CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-660

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-660 / N000
Drug Name:	Abraxane™ (ABI-007) [unit strength = 100 mg/50 mL vial]
Indication(s):	Metastatic Breast Cancer
Applicant:	American BioScience, Inc.
Date(s):	Submission Date: March 8, 2004 PDUFA Date: January 8, 2005
Review Priority:	Standard.
Biometrics Division:	Division of Biometrics I (HFD-710)
Statistical Reviewer:	Peiling Yang, Ph.D.
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Medical Division:	Division of Oncology Drug Product (HFD-150)
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Keywords: Superiority.

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1 EXECUTIVE SUMMARY

1.1 CONCLUSIONS AND RECOMMENDATIONS

In this reviewer's opinion, the study results from this randomized, multi-center, open-label, and phase III trial support the efficacy claim based on the primary endpoint, reconciled target lesion response rate.

It is to be noted that this NDA was filed under Section 505 (b)(2) of the Federal Food, Drug and Cosmetic Act, referencing the label, efficacy and safety of Taxol (paclitaxel) Injection. Taxol was approved 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*". The sponsor's proposed indication is: [redacted] The appropriateness of the patient population proposed by the sponsor is deferred to the clinical reviewer.

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

Abraxane™ (ABI-007), cytotoxic antineoplastic, was developed as a cremophor-free formulation of paclitaxel. It is to be administered intravenously over 30 minutes every 3 weeks. Patients may be treated for up to 6 cycles and patients without progression could be treated for a longer period.

In this NDA submission, efficacy data were collected by the sponsor in two trials: CA012-0 and CA002-0. Trial CA012-0 was a randomized, multi-center, open-label, Phase III trial, conducted at 70 sites, located in Russia/Ukraine, Canada, the U.S. and the United Kingdom. A total of 460 patients with metastatic breast cancer were randomized to receive either ABI-007 or Taxol. This trial included patients who had received first-line or subsequent-line of treatment, and some patients had not received prior anthracycline therapy. Trial CA002-0 was a phase 2 trial, conducted in patients with metastatic breast cancer and was to provide support to the efficacy and safety of ABI-007.

1.3 STATISTICAL ISSUES AND FINDINGS

In this NDA, Study CA012-0 was the only randomized pivotal study conducted to establish efficacy and safety. A total of 460 patients were randomized to this study. Of those, 233 patients were randomized to the ABI-007 arm and 227 patients to the Taxol arm. 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-07 arm and the 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 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 below or Table 14 for details)

This NDA was filed under Section 505 (b)(2) of the Federal Food, Drug and Cosmetic Act, referencing the label, efficacy and safety of Taxol (paclitaxel) Injection. A total of 272 patients (58%) in Study CA012-0 met the Taxol indication. Of those, 129 patients were randomized to the ABI-007 arm and 143 patients to the Taxol arm. Based on the FDA clinical reviewer's adjudication of response status, there were 20 and 12 responders in the ABI-07 arm and the Taxol arm, respectively. The observed response rates were 15.5% and 8.4%, respectively and the estimated ratio of response rates (ABI-007/Taxol) was 1.848 with a 95% confidence interval of 0.941 – 3.628. Although not statistically significant, the result from this subgroup of patients appeared trending towards the same direction as from the whole study population (Table 16).

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 Confidence Interval)	21.5% (16.19% – 26.73%)	11.1% (6.94% – 15.09%)
Ratio of Response Rates (ABI-007/Taxol) (95% Confidence Interval)[a]	1.899 (1.228 – 2.937)	
P-value[b]	0.003	

[a] 95% confidence interval 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 disease progression was a secondary endpoint. This endpoint was measured by this reviewer from the date of randomization, as opposed to the date of the first study dose that was used by the Sponsor. When documentation of disease progression was based on investigator's assessment including cycles beyond 6, 45.9% of the patients randomized to the ABI-007 and 54.6% of the patients randomized to the Taxol arm had progressive disease. The observed median time to disease progression was 21.9 weeks and 16.4 weeks (5.02 months and 3.77 months) respectively for the ABI-007 and Taxol arms respectively. When documentation of disease progression was based on reconciled assessment through cycle 6, 39.4% of the patients randomized to the ABI-007 and 52.0% of the patients randomized to the Taxol arm had progressive disease. The observed median time to disease progression was 17.0 weeks and 15.6 weeks (3.90 months and 3.57 months) respectively for the ABI-007 and Taxol arms respectively. In both approaches of documenting progressive disease, there was statistically significant difference in distributions of time to disease progression between treatment arms (Table 27; logrank p-values < 0.04; point estimates of hazard ratio (ABI-007/Taxol) ≤ 0.76).

Duration of response and overall survival were secondary endpoints. Data are not mature for a meaningful comparison between treatment arms as summarized below.

Statistical Issues:

[1] **Duration of Response.** Since the primary endpoint was reconciled target lesion response rate, a consistent analysis of duration of response would be based on reconciled assessment. However, the reconciled assessment was available only for the first 6 cycles. By the end of cycle 6, only 11 (14.7%) of the 75 FDA-confirmed responders had progressive disease (Table 24). Since most of the responders had not developed progressive disease, the median duration of response was unobservable in both treatment arms. When documentation of progressive disease was based on the either WorldCare assessment through cycle 6 or investigator's assessment including cycles beyond 6, there were only 34.7% of the responders who subsequently had documented progressive disease with observed median durations of response 23.4 weeks (5.38 months) and 27.0 weeks (6.20 months) for the ABI-007 and the Taxol arms, respectively (Table 25). Data are not mature for a meaningful comparison between treatment arms with respect to duration of response.

[2] **Overall survival.** Only 34% (= 157/460) of the patients died by the end of the trial (Table 28). Data are not mature for a meaningful comparison between treatment arms with respect to overall survival.

2 INTRODUCTION

2.1 OVERVIEW

This NDA was filed under Section 505 (b)(2) of the Federal Food , Drug and Cosmetic Act, referencing the label, efficacy and safety of Taxol (paclitaxel) Injection. Taxol was first approved in December 1992 for ovarian cancer and was subsequently approved for additional indications, including the breast cancer indication approved 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*".

Abraxane™ (ABI-007), cytotoxic antineoplastic, was developed as a cremophor-free formulation of paclitaxel. It is to be administered intravenously over 30 minutes every 3 weeks. Patients may be treated for up to 6 cycles and patients without progression could be treated for a longer period. The sponsor's proposed indication is: —

In this NDA submission, efficacy data were collected by the sponsor in two trials: CA012-0 and CA002-0. Trial CA012-0 was a randomized, multi-center, open-label, Phase III trial, conducted at 70 sites, located in Russia/Ukraine, Canada, the U.S. and the United Kingdom. A total of 460 patients with metastatic breast cancer were randomized to receive either ABI-007 or Taxol. This trial included patients who had received first-line or subsequent-line of treatment, and some patients had not received prior anthracycline therapy. Trial CA002-0 was a phase 2 trial, conducted in patients with metastatic breast cancer and was to provide additional support to the efficacy and safety of ABI-007.

Since Study CA012-0 was the only comparative study of efficacy, it is the only study reviewed by this statistical reviewer. The following bullets[1] summarize important milestone in product development with emphasis on Trial CA012-0 that may be relevant to statistical review. A more detailed summary of milestones is deferred to the clinical review.

- **May 12, 1998:** The original Investigational New Drug Application was submitted under IND No. 55974.

- **May 3, 2001:** An Initial draft of the phase 3 protocol (CA012-0) was discussed. FDA responses to the sponsor's submitted questions indicate acceptance of the proposed phase 3 protocol, with changes to the statistical analysis 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.*"

- **June 11, 2001 (SN. 070):** Phase 3 protocol (CA012-0) submitted, entitled "*A Controlled Randomized, Phase III, Multicenter, Open Label Study of ABI-007 (A Cremophor-Free,*

[1] Contents in some of the bullets were extracted from the Clinical Review by Dr. Scher.

Protein Stabilized, Nanoparticle Paclitaxel) and Taxol in Patients with Metastatic Breast Cancer."

- **June 19, 2001 (SN. 071):** 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.*"

- **October 29, 2001:** First patient randomized to Study CA012-0 (per the sponsor's data set "survival.xpt").

- **March 6, 2002 (SN. 115):** Protocol Amendment 1 for Study CA012-0 was submitted, where changes included

  - Changing definition of ITT population from exposure to ≥ 2 cycles to ≥ 1 cycle of therapy;
  - only target lesions (TLs) to be evaluated for the 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.

- **July 30, 2002 (SN. 161):** Protocol Amendment 2 for Study CA012-0 was submitted. WorldCare designated central image reader.

- **October 8, 2002:** Interim analysis for Study CA012-0 by Data Monitoring Committee after response assessed for 105 patients treated for ≥ 2 cycles in each arm. No change in sample size.

- **December 9, 2002 (SN. 198):** Statistical Analysis Plan, version 2.1, was submitted.

- **March 18, 2003:** Last patient randomized to Study CA012-0 (per the sponsor's data set "survival.xpt").

- **March 19, 2003 (SN. 217):** Pre-NDA meeting. Methods for response analysis were attached in the submission. 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 divided into two strata, anthracycline naïve and anthracycline treated.

- **April 7, 2003:** Data cut-off date for Study CA012-0 (per the sponsor's Study Report); patients with ongoing benefit continued treatment beyond 6 cycles.

