]

9 Use in Special Populations

9.1 Evaluation of Applicant's Efficacy and Safety Analyses of Effects of Gender, Age, Race, or Ethnicity

The randomized controlled trial, CA0120-0 enrolled only females. There were 97% Caucasians in each arm of the trial; in the entire trial, 6 patients (1%) were black and 5 (1%) were Hispanic. Therefore, no evaluation could be made regarding the effect of gender, race or ethnicity in the trial.

Age – Efficacy

The following is abstracted from a table provided by the applicant in response to FDA's request for analysis of multiple prognostic factors with potential influence on the *reconciled* Target Lesion Response Rate (*rec*TLRR), the primary efficacy endpoint. (The population is the applicant's ITT population [those patients who actually received any study drug], which represents 4 fewer ABI-007 and 2 fewer Taxol patients than the applicant's "All Randomized" and FDA's ITT population.

Table 49: Response Rate by Age Category and Treatment Arm

Age Category	ABI-007 *rec*TLRR[1]	Taxol *rec*TLRR[1]
< 65 years	46/199 (23%)	21/193 (11%)
>= 65 years	9/30 (30%)	4/32 (13%)

[1]Reconciled Target Lesion Response Rate

For both age groups, the *rec*TLRR is higher for ABI-007 patients than for Taxol patients. The number of patients ≥ age 65 is small, limiting the value of comparisons.

Age - Safety

In the ABI-007 arm of the trial, there were 199 (87%) patients younger than 65 years of age and 30 patients (13%) age 65 or older. In the Taxol arm, there were 193 patients (86%) younger than 65 years of age and 32 (14%) age 65 or older. The following comparisons are extracted directly from the applicant's study report (Section 12.2.2.3). For ABI-007, there were no AEs that occurred "notably more frequently" for patients ≥ 65 years old compared with younger patients. For Taxol patients, the percent of older patients with neutropenia, nausea and hyperglycemia was higher than for younger patients.

- Neutropenia — ABI-007: < 65 years: 35% ≥ 65 years: 23%; Taxol: < 65 years: 47% ≥ 65 years: 59%
- Nausea — ABI-007: < 65 years: 31% ≥ 65 years: 20%; Taxol: < 65 years: 18% ≥ 65 years: 38%
- Hyperglycemia — ABI-007: < 65 years: 2% ≥ 65 years: 0%; Taxol: < 65 years: 5% ≥ 65 years: 19%

For patients ≥ age 75 (4 ABI-007 and 5 Taxol), the applicant notes that "the incidence and nature of severe and serious adverse events does not suggest additional risk", but the numbers are small.

Reviewer comment: *The applicant has done the required analyses of efficacy and safety by demographic parameters. This information does not significantly add to the study results. The number of patients ≥ age 65 is too small for definite conclusions to be made.*

9.2 Pediatric Program

ABI-007 has not been evaluated in children.

9.3 Data Available or Needed in Other Populations Such as Renal or Hepatic Compromised Patients, or Use in Pregnancy

ABI-007 should not be used by women who are pregnant or who are nursing infants, based on preclinical data for paclitaxel.

ABI-007 has not been studied in patients with hepatic or renal dysfunction. In the randomized trial, patients were excluded for baseline serum bilirubin >1.5 mg/dL or baseline serum creatinine >2 mg/dL. Paclitaxel is known to undergo hepatic metabolism, by CYP2C8 and by CYP3A4. ABI-007 should be evaluated for safety and pharmacokinetics in subjects with hepatic impairment to determine the appropriate dosing adjustment for such patients.

10 Conclusions, Recommendations, and Labeling

10.1 Conclusions Regarding Safety and Efficacy

The randomized comparative phase 3 trial in 460 women with metastatic breast cancer demonstrated that ABI-007 260 mg/m2 IV over 30 minutes every 3 weeks was superior to Taxol 175 mg/m2 IV over 3 hours every 3 weeks for the primary response rate endpoint, with a similar safety profile. Data from 103 patients in two single arm trials was supportive of efficacy and safety of ABI-007.

In the comparative trial, 233 patients were randomized to the ABI-007 treatment arm, and 227 patients to the Taxol treatment arm. A total of 272 patients (58%) met the Taxol indication, of whom 129 were randomized to receive ABI-007 and 143 were randomized to receive Taxol. There were 189 patients (41%) who received study treatment as first-line therapy for metastatic breast cancer, 99 in the ABI-007 arm and 90 in the Taxol arm. The confirmed *rec*TLRR (the primary endpoint) was 21.5% for ABI-007 patients and 11.1% for Taxol patients (p=0.003). For the subgroup of 272 patients who met the Taxol indication, the responses were 15.5% and 8.4%, respectively. Although the difference was not statistically significant in this subgroup (p=0.069), the trend was in the same direction as for the overall study population. For the 189 first-line patients, the response rates were 31.3% and 17.8%, respectively, also favoring ABI-007.

Time to progression data from the randomized trial seemed to support the efficacy findings, but evaluation of this secondary endpoint was not rigorous enough to reach definite conclusions from a single, open-label trial. Survival data are not sufficiently mature to permit comparisons between the treatment arms.

