CONFIDENTIAL

PROTOCOL CA012-0 INCORPORATING AMENDMENT 3:

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

US IND Number: 55,974

Sponsor: [redacted]

Sponsor Signatory: [redacted]

Principal Investigator: [redacted]

Finalization Date: June 19, 2001

Amendment 1 January 28, 2002

Amendment 2 July 22, 2002

Amendment 3 May 23, 2003

PROTOCOL SIGNATURES AMENDMENT #3 23 MAY 2003

Sponsor Signatories:

Medical Monitor:

Name/Title	Signature	Date
[redacted]	_____	_____

Sponsor Signatories

Name/Title	Signature	Date
[redacted]	_____	_____
[redacted]	_____	_____
[redacted]	_____	_____

STUDY CONTACT INFORMATION

SPONSOR:

INVESTIGATOR'S PROTOCOL AGREEMENT

PROTOCOL NUMBER: CA012-0
Protocol Title: 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

I confirm that my staff and I have carefully read and understand this protocol, and agree to comply with the procedures and terms of the study specified herein. In particular, I/we agree to:

- Comply with all obligations stated on FDA Form 1572 and other local regulatory authority required document(s);
- Retain records and documents related to this trial for at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least two years have elapsed since the formal discontinuation of clinical development of the investigational product;
- Comply with Good Clinical Practice (GCP) and all applicable regulatory requirements;
- Maintain confidentiality and assure security of American BioScience, Inc. (ABI) confidential documents;
- Obtain Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval of the protocol, any amendments to the protocol, and periodic re-approval as required, and to keep the IRB/IEC informed of all adverse events which are serious, unexpected and thought by either the investigator or the sponsor to be related to study drug and periodically report the status of the study to them in compliance with individual IRB/IEC requirements;
- Not to implement any deviations from or changes to the protocol without agreement from the sponsor and prior review and written approval from the IRB/IEC, except where necessary to eliminate an immediate hazard to the subjects, or for administrative aspects of the study (where permitted by all applicable regulatory requirements);
- Assure that each patient enrolled into the trial, or legally authorized representative has read, understands, and has signed the Informed Consent;
- Ensure that I and all persons assisting me with the study are adequately informed and trained about the investigational drug and of their study-related duties and functions as described in the protocol;
- Report life threatening or fatal serious adverse events within 24 hours to American BioScience, Inc. and report SAE's that are not life-threatening or fatal within 48 hours to American BioScience, Inc.;
- Assure access by American BioScience, Inc, or other authorised sponsor representative monitors and/or FDA to original source documents;
- Prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated in the investigation;
- Arrange for the transfer of appropriate data from case histories to case report forms for the collection and transmission of data to the Sponsor;
- Cooperate fully with any study-related GCP audit as performed by ABI, PSI, ORION, or other authorised sponsor representative external quality assurance group specified by the sponsor;
- Comply with stipulations in the Disclosure of Data section and the manuscript preparation/authorship guidelines established at the outset of the study.

INVESTIGATOR'S PRINTED NAME _____	INVESTIGATOR'S SIGNATURE _____
INVESTIGATOR'S ADDRESS _____	DATE _____

PROTOCOL SYNOPSIS

PROTOCOL TITLE

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

PROTOCOL NUMBER

CA012-0

CLINICAL PHASE

III

INTRODUCTION AND RATIONALE

ABI-007 is a unique protein formulation of a non-crystalline, amorphous form of paclitaxel in an insoluble nanoparticle state. ABI-007 has been developed to reduce the toxicities associated with TAXOL, paclitaxel (from the native crystalline form) in solution with Cremophor as the solvent, while maintaining or improving its chemotherapeutic effect. The potential exists that enhanced efficacy could be seen in solid tumors as a consequence of (i) higher tolerated dose (260 mg/m^2), (ii) longer half-life, (iii) prolonged local tumor availability, and/or (iv) sustained in-vivo release.