- **September 3, 2003:** Data lock date for Study CA012-0.

- **October 20, 2003 (SN. 275):** Statistical Analysis Plan, version 3.0, was submitted, where 3 sets of response data (investigator, independent radiology group, and reconciled) were defined. The applicant specified that "reconciled response" was the "primary response dataset."

2.2 DATA SOURCES

Data used for review are from the electronic submission received between November 2003 and October 2004. The network path is \\Cdsesub1\n21660\N_000\" in the EDR.

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3 STATISTICAL EVALUATION

This Section only considers the comparative study CA012-0.

3.1 EVALUATION OF EFFICACY

3.1.1 STUDY DESIGN

This study was designed as a controlled, randomized, multi-center, open-label, Phase III, outpatient, non-inferiority study to evaluate the safety/tolerability and anti-tumor effect of intravenously (IV) administered ABI-007 compared to that of Taxol in patients with metastatic breast cancer.

Inclusion criteria of study population included the following:

- patient is female, non-pregnant and not lactating, and ≥ 18 years of age;
- patient has a histologically or cytologically confirmed measurable metastatic breast cancer and is a candidate for paclitaxel therapy in accordance with standard of care;
- if patient has received Taxol or docetaxel as adjuvant therapy, she has not relapsed with breast cancer within 1 year of completing adjuvant Taxol or docetaxel;
- patient has no other malignancy within the past 5 years, except non-melanoma skin cancer, cervical intraepithelial neoplasia (CIN), or in-situ cervical cancer (CIS);
- patient is a suitable candidate for single-agent paclitaxel treatment.

Complete inclusion criteria, as well as exclusion criteria, are referred to the Sponsor's Study Report or FDA Clinical Review by Dr. Scher.

Patients who received anthracycline prior to study enrollment were required to have a 4-week interval between the last dose of anthracycline and the first dose of study drug. Eligible patients were randomized in a 1:1 ratio to receive either of the following treatments:

- **Investigational arm:** ABI-007, 260 mg/m^2 IV over 30 minutes,
- **Control arm:** Taxol, 175 mg/m^2 IV over 3 hours.

Randomization was stratified by

- country;
- history of anthracycline use (anthracycline-exposed vs. -naïve).

Patients were to be treated for up to 6 cycles (3 weeks per cycle) 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.

3.1.2 EFFICACY ENDPOINTS

The primary efficacy endpoint and many secondary efficacy endpoints pertained to anti-tumor response. In this section, definitions of anti-tumor response are briefly described, followed by the definitions of efficacy endpoints.

Methods of tumor assessment included radiologic imaging or clinical evaluation. Lesions at the Baseline Visit were to be classified as either target or non-target lesions. At baseline, a maximum of 5 target lesions per organ and 10 target lesions in total were to be identified. The following defines several types of response per target or non-target lesions:

- **Target Response.** This was defined as achieving CR (complete response) or PR (partial response) of target lesions based on Response Evaluation Criteria in Solid Tumors (RECIST) guideline.
- **Non-target Response.** Complete non-target response was defined as the disappearance of all non-target lesions based on RECIST guideline for non-target lesions response criteria.
- **Overall Response.** This was determined based on target response, non-target response, and absence or appearance of new lesions.

Two versions (v. 2 and v. 3) of Statistical Analysis Plan were submitted to FDA during the drug development. In the latest version (v. 3), the sponsor defined the following 3 sets of response data:

- Response data as assessed by the investigator;
- Response data as assessed by an independent radiology laboratory (WorldCare);
- **Reconciled response assessment data** based upon independent assessment of images and investigator responses.

The reconciled response assessment data was to be the primary response dataset for efficacy evaluation and the other two sets were considered as the secondary response datasets.

The primary efficacy endpoint was

- ***rec*TLRR**: the percentage of patients who achieved confirmed complete or partial target lesion response using the reconciled response assessment data set.

Secondary efficacy endpoints were

- ***inv*ORR**: percentage of patients who achieved complete or partial overall response using the investigator's assessment data set;
- time to disease progression;
- patient survival;
- percentage of patients who achieved each target lesion response of CR, PR, SD, or PD;
- percentage of patients who achieved each overall response of CR, PR, SD, or PD;
- time to first complete or partial target lesion response;
- time to first complete or partial overall response;
- duration of complete or partial target lesion response;

- duration of first complete or partial overall response;
- number of cycles of therapy to maximum target lesion response;
- number of cycles of therapy to maximum overall response;
- duration of CR, PR, or SD for target lesion response;
- duration of CR, PR, or SD for overall response; and
- QOL evaluated by changes from baseline in scores on the ECOG (Zubrod) performance status scale, EORTC-QLQ-C30, and weight.

3.1.3 Hypothesis Test and Sample Size Considerations

The study was designed for testing non-inferiority hypothesis. The null hypothesis was that *rec*TLRR in the ABI-007 arm was no larger than 75% of that in the Taxol arm. The burden of the proof to establish non-inferiority was to provide statistical evidence against the null hypothesis. If non-inferiority was established, then superiority test was to proceed. If superiority was established, then superiority test was to further proceed only in the subgroup of patients who received study drug as the first-line therapy for metastatic cancer.

The initial sample size was 210 (approximately 230 enrolled) evaluable patients per treatment arm with at least 100 patients per arm that had been previously treated with anthracycline. This was based on the assumptions that the Taxol response rate was assumed to be 30% and the ABI-007 response rate was assumed to 36% (a relative improvement of a fifth).

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 was not changed from the initial estimate.

3.1.4 Statistical Analysis Plan

The primary analysis for the primary endpoint *rec*TLRR was based on the stratified Cochran-Mantel-Haenszel (CMH) test, stratified by whether study treatment was 1st line therapy versus > 1st line therapy. The primary analysis was the multiple nested testing as summarized below:

- **Step 1:** Test for non-inferiority of ABI-007 compared to TAXOL. Non-inferiority was to be established if the lower bound of the confidence limit for the ratio of response rates (ABI-007 / TAXOL) was greater than 0.75. If non-inferiority was established, then proceed to Step 2.

- **Step 2:** Repeat Step 1, but test for superiority. If superiority was established, then proceed to Step 3.

- **Step 3:** Test for superiority, but only in the subgroup of patients who received study drug as the 1st line therapy.

Because one interim analysis had been performed for possible sample size re-estimation, Step 1 was to be performed at the one-sided nominal significance level of 0.023475. Steps 2 and 3 each were to be performed (if ever) at the one-sided nominal significance level of 0.025.

Secondary Analysis of Primary Endpoint: Prognostic factors as listed in Table 2 were to be evaluated for potential influence on target response. For each prognostic factor, their effects on target response were to be tested using a logistic regression model.

Other Response Rate Endpoints were to be analyzed in a manner similar to analyses of the primary endpoint.

Time to Disease Progression was defined as the number of weeks from the first study dose to the start of disease progression. Patients who did not have disease progression were to be censored at the last known time that the patient was evaluated for response. Logrank test was to be used to compare the entire curves.

Analysis Populations were defined by the sponsor as follows:

- **All Randomized (AR) Patients:** All randomized patients even if they were not treated or had no treatment evaluations.
- **Intent-to-Treat (ITT) Population:** All randomized patients who received at least one dose of study drug.
- **Per Protocol (PP) Population:** All patients from the sponsor-defined ITT population who were evaluated for response after receiving at least 2 cycles of therapy and had no specific protocol violations. A detailed definition is referred to the Sponsor's Study Report or the FDA Clinical Review.

The Statistical Analysis Plan specified that the primary efficacy analysis was to be performed on the sponsor-defined ITT population. Analyses performed on all other populations were to be considered secondary analyses.

Table 2: Factors of Potential Influence on Response

[Source: In-Text Table 10 in Sponsor's Study Report; Statistical Analysis Plan submitted in S.N. 279]

Factor	Strata
Country	US (including Canada), UK, Russia/Ukraine
Age Category	< 65, ≥ 65 years
Race	Caucasian, Other
Menopausal Status	Premenopausal, Postmenopausal
Baseline ECOG	0, 1, 2
Number of Prior Metastatic Treatment	0, 1, ≥ 2
Regimens	Yes, No
Prior Adjuvant Chemotherapy	Yes, No
Prior Adjuvant Anthracycline Therapy	Yes, No
Prior Adjuvant Taxane Therapy	Yes, No
Prior Metastatic Chemotherapy	Yes, No
Prior Metastatic Anthracycline Therapy	Yes, No
Prior Anthracycline Therapy (Adjuvant or Metastatic)	Yes, No
Prior Adjuvant Hormonal Therapy	Yes, No
Prior Metastatic Hormonal Therapy	Yes, No
Prior Radiotherapy	Yes, No
Prior Surgery	Yes, No
Initial Histology	Ductal or Lobular Carcinoma, Inflammatory Breast Cancer, Other
AJCC Cancer Stage	0, I, II, III, IV
Time from Initial Diagnosis to Most Recent Relapse	< 1, ≥ 1 year
Number of Metastatic Sites at Relapse	1, 2-3, > 3
Dominant Site of Relapse	Liver; Other Visceral; Lung; Bone; Only Lymph Node, Soft Tissue, and/or Breast
ER Status at Relapse	Positive, Negative
PgR Status at Relapse	Positive, Negative
HER-2 / neu Status at Relapse	Not Overexpressed, 1+, 2+, 3+
Number of Lesion Sites (Target and Non-target) at Baseline	1, 2-3, > 3
Dominant Lesion Site (Target and Non-target) at Baseline	Liver; Abdominal; Lung; Bone; Only Lymph Node, Soft Tissue, and/or Breast

Reviewer Comments:

[1] The three shaded prognostic factors were not listed in the Statistical Analysis Plan, but were included in the Sponsor's Study Report.