The toxicity profile for ABI-007 was generally similar to that of Taxol, in spite of the 59% higher dose of paclitaxel delivered with each ABI-007 treatment. The substitution of albumin in ABI-007 for the Cremophor in Taxol as a solubilizing agent for paclitaxel has improved the safety profile and permitted the use of a more intense dosing regimen. Although routine corticosteroid premedication was not given with ABI-007, hypersensitivity reactions were significantly fewer in the ABI-007 arm compared with the Taxol treatment group (4% vs.12%). The percent of patients with neutropenia <0.5 X 10^9/L was less for ABI-007 (9%) than for Taxol (22%). The incidence of febrile neutropenia was low for both groups (2% and 1%, respectively). No grade 4 sensory neuropathy occurred, but the percent of patients with any sensory neuropathy or grade 3 was higher for ABI-007 (71% and 10%, respectively) than for Taxol (56 % and 2%, respectively).

Overall, the risk-benefit considerations support approval of ABI-007 for the Taxol indication in metastatic breast cancer. A higher response rate is achieved with ABI-007. Toxicity may be diminished or comparable, in spite of the much higher dose of paclitaxel delivered with each treatment, except for the increased incidence of grade 3 peripheral neuropathy. In some patients, the neuropathy improved so that therapy with ABI-007 could be continued at a lower dose. The absence of Cremophor in the ABI-007 formulation improves safety and permits administration of a higher dose of paclitaxel. The absence of Cremophor also improves convenience and , potentially, cost of chemotherapy administration by removing the need for routine "triple" premedication (to prevent hypersensitivity reactions), eliminating the need for special containers and IV tubing, and permitting shorter infusion time.

10.2 Recommendations on Approvability

As a 505(b)(2) application with reference to the label, safety and efficacy of Taxol, we recommend approval of ABI-007 for the indication in the paclitaxel injection label. ABI-007 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."

Data from 460 patients in a randomized controlled comparative trial provided evidence of safety and efficacy of ABI-007 with reference to Taxol in metastatic breast cancer. Data from 106 patients accrued in two single arm open label studies provided additional support.

10.3 Labeling

As a 505(b)(2) application with reference to the label, efficacy and safety of Taxol, much of the content of the innovator label was preserved, but specific information was incorporated regarding the new formulation, pharmacokinetics and demonstrated efficacy and safety of ABI-007 from clinical trials. The Indication conforms to the Taxol Indication. —

To the Black Box Warning, an additional warning was added, "DO NOT SUBSTITUTE FOR OR WITH OTHER PACLITAXEL FORMULATIONS."

For the randomized comparative trial, results of the primary efficacy endpoint , the Reconciled Target Lesion Response Rate (*rec*TLRR) were presented in tabular form for both all randomized patients and for patients who met the Taxol indication. FDA did not allow inclusion in the label of the —

A safety warning was added that ABI-007 "has not been studied in patients with hepatic or renal dysfunction"...and the randomized trial..."excluded patients..."for baseline serum bilirubin > 1.5 mg/dL or baseline serum creatinine > 2 mg/dL." Pregnancy Category D was specified and data from pre-clinical gestational studies added under Warnings. A Warning was added "not to father a child while receiving treatment..." New (standard) language was added regarding the theoretical risk of disease transmission from human albumin, which is a component of the drug. Risk of anaphylaxis and severe hypersensitivity reactions was removed from Warnings, in view of the absence of Cremophor from ABI-007 and clinical trial results.

From Precautions, information specific to Taxol was deleted regarding the need for special containers and filters. The precautions regarding sensory neuropathy were modified. The language regarding cardiovascular risk does not appear in the ABI-007 label under Warnings and Precautions, but is included in the "Adverse Events by Body System" section of the label.

The adverse events table is expanded to show the percent of patients experiencing severe symptoms as well as any incidence of important treatment emergent AEs in the randomized trials. FDA did not agree to include

The Adverse Events by Body System section following the table was modified from the Taxol label to include data from the ABI-007 clinical trials, particularly the randomized trial.

The Dosage and Administration section was modified to reflect more accurately the language from the Indication section in both the Taxol and (FDA proposed) ABI-007 labels. The dosing adjustments for hepatic impairment from the Taxol label were *not* included in the ABI-007 label and "appropriate dose" of ABI-007 was said to be "not known" for patients with bilirubin greater than 1.5 mg/dL. Studies of dosing in hepatic impairment are being requested from the applicant as a phase 4 commitment.

During negotiations, the applicant submitted extensive pre-clinical data to support inclusion in the

The proposal was reviewed in detail by the pharmacologists and the clinical review team. The decision was made not to incorporate the applicant-proposed wording. Dr. John Leighton summarized, "The data to support the statements are generated from a limited set

of

Appendix

1 Individual More Detailed Study Reviews, if Performed

Not applicable

2 Detailed Labeling Changes or Revised Drug Label

The approved drug label will be attached to the Approval Letter.

3 Bibliography

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