This protocol describes a Phase III trial comparing ABI-007 to TAXOL to determine the response rate in metastatic breast cancer patients. The study is designed as a non-inferiority study intended to have an 80% power of detecting an effect 75% or greater as compared to TAXOL. In addition, an evaluation of the safety and tolerability of ABI-007 monotherapy compared to that of TAXOL will be assessed.

ABI-007 may have advantages compared to available taxanes with regards to reduced toxicity, potential enhanced efficacy with ease of administration, shorter drug infusion time, and avoidance of hypersensitivity reactions attributable to the Cremophor component of the currently available TAXOL (paclitaxel) formulation.

BACKGROUND

Paclitaxel (Taxol®, Bristol-Myers Squibb [BMS]) is active against carcinomas of the ovary, breast, lung, esophagus and head and neck. A number of dose schedules of TAXOL have been tested in breast cancer. Initial trials used 250 mg/m^2 as a continuous infusion over 24 hours. Subsequently, shorter infusions of TAXOL over three hours were tested at a dose of 175 mg/m^2, with response rates of 30% to 40%. Phase II studies utilizing higher doses of TAXOL at 200-250 mg/m^2 had a response rate of 56% in metastatic breast cancer patients. However, at these doses, significant toxicities occurred, including neuropathy and median granulocyte count nadir at 100-200/mm^3 for the majority of courses administered. Thus, TAXOL as currently used can produce significant acute and cumulative toxicity, notably neutropenic fever, anaphylactic reaction, and peripheral neuropathy.

Use of TAXOL involves two major limitations in administration. First, because paclitaxel is poorly soluble in water, Cremophor is used as a solvent, requiring large infusion volumes and special tubing and filters. Second, Cremophor is associated with side effects that can be severe, including anaphylaxis and other hypersensitivity reactions that can be severe and require pretreatment with corticosteroids, antihistamines, and H_2 blockers. Both considerations mean that administration takes a long period of time, generally six to eight hours, and is often slowed or halted because of adverse reactions. Although docetaxel (Taxotere™), another taxane used in treatment of anthracycline-resistant breast cancer, can be administered over approximately one hour, it also has side effects of fluid retention that can be severe.

POTENTIAL ADVANTAGES OF ABI-007

ABI-007 is a novel Cremophor-free, protein stabilized, colloidal nanoparticle formulation of a non-crystalline, amorphous form of paclitaxel suspended in normal saline with several potential advantages over TAXOL:

- Higher tolerated doses, with greater efficacy. The maximum tolerated dose (MTD) in a Phase I study of 300 mg/m^2, considerably greater than that generally tolerated with TAXOL (175 mg/m^2) and may contribute to higher effectiveness of ABI-007. Reports suggest response rates in excess of 30% when TAXOL dose is increased above 175 mg/m^2, suggesting that if paclitaxel, the active ingredient in TAXOL, could be administered at higher doses, greater efficacy may result.
- Due to the nanoparticle formulation of ABI-007, the paclitaxel which is in a non-crystalline, amorphous, insoluble form may persist in carcinomas longer than it does with other formulations in which the active agent is in solution. This contributes to the possibility of greater efficacy of ABI-007.
- The infusion time for ABI-007 is reduced because of the absence of Cremophor. The major components of ABI-007 are unmodified paclitaxel and human albumin, which is readily soluble in saline.
- Reduced risk of hypersensitivity and lack of need for premedication as compared to TAXOL, because ABI-007 is Cremophor-free.
- ABI-007 requires no special tubing or in-line filters. The Cremophor constituent in TAXOL requires special non-DEHP tubing and in-line filters for intravenous administration, since Cremophor causes leaching of the tubing plasticizers.
- More rapid distribution of paclitaxel into the tissues based on pharmacokinetic evaluation of ABI-007 in Phase I patients, which could result in higher tumor concentrations of the drug and may enhance effectiveness and/or aid in overcoming TAXOL resistance. Phase I and Phase II studies of ABI-007 in patients with metastatic breast cancer with prior taxane therapy, suggest that ABI-007 may be effective in this patient population (partial response or stable disease).