3.1.5 SPONSOR'S RESULTS AND REVIEWER'S COMMENTS

3.1.5.1 Patient Disposition

Table 3 is the sponsor's summary of patient disposition. A total of 460 patients were randomzied to the trial. Patients were enrolled at 28 sites in Russia/Ukraine (353 patients; 77% of patients), 20 sites in the United Kingdom (67; 15%), and 22 sites in the US/Canada (40; 9%). Per the Sponsor's Study Report, no important differences between treatment arms were noted in the proportion of patients in each country who were randomized, received ≥ 6 cycles or received < 6 cycles and most of patients came off therapy because they had progressive disease (ABI-007: 46%; Taxol: 55%).

Table 3: Sponsor's Summary of Patient Disposition

[Source: Table 3.1 in Appendix of Sponsor's Study Report]

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%)
United Kingdom (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%)
All Countries (70)	**Randomized**	**233**	**227**	**460**
	Received ≥ 6 cycles	129 (55%)	112 (49%)	241 (52%)
	Received < 6 cycles	104 (45%)	115 (51%)	219 (48%)

Reviewer Comments:

[1] There were a slightly numerically higher percentage of patients receiving at least 6 cycles of therapy in the ABI-007 arm compared to the Taxol arm (55% vs. 49%). Since patients without disease progression could be treated for a longer period of time (> 6 cycles), the numerical difference in percentages could be attributed to several sources, such as the effectiveness of ABI-007 and the open-label nature of study design.

3.1.5.2 Analysis Population

Table 4 is the sponsor's summary of the number of patients in each treatment arm for each defined population. A total of 460 patients were included in the AR population and 454 patients in the sponsor-defined ITT population. The PP population excluded 25 patients from the sponsor-defined ITT population. Of these 25 patients, 9 had protocol deviations and 16 received only 1 dose of study drug.

Table 4: Sponsor's Summary of Patient Populations for Analysis

[Source: In-Text Table 20 in Sponsor's Study Report]

Patient 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)	211	218	429
Safety	229	225	454

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3.1.5.3 Demographics

Table 5 is the sponsor's summary of patient demographics. Per the sponsor's summary, all patients were female, 83% were postmenopausal, and 97% were Caucasian. No important differences between the treatment groups were noted in demographic parameters.

Table 5: Sponsor's Results of Patient Demographics (Sponsor-Defined ITT Population)

[Source: In-Text Table 21 in Sponsor's Study Report]

Variable	ABI-007 [N = 229]	*P-value*[a]	Taxol [N = 225]	All [N = 454]
Age (yr)				
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 (%)				
< 65 yr	199 (87%)	*0.669*	193 (86%)	392 (86%)
≥ 65 yr	30 (13%)		32 (14%)	62 (14%)
Race, n (%)				
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)[b]				
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)				
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 (%)				
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.

[b] based on 225 patients from the ABI-007 arm and 223 patients from the Taxol arm.

3.1.5.4 Other Baseline Characteristics

Table 6 is the sponsor's summary of initial diagnosis of breast cancer. Per the sponsor's Study Report, the difference between treatment arms in positive PgR status was statistically significant but was not considered clinically significant.

Table 6: Sponsor's Results of Initial Diagnosis of Breast Cancer (Sponsor-Defined ITT Population)

[Source: In-Text Table 22 in Sponsor's Study Report]

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; * $P < 0.05$.

Reviewer Comments:

[1] Since the initial ER status and initial PgR status were missing in 55% and 67% of the patients, respectively, results from comparison between treatment arms in these types of status are not interpretable.

Per the sponsor's Study Report, distributions of initial histology, initial treatment of breast cancer, and ECOG Performance Status at baseline appeared balanced between treatment arms (summary table omitted from this Statistical Review). Table 7 is the sponsor's summary of prior therapies at baseline and Table 8 is the sponsor's summary of prior metastatic treatments at baseline. Data in these tables appeared numerically balanced between treatment arms.

Table 7: Sponsor's Results of Prior Therapies at Baseline (on Sponsor's ITT Population)

[Source: In-Text Table 27 in Sponsor's Study Report]

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

Table 8: Sponsor's Results of History of Prior Metastatic Treatments at Baseline (on Sponsor's ITT Population)

[Source: In-Text Table 28 in Sponsor's Study Report]

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

3.1.5.5 Primary Endpoint: Reconciled Target Lesion Response Rate (*rec*TLRR)

Table 9 is the sponsor's results of reconciled target lesion response by response type. Based on this table, 55 patients (24%) from the ABI-007 arm and 25 patients (11%) from the Taxol arm had reconciled CR or PR target response.

Table 9: Sponsor's Results of Reconciled Target Lesion Response by Response Type (Sponsor-Defined ITT population)

[Source: In-Text Table 42 of Sponsor's Study Report]

Category[a]	Number (%) of Patients	
	ABI-007 [N = 229]	Taxol [N = 225]
Complete Response (CR)	7 (3%)	1 (<1 %)
Partial Response (PR)	48 (21%)	24 (11%)
Stable Disease (SD)	98 (43%)	114 (51%)
Progressive Disease (PD)	61 (27%)	76 (34%)
Clinical Non-responder[b]	15 (7%)	10 (4%)

[a] Patients were categorized based on their maximum response.
[b] Clinical nonresponders consist of patients taken off-study by the Investigator for a reason other than disease progression prior to cycle 4 or patients with nonevaluable response assessments during the study.

The sponsor's results of the primary analysis are summarized in the following bullets:

- **Step 1: Test of non-inferiority on the sponsor-defined ITT population.** The nominal one-sided 97.6525% lower confidence limit (or equivalently, the lower limit of two-sided 95.305% confidence interval) for the ratio of response rates (ABI-007/ Taxol) was 1.368 (Table 10), which was larger than the threshold 0.75. This suggested non-inferiority of ABI-007 to Taxol on the sponsor-defined ITT population. Proceed to Step 2.

- **Step 2: Test of superiority on the sponsor-defined ITT population.** The one-sided 97.5% lower confidence limit (or equivalently, the lower limit of two-sided 95% confidence interval) for the ratio of response rates was 1.376 (Table 10), which was larger than the threshold 1. This suggested superiority of ABI-007 compared to Taxol on the sponsor-defined ITT population. Proceed to Step 3.

- **Step 3: Test of superiority on a subset of the sponsor-defined ITT population who received treatment as the first line therapy.** The one-sided 97.5% lower confidence limit (or equivalently, the lower limit of two-sided 95% confidence interval) for the ratio of response rates was 1.121 (Table 11), which was larger than the threshold 1. This suggested superiority of ABI-007 compared to Taxol in patients receiving treatment as the first line therapy.

The influence of prognostic factors (listed in Table 2) was assessed by the sponsor. Per the sponsor's Study Report, the treatment effect of ABI-007 and Taxol appeared generally consistent between strata of prognostic factors.

Table 10: Sponsor's Results of *rec*TLRR (Sponsor-Defined ITT Population)

[Source: In-Text Tables 39 & 40 in Sponsor's Study Report]

Reconciled Target Lesion Response Assessment Dataset	**ABI-007 [N = 229]**	**Taxol [N = 225]**
No. of Responders	55	25
Response Rate (95% Binomial Confidence Interval)	24.0% (18.48% – 29.55%)	11.1% (7.00% – 15.22%)
Ratio of Response Rates (ABI-007/Taxol) (Confidence Interval)[a]	2.110 **For non-inferiority: (1.368 – 3.254)** **For Superiority: (1.376 – 3.236)**	
P-value[b]	< 0.001	

[a] 95.305% and 95% confidence intervals of the ratio for non-inferiority test and superiority test, respectively, associated with the stratified CMH test stratified by 1st line vs. > 1st line therapy.
[b] P-value based on stratified CMH test.

Table 11: Sponsor's Results of *rec*TLRR in Patients Receiving 1st-Line Therapy (Sponsor-Defined ITT Population)

[Source: In-Text Table 41 in Sponsor's Study Report]

Reconciled Target Lesion Response Assessment Dataset	**ABI-007 [N = 97]**	**Taxol [N = 89]**
No. of Responders	33	16
Response Rate (95% Binomial Confidence Interval)	34.0% (24.59% – 43.45%)	18.0% (10.00% – 25.96%)
Ratio of Response Rates (ABI-007/Taxol) (95% Confidence Interval)	1.892 (1.121 – 3.193)	
P-value from Chi-Square Test	0.013	

This NDA was filed under Section 505 (b)(2) of the Federal Food , Drug and Cosmetic Act, referencing the label, efficacy and safety of Taxol (paclitaxel) Injection. Taxol was first approved in December 1992 for ovarian cancer and was subsequently approved for additional indications, including the breast cancer indication approved 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 anthracycline unless clinically contraindicated"*. Upon the FDA request in October 2004, the sponsor provided relevant information for the subgroup of patients who met the Taxol indication. Based on the sponsor's results (Table 12), a total of 269 patients (59.3%) from the sponsor-defined ITT population met this indication. Of those, 18.1% and 8.5% from the ABI-007 arm and Taxol arm, respectively, had reconciled target lesion response. The observed ratio of the response rates was 2.143 (ABI-007 18.1% / Taxol 8.5%) with a nominal p-value of 0:019 from chi-square test,

suggesting a statistically significant difference between treatment arms in this subgroup of patients.

Table 12: Sponsor's Results of *rec*TLRR in Patients Who Met Taxol Indication (Sponsor-defined ITT Population)

[Source: Faxed document received October 19, 2004]

Reconciled Target Lesion Response Assessment Dataset	ABI-007 [N = 127]	Taxol [N = 142]
No. of Responders	23	12
Response Rate (95% Binomial Confidence Interval)	18.1% (11.41% – 24.81%)	8.5% (3.88% – 13.03%)
Ratio of Response Rates (ABI-007/Taxol) (95% Confidence Interval)	2.143 (1.113 – 4.128)	
P-value from Chi-Square Test	0.019	

REVIEWER COMMENTS:

[1] The clinical reviewer adjudicated response status and identified discrepancy in response status in 5 patients (Table 13). All of these 5 patients were randomized to the ABI-007 arm. This resulted in only 50 responders, as opposed to 55 responders, in the ABI-007 arm.

Table 13: Discrepancy in Response Status between FDA and Sponsor

[Source: FDA medical reviewer's adjudication]

Site No.	Patient ID	Tagret Lesion Response Status			
		Reconciled	Investigator	WorldCare	FDA
309	342	CR	CR	--	Not evaluable
302	303	PR	PR	--	PD
335	430	PR	SD	PR	PD
308	161	PR	PR	--	SD
318	225	PR	PR	--	SD

[2] The sponsor's primary efficacy analysis was performed on the sponsor-defined ITT population, consisting of 454 patients, as opposed to 460 patients that were randomized (Table 4 on p. 13). Nevertheless, when the primary analysis (sequential test) was performed on the all randomized patients using the FDA clinical reviewer's adjudication of response status, the results were consistent with the sponsor's; that is, ABI-007 yielded a larger *rec*TLRR as compared to Taxol in the whole study population (Table 14), as well as in patients who received study treatment as the 1st line therapy (Table 15).

Table 14: 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 Confidence Interval)	21.5% (16.19% – 26.73%)	11.1% (6.94% – 15.09%)
Ratio of Response Rates (ABI-007/Taxol) (Confidence Interval) [a]	1.899 **For non-inferiority: (1.221 – 2.954)** **For Superiority: (1.228 – 2.937)**	
P-value [b]	0.003	

[a] 95.305% and 95% confidence intervals of the ratio for non-inferiority test and superiority test, respectively, associated with the stratified CMH test, stratified by 1st line vs. > 1st line therapy. The point estimate of the corresponding odds ratio was 2.205 with a 95% confidence interval (1.298 – 3.744).

[b] P-value from stratified CMH test.

Table 15: Reviewer's Results of FDA-Confirmed *rec*TLRR in Patients Receiving 1st-Line Therapy (All Randomized Patients)

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	

[3] This reviewer's results from analysis of *rec*TLRR in the Taxol-indicated subgroup are summarized in Table 16, where response rate was based on the FDA-confirmed responders. Based on this reviewer's results, there was no statistically significant difference between treatment arms at a significance level of 0.05 (p-value = 0.069 as opposed to 0.019 that was reported by the sponsor). Although, not statistically significant, the results appeared numerically trending towards the same direction as those from the whole study population.

Table 16: Reviewer's Results of FDA-Confirmed *rec*TLRR in Patients Who Met Taxol Indication (All Randomized Patients)

Reconciled Target Lesion Response Assessment Dataset	ABI-007 [N = 129]	Taxol [N = 143]
No. of FDA-Confirmed Responders	20	12
Response Rate (95% Binomial Confidence Interval)	15.5% (9.26% – 21.75%)	8.4% (3.85% – 12.94%)
Ratio of Response Rates (ABI-007/Taxol)[a] (95% Confidence Interval)	1.848 (0.941 – 3.628)	
P-value from Chi-Square Test	0.069	

[a] The point estimate of the corresponding odds ratio was 2.003 with a 95% confidence interval (0.937 – 4.281).

[4] The results on the per-protocol population were consistent with those on the all-randomized population.

3.1.5.6 Secondary Endpoint: Investigator-Assessed Overall Response Rate (*inv*ORR)

Overall response rate based on the investigator's assessment (*inv*ORR) was a secondary endpoint. Table 17 is the sponsor's comparisons between this endpoint and the primary endpoint *rec*TLRR. The sponsor placed more emphasis on *inv*ORR than *rec*TLRR because of the following reasons described in the sponsor's Study Report:

- the *inv*ORR is more clinically meaningful than the *rec*TLRR;
- the *inv*ORR is comparable with response rates for taxanes reported in the literature;
- the primary efficacy tests of non-inferiority and superiority, which were based on *rec*TLRR, were met and surpassed;
- analyses of *inv*ORR and *rec*TLRR yield the same conclusions with regard to the relative efficacy of ABI-007 versus Taxol.

Table 17: Sponsor's Comparison of *inv*ORR and *rec*TLRR

[Source: In-Text Table 33 of Sponsor's Study Report]

Dimension	*inv*ORR	*rec*TLRR
Lesions	Target and non-target lesions	Target lesions
Time	All cycles in study	Cycles 1 – 6
Dataset	Investigator Response Assessment Dataset	Reconciled Response Assessment Dataset[a]
Confirmation of response	Required	Required
Evaluation criteria	RECIST	RECIST

[a] A conservative reconciliation of the differences between the IRL and Investigator Response Assessment Datasets using a predefined algorithm (Section 9.5.1.3 in Sponsor's Study Report).

Table 18 is the sponsor's results of *inv*ORR by response type on the sponsor-defined ITT population. Based on this table, 76 patients (33.2%) from the ABI-007 arm and 42 patients (18.7%) from the Taxol arm had overall response as assessed by the investigator.

Based on the sponsor's analysis, ABI-007 was statistically significantly superior to Taxol with respect to *inv*ORR in the whole study population (Table 19), as well as in patients who received study drug as the 1st line therapy (Table 20).

Similar to the analysis of the primary endpoint, the influence of prognostic factors was assessed by the sponsor. Per the sponsor's Study Report, the treatment effect of ABI-007 and Taxol appeared generally consistent between strata of prognostic factors.

Table 18: Sponsor's Results of Investigator-Assessed Overall Response by Response Type (on Sponsor-Defined ITT Population)

[Source: In-Text Table 35 of Sponsor's Study Report]

Category [a]	Number (%) of Patients	
	ABI-007 [N = 229]	Taxol [N = 225]
Complete Response (CR)	2 (<1%)	3 (1%)
Partial Response (PR)	74 (32%)	39 (17%)
Stable Disease (SD)	75 (33%)	98 (44%)
Progressive Disease (PD)	61 (27%)	68 (30%)
Clinical Nonresponder [b]	17 (7%)	17 (8%)

[a] Patients were categorized based on their maximum response.
[b] Clinical nonresponders consist of patients taken off-study by the Investigator for a reason other than disease progression prior to Cycle 4 or patients with nonevaluable response assessments during the study.

Table 19: Sponsor's Results of *inv*ORR (Sponsor-Defined ITT Population)

[Source: In-Text Table 34 in Sponsor's Study Report]

Investigator's Overall Response Assessment Dataset	ABI-007 [N = 229]	Taxol [N = 225]
No. of Responders	76	42
Response Rate (95% Binomial Confidence Interval)	33.2% (27.09% – 39.29%)	18.7% (13.58% – 23.76%)
Ratio of Response Rates (ABI-007/Taxol) (Confidence Interval) [a]	1.748 (1.265 – 2.417)	
P-value [b]	0.001	

[a] 95% confidence interval of the ratio based on the stratified CMH test, stratified by 1st line vs. >1st line therapy.
[b] P-value from the stratified CMH test.

Table 20: Sponsor's Results of *inv*ORR in Patients Receiving 1st-Line Therapy (Sponsor-Defined ITT Population)

[Source: In-Text Table 36 in Sponsor's Study Report]

Investigator's Overall Response Assessment Dataset	ABI-007 [N = 97]	Taxol [N = 89]
No. of Responders	41	24
Response Rate (95% Binomial Confidence Interval)	42.3% (32.44% – 52.10%)	27.0% (17.75% – 36.19%)
Ratio of Response Rates (ABI-007/Taxol) (95% Confidence Interval)	1.567 (1.037 – 2.370)	
P-value from Chi-Square Test	0.029	

REVIEWER COMMENTS:

[1] The results on all randomized patients (Table 21) are consistent with those on the sponsor-defined ITT population (Table 19). Results from analyses of secondary endpoints are generally considered exploratory.

Table 21: Reviewer's Results of *inv*ORR (All Randomized Patients)

Investigator's Overall Response Assessment Dataset	ABI-007 [N = 233]	Taxol [N = 227]
No. of Responders	76	42
Response Rate (95% Binomial Confidence Interval)	32.6% (26.60% – 38.64%)	18.5% (13.45% – 23.55%)
Ratio of Response Rates (ABI-007/Taxol) (Confidence Interval)[a]	1.733 (1.253 – 2.398)	
P-value[b]	0.001	

[a] 95% confidence intervals of the ratio based on the stratified CMH test, stratified by 1st line vs. >1st line therapy.