INVESTIGATIONAL PRODUCTS

ABI-007 is a Cremophor-free, nanoparticle formulation of paclitaxel for injection. Each 50 mL vial contains 100 mg of paclitaxel, and human albumin, as a white to off-white sterile lyophilized powder for reconstitution with 20 mL of 0.9% Sodium Chloride Injection USP.

Patients randomized to Treatment Arm A (ABI-007) will receive up to 6 cycles starting at 260 mg/m^2 administered over 30 minutes repeated every 3 weeks without steroid premedication or G-CSF prophylaxis (unless modified as described within section 3.4.1).

Patients randomized to Treatment Arm B (TAXOL) will receive up to 6 cycles starting at 175 mg/m^2 administered over 3 hours repeated every 3 weeks with standard premedication per the TAXOL package insert (refer also to the study manual for premedication and G-CSF prophylaxis procedures).

Patients who complete 6 cycles of therapy and do not have progressive disease will be able to continue their arm of treatment (ABI-007 or TAXOL) at the investigator's discretion, provided the withdrawal criteria as defined in Section 3.3.4 have not been met

STUDY DESIGN

This is a controlled, randomized, multicenter, open label, phase III study to evaluate the safety/tolerability and anti-tumor effect of intravenously administered ABI-007 compared to that of TAXOL in patients with metastatic breast cancer. Patients who received anthracycline prior to study enrollment must have a four week interval between last dose of anthracycline and starting study drug. Within each country, patients will be randomized separately according to whether they have or have not received prior therapy with anthracyclines. Patients will receive either ABI-007 or TAXOL for up to 6 cycles. In addition, patients who complete 6 cycles of therapy and do not have progressive disease will be able to continue their arm of treatment (ABI-007 or TAXOL) at the investigator's discretion, provided the withdrawal criteria as defined in Section 3.3.4 have not been met. All patients who were randomized and received at least one dose of ABI-007 or TAXOL will be included in the intent to treat population and will be evaluated for efficacy. All patients in the intent to treat population will be assessed every month for the first three months after completion/withdrawal from this study and then every three months thereafter for survival and time to disease progression.

PLANNED SAMPLE SIZE

The current study is designed for approximately 210 evaluable patients (230 enrolled) per treatment arm with at least 100 patients per arm that have been previously treated with anthracyclines. Patients that discontinue early from the study will not be replaced. An interim analysis for the purpose of re-estimating sample size will be performed after approximately 105 patients in each arm have been treated and evaluated for a minimum of two treatment cycles.

TREATMENT DURATION

Patients will receive ABI-007 or TAXOL on an outpatient basis for a maximum of six cycles. Patients who complete 6 cycles of therapy and do not have progressive disease will be able to continue their arm of treatment (ABI-007 or TAXOL) at the investigator's discretion, provided the withdrawal criteria as defined in Section 3.3.4 have not been met.

INCLUSION CRITERIA

A patient will be eligible for inclusion in this study only if all of the following criteria are met:

1. Patient is female, non-pregnant and not lactating, and ≥ 18 years of age. If patient is of child-bearing potential, as evidenced by regular menstrual periods, she must have a negative serum pregnancy test (β-hCG) within 72-hours prior to first study drug administration and, if sexually active, agrees to utilize contraception considered adequate and appropriate by the investigator;
2. Patient has histologically or cytologically confirmed measurable metastatic breast cancer who 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 have 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 cancer, 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 liver metastases;
   - AST (SGOT), ALT (SGPT) ≤ 5.0 x upper limit of normal range (ULN), total bilirubin ≤ 26 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.

EXCLUSION CRITERIA

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

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.

STUDY OBJECTIVES

PRIMARY OBJECTIVES

- To compare antitumor activity of ABI-007 with that of TAXOL in metastatic breast cancer patients; and,
- To evaluate the safety/tolerability of ABI-007 compared to that of TAXOL.