[b] P-value from the stratified CMH test.

3.1.5.7 Secondary Endpoint: Duration of Response

Duration of response was defined as the time from the date of first documented response to the date of the first documented progressive disease. Patients who did not have progressive disease were censored as the last known time the patient was evaluated for response.

There were several approaches to documenting progressive disease. Three approaches that were used by the sponsor in analyzing duration of response and/or time to disease progression (next section) are summarized as follows:

- **Approach 1:** Based on investigator's assessment of target and non-target lesions including cycles beyond 6.

- **Approach 2:** Based on reconciled (investigator and independent radiology laboratory WorldCare) assessment of target lesions through cycle 6. In this approach, although assessment was based on target lesions, the patient was still considered to have progressive disease if a new lesion appeared or any non-target lesion progressed.

- **Approach 3:** Patients was considered to have progressive disease if disease progression was documented based on WorldCare assessment through cycle 6 or based on investigator's assessment including cycles beyond 6. Target and non-target lesions were considered.

Duration of response was analyzed by the sponsor in 2 groups of responders. One group of responders was defined as those who had reconciled target lesion response as summarized in Section 3.1.5.5 (associated with the primary endpoint *rec*TLRR). A total of 80 responders were identified in this group and progressive disease was documented by Approach 3. The other group of responders was defined as those who had overall response based on investigator's assessment including cycles beyond 6 as summarized in Section 3.1.5.6 (associated with the secondary endpoint *inv*ORR). A total of 118 responders were identified in this group and progressive disease was documented by Approach 1. The sponsor's results on these two groups of responders are summarized in Table 22 and Table 23, respectively. There was no statistically significant difference in duration of response between these two treatment arms.

Table 22: Sponsor's Results of Duration of Response on Responders Who Had Reconciled Target Lesion Response

[Source: Table 16.1 in Appendix of Sponsor's Study Report]

Category	ABI-007 [N = 55]	Taxol [N = 25]
No. of Responders Who Subsequently Had Progressive Disease[a]	20 (36.4%)	9 (36.0%)
Kaplan-Meier Median Duration of Response in Weeks (95% Confidence Interval)	22.1 (16.0 – 30.3)	27.0 (17.4 – 33.4+)[b]
P-value from (two-sided) Logrank Test	0.901	

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 as assessed by WorldCare or investigators. Patients that did not have disease progression are censored at the last known time the patient was evaluated for response.

[a] Obtained by this statistical reviewer's re-running the sponsor's SAS program.

[b] The upper bound was not available, but was at least 33.4 weeks.

Table 23: Sponsor's Results of Duration of Response on Responders Who Had Overall Response Based on Investigator Response Assessment Dataset Including Cycles > 6

[Source: In-text Table 52 in Sponsor's Study Report]

Category	ABI-007 [N = 76]	Taxol [N = 42]
No. of Responders Who Subsequently Had Progressive Disease[a]	25 (32.9%)	14 (33.3%)
Kaplan-Meier Median Duration of Response in Weeks (95% Confidence Interval)	18.3 (16.0 – 30.3)	26.9 (15.9 – 33.4+)[b]
P-value from (two-sided) Logrank Test	0.856	

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 as assessed by investigators. Patients that did not have disease progression are censored at the last known time the patient was evaluated for response.

[a] Obtained by this statistical reviewer's re-running the sponsor's SAS program.

[b] The upper bound was not available, but was at least 33.4 weeks.

REVIEWER COMMENTS:

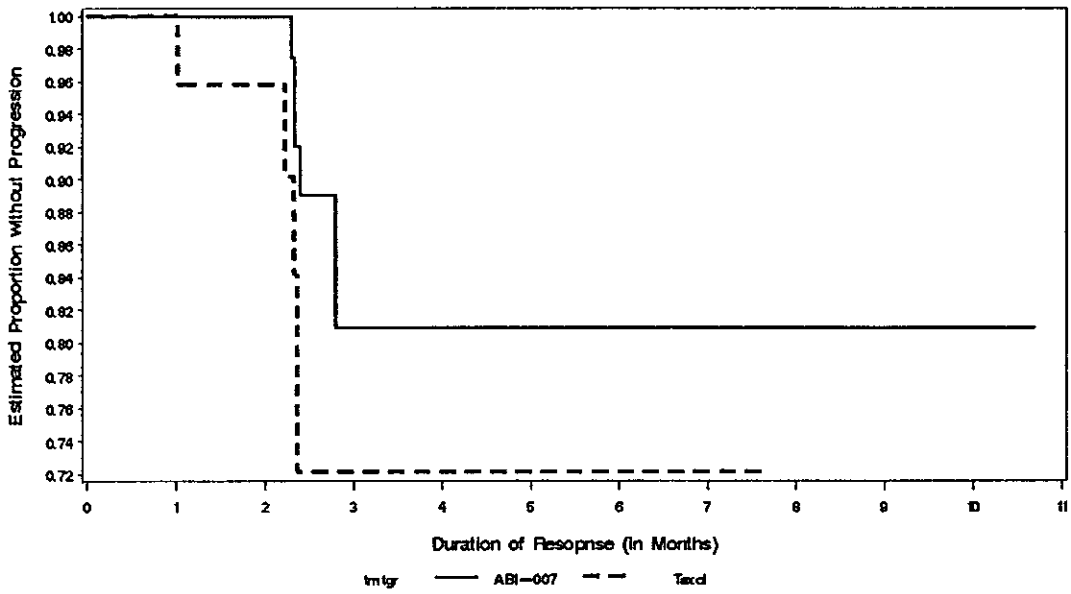
[1] In analysis of duration of response on responders who had reconciled target lesions response, it would have been more appropriate to document progressive disease based on reconciled assessment (i.e., Approach 2 as described in the beginning of this Section) as opposed to investigator's assessment. However, since reconciled assessment was available only for the first 6 cycles, only 8 of the 55 sponsor-reported responders (6 of the 50 FDA-confirmed responders) from the ABI-007 arm, and 5 of the 25 sponsor-reported responders from the Taxol arm had documented progressive disease by the end of Cycle 6 (Table 24). As shown in the Kaplan-Meier curves of durations of response (Figure 1), the median duration of response could not be observed in either treatment arm because data was very immature. In lieu of such immature data, analysis of duration of response based on reconciled assessment through cycle 6 appears meaningless.

Table 24: Reviewer's Results Duration of Response on FDA-Confirmed Responders (Based on Reconciled Assessment through Cycle 6)

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.

Figure 1: Reviewer's Kaplan-Meier Curves of Duration of Response for FDA-Confirmed Responders (Based on Reconciled Assessment through Cycle 6)



[2] Analogous to the sponsor's analysis (as summarized in Table 22; by Approach 3), this reviewer performed an exploratory analysis of duration of response on FDA-confirmed responders, where the date of response was based on the reconciled assessment on target lesions and the date of documented progressive disease was based either WorldCare assessment through cycle 6 or investigator's assessment including cycles beyond 6. The result, as summarized in Table 25, is consistent with that in Table 22. However, since there were only 75 responders and only 34.7% of them had progressive disease, the result may not be interpretable. Figure 2 (page 28) is the corresponding Kaplan-Meier curves of duration of response.

Table 25: Reviewer's Results of Duration of Response on FDA-Confirmed Responders (Based on Investigator's Assessment including Cycles beyond 6 or WorldCare Assessment through Cycle 6)

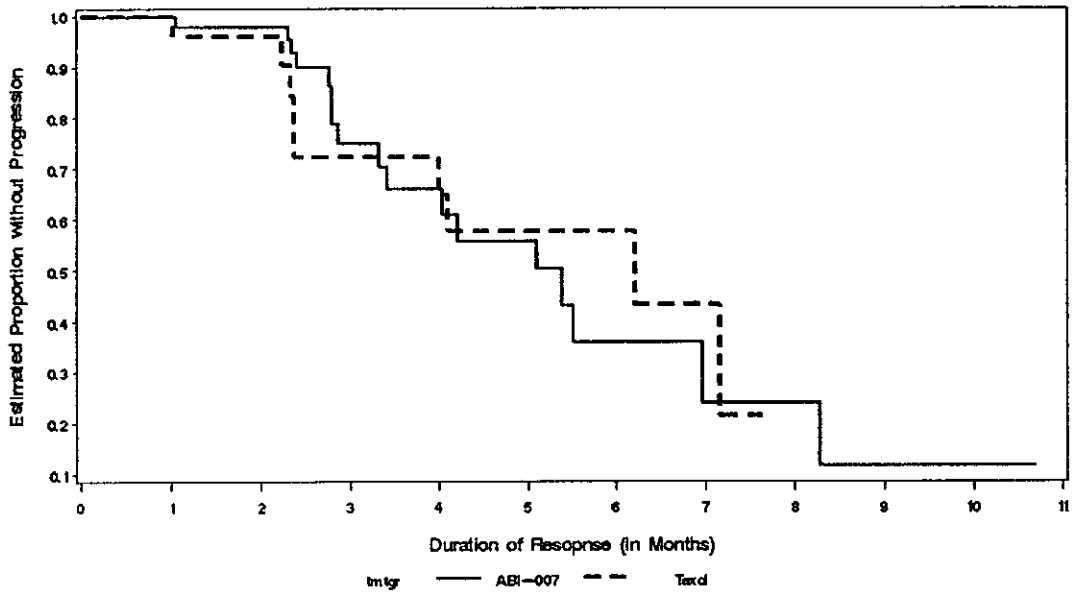
Category		ABI-007 [N = 50]	Taxol [N = 25]
No. of FDA-Confirmed Responders Who Subsequently Had Progressive Disease		17 (34.7%)	9 (36.0%)
Kaplan-Meier Median Duration of Response	in weeks	23.4 (14.9 – 30.3)	27.0 (17.4 – 33.4+)[a]
(95% Confidence Interval)	in months	5.38 (3.41 – 6.95)	6.20 (4.00 – 7.67+)[a]
P-value from (two-sided) Logrank Test		0.917	

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.

[a] The upper bound was not available, but was at least 33.4 weeks (7.67 months).

[3] The sponsor's results as summarized in Table 23 corresponded to the secondary endpoint overall response rate based on investigator's assessment of target and non-target lesions. Based on this assessment, only 33% (39/ 118) of the responders had documented progressive disease. Since data are immature, the result may not be interpretable, especially when the duration of response was measured on responders as defined by a secondary endpoint, not by the primary endpoint.

Figure 2: Reviewer's Kaplan-Meier Curves of Duration of Response for FDA-Confirmed Responders (Based on Investigator's Assessment including Cycles beyond 6 or WorldCare Assessment through Cycle 6)



3.1.5.8 Secondary Endpoint: Time to Disease Progression

Several approaches were used by the sponsor to document progressive disease as described in the beginning of Section 3.1.5.7 (p. 23). This endpoint was measured by the sponsor as the time from the date of the first dose, as opposed to the randomization date that is typically used in regulatory review of oncology registration trials. Per the sponsor's results (Table 26), there was statistically significant difference in time to disease progression between treatment arms by each of Approaches 1 and 2 (p-values from the two-sided logrank test comparing distributions of time to disease progression between treatment arms were 0.030 and 0.016, respectively).

Table 26: Sponsor's Results of Time to Disease Progression

[Source: In-Text Table 48 (with Tables 19.0 & 19.3 in Appendix of Sponsor's Study Report]

Category		ABI-007 [N = 229]	Taxol [N = 225]
Investigator Response Assessment Dataset Including Cycles > 6			
No. of Patients Evaluated for Disease Progression		220	215
No. (%) of Patients With Disease Progression		107 (49%)	124 (58%)
Kaplan-Meier Median Time to Disease Progression (95% Confidence Interval)	in weeks	21.9 (18.3 – 28.4)	16.1 (15.1 – 21.0)
	in months[a]	5.0 (4.2 – 6.5)	3.7 (3.5 – 4.8)
P-value from (two-sided) Logank Test		0.030	
Reconciled Response Assessment Dataset Through Cycle 6			
No. of Patients Evaluated for Disease Progression		222	219
No. (%) of Patients With Disease Progression		92 (41%)	118 (54%)
Kaplan-Meier Median Time to Disease Progression (95% Confidence Interval)	in weeks	16.6 (15.6 – 21.4+)[b]	15.4 (14.9 – 16.1)
	in months[a]	3.8 (3.6 – 4.9+)[b]	3.5 (3.4 – 3.7)
P-value from (two-sided) Logank Test		0.016	

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

[b] The upper bound was not available, but was at least 21.4 weeks (4.9 months).

REVIEWER COMMENTS:

[1] Time to disease progression was re-calculated by this reviewer as the time from the randomization date as opposed to the date of the first dose. The results of analysis based on this re-calculation when performed on all randomized patients were consistent with those of the sponsor's (Table 27 as compared to Table 26). Figure 3 and Figure 4 are the corresponding Kaplan-Meier curves of time to disease progression.

[2] This reviewer also performed an exploratory analysis on the subgroup of patients who met the Taxol indication. Although not statistically significant at a level of 0.05, the result from this subgroup analysis suggests marginally statistical significance and appears numerically trending towards the same direction as that from the whole study population.

Table 27: Reviewer's Results of Time to Disease Progression (All Randomized Patients)

Category		ABI-007 [N = 233]	Taxol [N = 227]
Investigator Response Assessment Dataset Including Cycles > 6			
No. (%) of Patients With Disease Progression		107 (45.9%)	124 (54.6%)
Kaplan-Meier Median Time to Disease Progression (95% Confidence Interval)	in weeks	21.9 (18.4 – 28.6)	16.4 (15.6 – 21.0)
	in months[a]	5.02 (4.23 – 6.56)	3.77 (3.57– 4.82)
P-value from (two-sided) Logrank Test		0.037	
Hazard Ratio[b] (95% Confidence interval)		0.760 (0.586 – 0.986)	
Reconciled Response Assessment Dataset Through Cycle 6			
No. (%) of Patients With Disease Progression		92 (39.4%)	118 (52.0%)
Kaplan-Meier Median Time to Disease Progression (95% Confidence Interval)	in weeks	17.0 (15.9 – 19.3)	15.6 (15.1 – 16.4)
	in months[a]	3.90 (3.64 – 4.43)	3.57 (3.48 – 3.77)
P-value from (two-sided) Logrank Test		0.036	
Hazard Ratio[b] (95% Confidence interval)		0.749 (0.570 – 0.984)	

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

[b] Hazard ratio of ABI-007/ Taxol, based on Cox regression model without any covariate.

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Figure 3: Reviewer's Kaplan-Meier Curves of Time to Disease Progression (Investigator's Assessment Including Cycle > 6; All Randomized Patients)

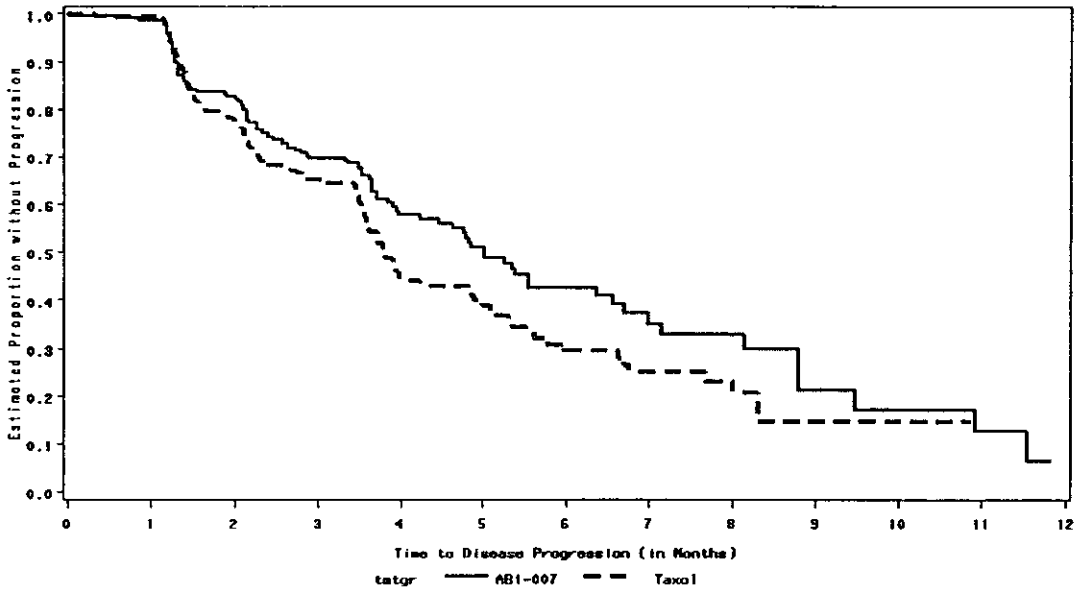
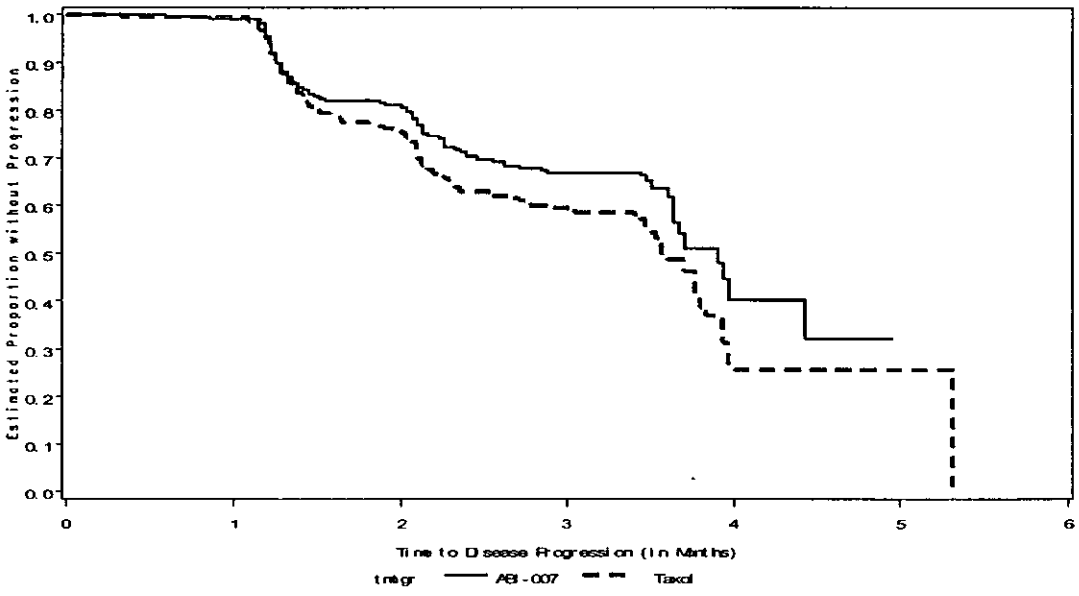


Figure 4: Reviewer's Kaplan-Meier Curves of Time to Disease Progression (Reconciled Assessment through Cycle 6; All Randomized Patients)



3.1.5.9 Secondary Endpoint: Overall Survival

A total of 157 patients (34%) died by the end of the study. Overall survival was measured by the sponsor from the date of the first study dose as opposed to the randomization date. Based on the sponsor's analysis results (Table 28) on the sponsor-defined ITT population, the observed median survival times were 9.2 months for the ABI-007 arm and 8.7 months for the Taxol arm. The p-value was 0.636 from the logrank test comparing the distributions of overall survival between treatment arms, which did not suggest survival benefit of ABI-007 over Taxol.