SECONDARY OBJECTIVES

- To evaluate time to disease progression and survival;
- To evaluate changes from Baseline in Quality of Life (QOL); and
- To determine the pharmacokinetics of ABI-007.

STUDY ENDPOINTS

PRIMARY EFFICACY ENDPOINT

Percentage of patients in ABI-007 and TAXOL arms who achieve complete or partial responses for target lesions after a minimum of two cycles of treatment.

SECONDARY EFFICACY ENDPOINTS

- Time to disease progression;
- Survival; and
- Quality of life evaluated by changes from Baseline in scores on the ECOG (Zubrod) performance status scale, EORTC QLQ-C30 and weight.

SAFETY/TOLERABILITY ENDPOINTS

- Adverse events (AEs) and serious adverse events (SAEs) that occur during treatment;
- Maximal degree of myelosuppression (nadir of white count);
- Changes from Baseline in CBC, platelet count, and chemistries;
- Physical examination, EKG, echocardiogram/MUGA (if clinically indicated), vital signs during study drug dosing.

PHARMACOKINETIC ENDPOINTS

A subset of 12 patients undergoing treatment with ABI-007 will also have blood, urine, and feces collected to determine drug pharmacokinetics (PK), including elimination rate constant, half-life, volume of distribution, C_{max}, $T_{max,}$ AUC_{inf}, clearance, urinary clearance, and excretion.

PLANNED CLINICAL TRIAL PERIOD

Anticipated Start Date: October 2001
Anticipated End Date: January 2003

STUDY SITES

This multi-national study will be conducted globally, and will include sites in North America, Europe, Russia, and Ukraine. Multiple sites will be used to perform the pharmacokinetic sub-study.

CLINICAL AND LABORATORY EVALUATIONS

See the attached Schedule of Assessments for planned study evaluations.

Schedule of Assessments

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[l]	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[j]	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 $\geq 1.5 \times 10^9$ cells/L and platelets have returned to $\geq 100 \times 10^9$ 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.

LIST OF ABBREVIATIONS

ABI	American BioScience, Inc.
AC	Adriamycin/Cyclophosphamide
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AR	All Randomized
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BMS	Bristol-Myers Squibb
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CIB	Clinical Investigator's Brochure
CIN	Cervical Intraepithelial Neoplasia
CNS	Central Nervous System
CRF	Case Report Form
CR	Complete Response
CRO	Contract Research Organization
CT	Computed Tomography
CXR	Chest X-ray
DMC	Data Monitoring Committee
DHHS	Department of Health and Human Services
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
EDTA	Ethylenediaminetetraacetic acid
EKG	Electrocardiogram
EORTC	European Organisation for Research and Treatment of Cancer
EOS	End of Study
FAC	Fluorouracil/Adriamycin/Cyclophosphamide
FDA	Food and Drug Administration
F/U	Follow Up
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony Stimulating Factor
HA	Human Albumin
Hgb	Hemoglobin
Hct	Hematocrit
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-Treat
IV	Intravenous
LDH	Lactate Dehydrogenase
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
MUGA	Multigated (radionuclide) angiogram

NA	Not Applicable
NAV	Not Available
NCI	National Cancer Institute
ND	Not Done
NIH	National Institutes Of Health
PEE	Primary Efficacy Endpoint
PD	Progressive Disease
PO	By mouth
PP	Per-Protocol
PK	Pharmacokinetic
PR	Partial Response
QOL	Quality of Life
RBC	Red Blood Cell
RECIST	Response Evaluation Criteria In Solid Tumours
SAE	Serious Adverse Event
SD	Stable Disease
S.D.	Standard Deviation
SGOT	Serum Glutamate Oxaloacetate Transaminase
SGPT	Serum Glutamate Pyruvate Transaminase
SOP	Standard Operating Procedure
ULN	Upper Limit of Normal
UK	United Kingdom
US	United States
WBC	White Blood Cell
WHO	World Health Organization