Table 28: Sponsor's Results of Overall Survival on Sponsor-Defined ITT Population

[Source: In-text Table 50 in Sponsor's Study Report]

Category		ABI-007 [N = 229]	Taxol [N = 225]
No. of Deaths		73 (32%)	84 (37%)
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	9.2 (8.0 – 10.3)	8.7 (7.9 – 9.3)
P-value from Logrank Test		0.636	

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.

REVIEWER COMMENTS:

[1] Overall survival was re-calculated by this reviewer as the time from the randomization date as opposed to the date of the first dose. The results of analysis based on this re-calculation when performed on all randomized patients were consistent with those of the sponsor's (Table 29 as compared to Table 28). Figure 5 is the corresponding Kaplan-Meier curves of overall survival.

[2] The survival data appears immature. The results are considered exploratory.

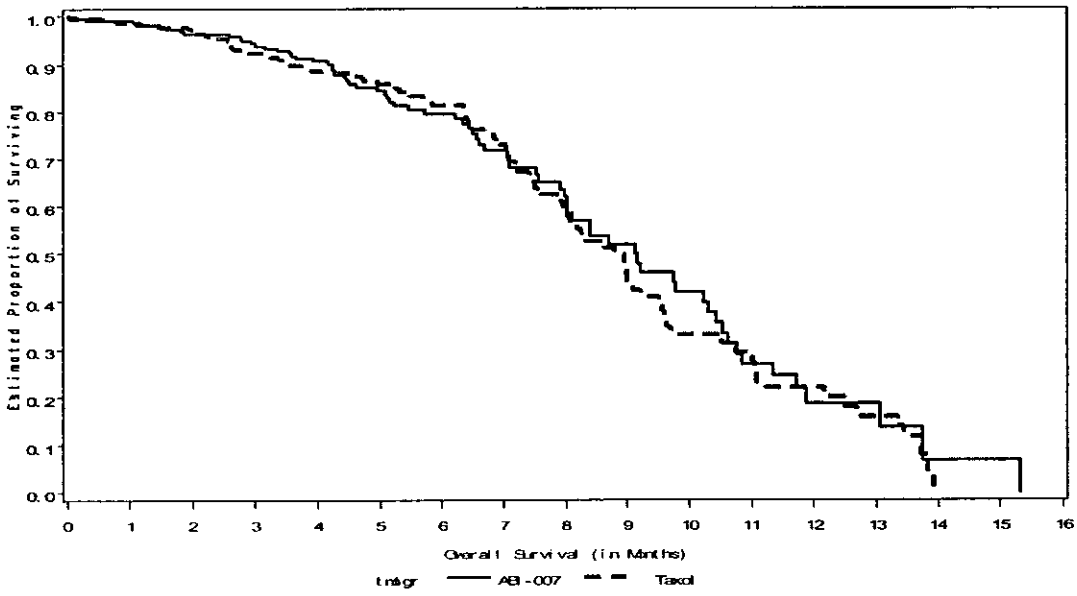
Table 29: Reviewer's Results of Overall Survival (All Randomized Patients)

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.

Figure 5: Reviewer's Kaplan-Meier Curves of Overall Survival (All Randomized Patients)



3.2 EVALUATION OF SAFETY

Safety evaluation is deferred to the clinical reviewer Dr. Scher.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Code of Federal Regulations (21 CFR 314.50) requires that efficacy data be presented by gender, age, and racial subgroups when applying for FDA approval to market a new drug. Included in this Section are this reviewer's exploratory subgroup analyses of FDA-confirmed *rec*TLRR by these demographic factors as well as by some other important factors.

4.1 GENDER, RACE AND AGE

4.1.1 GENDER

All patients randomized to the trial were women.

4.1.2 RACE

Most of the patients (96.7%) were Caucasian.

Table 30: Subgroup Analysis by Race: Reviewer's Exploratory Results of FDA-Confirmed *rec*TLRR (All Randomized Patients)

Category	ABI-007 [N = 233]	Taxol [N = 227]
Caucasian:		
No. of Patients	225	220
No. of FDA-Confirmed Responders	50	24
Response Rate (95% Binomial Confidence Interval)	22.2% (16.79% – 27.65%)	10.9% (6.79% – 15.03%)
Ratio of Response Rates (ABI-007/Taxol) (95% Confidence Interval)	2.037 (1.299 – 3.194)	
P-value from Chi-Square Test	0.001	
Other:		
No. of Patients	8	7
No. of FDA-Confirmed Responders	0	1
Response Rate (95% Binomial Confidence Interval)	0%	14.3% (0.36% – 57.86%)
Ratio of Response Rates (ABI-007/Taxol) (95% Confidence Interval)	-- [a]	
P-value from Chi-Square Test	-- [a]	

[a] data was too sparse for a meaningful exploratory analysis.

4.1.3 AGE

Most of the patients (86%) were younger than 65 years. The results from exploratory analyses did not suggest any inconsistency in response rates across subgroups.

Table 31: Subgroup Analysis by Age: Reviewer's Exploratory Results of FDA-Confirmed *rec*TLRR (All Randomized Patients)

Category	ABI-007 [N = 233]	Taxol [N = 227]
Age < 65:		
No. of Patients	201	195
No. of FDA-Confirmed Responders	41	21
Response Rate (95% Binomial Confidence Interval)	20.4% (14.83% – 25.97%)	10.8% (6.42% – 15.12%)
Ratio of Response Rates (ABI-007/Taxol) (95% Confidence Interval)	1.894 (1.163 – 3.085)	
P-value from Chi-Square Test	0.008	
Age ≥ 65:		
No. of Patients	32	32
No. of FDA-Confirmed Responders	9	4
Response Rate (95% Binomial Confidence Interval)	28.1% (15.55% – 43.70%)	12.5% (3.51% – 28.99%)
Ratio of Response Rates (ABI-007/Taxol) (95% Confidence Interval)	2.250 (0.771 – 6.566)	
P-value from Chi-Square Test	0.120	

4.2 OTHER SPECIAL/SUBGROUP POPULATIONS

4.2.1 LINE OF THERAPY

A total of 189 patients (41%) received study treatment as the 1st line therapy. The results from exploratory analyses did not suggest any inconsistency in response rates across subgroups.

Table 32: Subgroup Analysis by Line of Therapy: Reviewer's Exploratory Results of FDA-Confirmed *rec*TLRR (All Randomized Patients)

Category	ABI-007 [N = 233]	Taxol [N = 227]
Patients Receiving Treatment as 1st-line Therapy:		
No. of Patients	99	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	
Patients Receiving Treatment as 2nd-line or Subsequent Therapy:		
No. of Patients	134	137
No. of FDA-Confirmed Responders	19	9
Response Rate (95% Binomial Confidence Interval)	14.2% (8.27% – 20.09%)	6.6% (2.42% – 10.72%)
Ratio of Response Rates (ABI-007/Taxol) (95% Confidence Interval)	2.158 (1.013 – 4.599)	
P-value from Chi-Square Test	0.040	

4.2.2 PRIOR ANTHRACYCLINE THERAPY

A total of 354 patients (77%) had prior adjuvant or metastatic anthracycline therapy. Of those 354 patients, 248 patients had prior metastatic anthracycline therapy. The results from exploratory analyses did not suggest any inconsistency in response rates across subgroups.

Table 33: Subgroup Analysis by Prior Anthracycline Therapy: Reviewer's Exploratory Results of FDA-Confirmed *rec*TLRR (All Randomized Patients)

Category	ABI-007 [N = 233]	Taxol [N = 227]
Patients with Prior Anthracycline Therapy (Adjuvant or Metastatic):		
No. of Patients	178	176
No. of FDA-Confirmed Responders	38	18
Response Rate (95% Binomial Confidence Interval)	21.3% (25.33% – 27.37%)	10.2% (5.75% – 14.70%)
Ratio of Response Rates (ABI-007/Taxol) (95% Confidence Interval)	2.087 (1.240 – 3.513)	
P-value from Chi-Square Test	0.004	
Patients with Prior Metastatic Anthracycline Therapy:		
No. of Patients	117	131
No. of FDA-Confirmed Responders	17	9
Response Rate (95% Binomial Confidence Interval)	14.5% (8.1% – 20.92%)	6.9% (2.54% – 11.20%)
Ratio of Response Rates (ABI-007/Taxol) (95% Confidence Interval)	2.115 (0.981 – 4.561)	
P-value from Chi-Square Test	0.049	
Patients without Prior Anthracycline Therapy:		
No. of Patients	55	51
No. of FDA-Confirmed Responders	12	7
Response Rate (95% Binomial Confidence Interval)	21.8% (10.90% – 32.73%)	13.7% (4.28% – 23.17%)
Ratio of Response Rates (ABI-007/Taxol) (95% Confidence Interval)	1.590 (0.679 – 3.722)	
P-value from Chi-Square Test	0.278	

4.2.3 PATIENT POPULATION IN TAXOL INDICATION

Taxol was approved 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*". In this study, a total of 272 patients (59%) met the Taxol indication. Exploratory analyses were performed respectively in two subgroups: (a) patients who met this indication, and (b) patients who did not meet this indication. The results did not suggest any inconsistency in response rates across subgroups.

Table 34: Subgroup Analysis by Taxol Indication: Reviewer's Exploratory Results of FDA-Confirmed *rec*TLRR (All Randomized Patients)

Category	ABI-007 [N = 233]	Taxol [N = 227]
Patients Who Met Taxol Indication:		
No. of Patients	129	143
No. of FDA-Confirmed Responders	20	12
Response Rate (95% Binomial Confidence Interval)	15.5% (9.26% – 21.75%)	8.4% (3.85% – 12.94%)
Ratio of Response Rates (ABI-007/Taxol) (95% Confidence Interval)	1.848 (0.941 – 3.628)	
P-value from Chi-Square Test	0.069	
Patients Who Did Not Meet Taxol Indication:		
No. of Patients	104	84
No. of FDA-Confirmed Responders	30	13
Response Rate (95% Binomial Confidence Interval)	28.8% (20.14% – 37.55%)	15.5% (7.74% – 23.21%)
Ratio of Response Rates (ABI-007/Taxol) (95% Confidence Interval)	1.864 (1.040 – 3.342)	
P-value from Chi-Square Test	0.030	

4.2.4 COUNTRY

Nearly 77% of the patients were from Russia and only 8.7% of the patients were from United States or Canada. For patients who were randomized to the Taxol arm, the observed response rate in the US. and Canada subgroup appeared to be much larger compared to those in United Kingdom and Russia subgroups. However, it is noted that the sample size in each subgroup other than Russian was very small. Despite this, the results from exploratory analyses did not suggest any qualitative inconsistency in response rates across subgroups; that is, in each subgroup the observed response rate was numerically higher in the ABI-007 arm than in the Taxol arm.

Table 35: Subgroup Analysis by Country: Reviewer's Exploratory Results of FDA-Confirmed *rec*TLRR (All Randomized Patients)

Category	ABI-007 [N = 233]	Taxol [N = 227]
US. and Canada:		
No. of Patients	21	19
No. of FDA-Confirmed Responders	5	4
Response Rate (95% Binomial Confidence Interval)	23.8% (8.22% – 47.17%)	21.1% (6.05% – 45.57%)
Ratio of Response Rates (ABI-007/Taxol) (95% Confidence Interval)	1.131 (0.355 – 3.604)	
P-value from Chi-Square Test	0.835	
United Kingdom:		
No. of Patients	34	33
No. of FDA-Confirmed Responders	6	2
Response Rate (95% Binomial Confidence Interval)	17.6% (4.83% – 30.46%)	6.1% (0.74% – 20.23%)
Ratio of Response Rates (ABI-007/Taxol) (95% Confidence Interval)	2.912 (0.632 – 13.406)	
P-value from Chi-Square Test	0.144	
Russia:		
No. of Patients	178	175
No. of FDA-Confirmed Responders	39	19
Response Rate (95% Binomial Confidence Interval)	21.9% (15.83% – 27.99%)	10.9% (6.25% – 15.47%)
Ratio of Response Rates (ABI-007/Taxol) (95% Confidence Interval)	2.018 (1.215 – 3.351)	
P-value from Chi-Square Test	0.005	

5 SUMMARY AND CONCLUSIONS

This NDA was filed under Section 505 (b)(2) of the Federal Food , Drug and Cosmetic Act, referencing the label, efficacy and safety of Taxol (paclitaxel) Injection. Taxol was first approved in December 1992 for ovarian cancer and was subsequently approved for additional indications, including the breast cancer indication approved 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*". The sponsor's proposed indication is: " [redacted]

[redacted]

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

In this NDA, Study CA012-0 was the only randomized pivotal study conducted to establish efficacy and safety. A total of 460 patients were randomized to this study. Of those, 233 patients were randomized to the ABI-007 arm and 227 patients to the Taxol arm. The primary efficacy endpoint was response rate based on reconciled (investigators and independent radiology experts) assessment of target lesions. 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 the 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 of 1.228 – 2.937. This suggests the superiority of ABI-007 with respect to the primary endpoint in the whole study population (Table 14).

A total of 189 patients (41%) in Study CA012-0 received study treatment as the first line therapy. Of those, 99 patients were randomized to the ABI-007 arm and 90 patients to the Taxol arm. Based on the FDA clinical reviewer's adjudication of response status, there were 31 and 16 responders in the ABI-07 arm and the Taxol arm, respectively. The observed response rates were 31.3% and 17.8%, respectively and the estimated ratio of response rates (ABI-007/Taxol) was 1.761 with a 95% confidence interval of 1.035 – 2.997. This suggests superiority of ABI-007 with respect to the primary endpoint in the subgroup of patients who received study treatment as the first line therapy (Table 15).

A total of 272 patients (58%) in Study CA012-0 met the Taxol indication. Of those, 129 patients were randomized to the ABI-007 arm and 143 patients to the Taxol arm. Based on the FDA clinical reviewer's adjudication of response status, there were 20 and 12 responders in the ABI-07 arm and the Taxol arm, respectively. The observed response rates were 15.5% and 8.4%, respectively, and the estimated ratio of response rates (ABI-007/Taxol) was 1.848 with a 95% confidence interval of 0.941 – 3.628. Although not statistically significant, the result from this subgroup of patients appeared trending towards the same direction as from the whole study population (Table 16).

Response rate based on investigator's overall (target and non-target lesions) assessment was a secondary endpoint. The analysis results supported the findings in the primary endpoint.

Time to disease progression was a secondary endpoint. This endpoint was measured by this reviewer from the date of randomization, as opposed to the date of the first study dose that was used by the Sponsor. When documentation of disease progression was based on investigator's assessment including cycles beyond 6, 45.9% of the patients randomized to the ABI-007 and 54.6% of the patients randomized to the Taxol arm had progressive disease. The observed median time to disease progression was 21.9 weeks and 16.4 weeks (5.02 months and 3.77 months) respectively for the ABI-007 and Taxol arms respectively. When documentation of disease progression was based on reconciled assessment through cycle 6, 39.4% of the patients randomized to the ABI-007 and 52.0% of the patients randomized to the Taxol arm had progressive disease. The observed median time to disease progression was 17.0 weeks and 15.6 weeks (3.90 months and 3.57 months) respectively for the ABI-007 and Taxol arms respectively. In both approaches of documenting progressive disease, there was statistically significant difference in distributions of time to disease progression between treatment arms (Table 27; logrank p-values < 0.04; point estimates of hazard ratio (ABI-007/Taxol) ≤ 0.76).

Duration of response and overall survival were secondary endpoints. Data are not mature for a meaningful comparison between treatment arms as summarized below.

Statistical Issues:

[1] **Duration of Response.** Since the primary endpoint was reconciled target lesion response rate, a consistent analysis of duration of response would be based on reconciled assessment. However, the reconciled assessment was available only for the first 6 cycles. By the end of cycle 6, only 11 (14.7%) of the 75 FDA-confirmed responders had progressive disease (Table 24). Since most of the responders had not developed progressive disease, the median duration of response was unobservable in both treatment arms. When documentation of progressive disease was based on the either WorldCare assessment through cycle 6 or investigator's assessment including cycles beyond 6, there were only 34.7% of the responders who subsequently had documented progressive disease with observed median durations of response 23.4 weeks (5.38 months) and 27.0 weeks (6.20 months) for the ABI-007 and the Taxol arms, respectively (Table 25). Data are not mature for a meaningful comparison between treatment arms with respect to duration of response.

[2] **Overall survival.** Only 34% (= 157/460) of the patients died by the end of the trial (Table 28). Data are not mature for a meaningful comparison between treatment arms with respect to overall survival.

5.2 CONCLUSIONS AND RECOMMENDATIONS

In this reviewer's opinion, the study results from this randomized, multi-center, open-label, and phase III trial support the efficacy claim based on the primary endpoint, reconciled target lesion response rate.

It is to be noted that this NDA was filed under Section 505 (b)(2) of the Federal Food, Drug and Cosmetic Act, referencing the label, efficacy and safety of Taxol (paclitaxel) Injection. Taxol was approved 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". The sponsor's proposed indication is: "

The appropriateness of the sponsor-proposed patient population is deferred to the clinical reviewer.

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