TABLE OF CONTENTS

TABLES

LIST OF APPENDICES

1. INTRODUCTION

1.1. Background

ABI-007 is a unique protein formulation of a non-crystalline, amorphous form of paclitaxel in an insoluble nanoparticle state. ABI-007 has been developed to reduce the toxicities associated with TAXOL, paclitaxel (from the native crystalline form) in solution with Cremophor as the solvent, while maintaining or improving its chemotherapeutic effect. The potential exists that enhanced efficacy could be seen in solid tumors as a consequence of (i) higher tolerated dose (260 mg/m^2), (ii) longer half-life, (iii) prolonged local tumor availability, and/or (iv) sustained in-vivo release.

This protocol describes a Phase III trial comparing ABI-007 to TAXOL to determine the response rate in metastatic breast cancer patients. The study is designed as a non-inferiority study intended to have an 80% power of detecting an effect 75% or greater as compared to TAXOL. In addition, an evaluation of the safety and tolerability of ABI-007 monotherapy compared to that of TAXOL will be assessed.

ABI-007 may have advantages compared to available taxanes with regards to reduced toxicity, potential enhanced efficacy with ease of administration, shorter drug infusion time, and avoidance of hypersensitivity reactions attributable to the Cremophor component of the currently available TAXOL (paclitaxel) formulation.

The anticancer agent paclitaxel (Taxol® for Injection Concentrate, Bristol-Myers Squibb, BMS) has a broad spectrum of activity against several human cancers including carcinomas of ovary, breast, lung, esophagus and head and neck cancer[1]. TAXOL has shown remarkable activity against metastatic breast cancer yielding response rates in the range of 40% to 60% in chemotherapy-naïve patients and 25% and 30% in patients refractory to anthracycline-containing regimens[3,4] (see also Appendix D for the TAXOL package insert). Based on these data, TAXOL was approved for the treatment of breast cancer patients who have failed one prior regimen of adriamycin-containing combination chemotherapy such as fluorouracil/ adriamycin/cyclophosphamide (FAC) or adriamycin/cyclophosphamide (AC). Currently, TAXOL is used as standard therapy for breast cancer at the approved doses of 135 or 175 mg/m^2 over 3-24 hours given every 3 weeks with reported response rates of 22-28%.

The major limitation of TAXOL is its poor water solubility requiring Cremophor® as a solvent, which means TAXOL has to be dissolved in a large volume of fluid diluent to administer it over a period of 3 to 24 hours. A number of dose schedules of TAXOL have been tested in breast cancer. The initial trials used TAXOL in a dose level of 250 mg/m^2 given over 24 hours as a continuous infusion[3]. Subsequently shorter infusions of TAXOL given over 3 hours were tested at a dose level of 175 mg/m^2 and consistent activity was observed with response rates of 30% to 40%[4]. Phase II studies utilizing higher doses of TAXOL at 200-250 mg/m^2 indicate response rates of 56% in metastatic breast cancer patients. However, at these doses, significant toxicities were reported including neuropathy and neutropenia with the median granulocyte count nadir consistently at 100-200/mm^3 for the majority of courses administered. Thus, the current formulation and schedules of TAXOL can result in significant acute and cumulative toxicity, most notable neutropenic fever, peripheral neuropathy and anaphylactic reactions.

The other limitation of TAXOL also involves the Cremophor solvent, which has side effects including the risk of anaphylaxis and other hypersensitivity reactions[2]. Given the potential side effects of the Cremophor solvent, premedication including corticosteroids and antihistamines are used as a preventive measure when dosing with TAXOL. These premedications may include; dexamethasone 20 mg starting at 12 hours prior to initiation of TAXOL with a repeat dose given at 6-hours prior to TAXOL administration, IV benadryl, and cimetidine.

Taxotere™ (docetaxel) is the second taxane approved for treatment of anthracycline-resistant breast cancer. It has an advantage of shorter infusion time of 1-hour and an equivalent level of activity. Unfortunately, TAXOTERE has a rather unique toxicity of fluid retention, which requires concomitant use of steroids. As a result, dexamethasone is now a required pre-medication preceding the administration of TAXOTERE (see Appendix E for TAXOTERE package insert).

Potential Advantages of ABI-007:

ABI-007 is a novel Cremophor-free, protein stabilized, colloidal nanoparticle formulation of a non-crystalline, amorphous form of paclitaxel suspended in normal saline with several potential advantages over TAXOL:

- Higher tolerated doses, with greater efficacy. The maximum tolerated dose (MTD) in a Phase I study of 300 mg/m^2, considerably greater than that generally tolerated with TAXOL (175 mg/m^2) and may contribute to higher effectiveness of ABI-007. Reports suggest response rates in excess of 30% when TAXOL dose is increased above 175 mg/m^2, suggesting that if paclitaxel, the active ingredient in TAXOL, could be administered at higher doses, greater efficacy may result.
- Due to the nanoparticle formulation of ABI-007, the paclitaxel which is in a non-crystalline, amorphous, insoluble form may persist in carcinomas longer that it does with other formulations in which the active agent is in solution. This contributes to the possibility of greater efficacy of ABI-007.
- The infusion time for ABI-007 is reduced because of the absence of Cremophor. The major components of ABI-007 are unmodified paclitaxel and human albumin, which is readily soluble in saline.
- Reduced risk of hypersensitivity and lack of need for premedication as compared to TAXOL, because ABI-007 is Cremophor free.
- ABI-007 requires no special tubing or in-line filters. The Cremophor constituent in TAXOL requires special non-DEHP tubing and in-line filters for intravenous administration, since Cremophor causes leaching of the tubing plasticizers.
- More rapid distribution of paclitaxel into the tissues based on pharmacokinetic evaluation of ABI-007 in Phase I patients, which could result in higher tumor concentrations of the drug and may enhance effectiveness and/or aid in overcoming TAXOL resistance. Phase I and Phase II studies of ABI-007 in patients with metastatic breast cancer with prior taxane therapy, suggest that ABI-007 may be effective in this patient population (partial response or stable disease).

Preclinical Studies:

Preclinical studies comparing ABI-007 to TAXOL demonstrated dramatically lower acute toxicities, with an LD_{50} approximately 50 fold higher for ABI-007 compared to TAXOL with lower myelosuppression and superior efficacy profiles in a xenograft tumor model of human mammary adenocarcinoma when compared at equi-doses of TAXOL. In addition, at equi-molar paclitaxel doses, ABI-007 was found to be more efficacious than TAXOL in in-vivo nude mice tumor models with human mammary adenocarcinoma (MX-1).

Phase I Clinical Trials:

1. DM97-123: ABI-007 at 135-375 mg/m^2 q 3 weeks:

A Phase I, open-label, dose escalating, study to evaluate the safety/tolerability and antitumor effect of intravenously administered ABI-007 every three weeks monotherapy in patients with advanced solid tumors.

The primary diagnoses for the 19 patients enrolled were: Six (31.6%) patients had melanoma, 12 (63.2%) had breast cancer and 1 (5.3%) had a primary diagnosis of unknown origin. Histology showed 11 (57.9%) patients diagnosed with invasive ductal carcinoma; 6 (31.6%) patients had malignant melanoma; 1 (5.3%) patient diagnosed with invasive lobular carcinoma, and 1 (5.3%) patient with Paget's disease of the nipple.

Although protocol response was not a formal endpoint in the Phase I study, partial responses were noted for two (11%) patients, stable disease for nine (47%) patients, and progressive disease for eight (42%) patients. Over a dose range of 135-375 mg/m^2 (n=19) in the Phase I trial, hematological toxicity was mild and played virtually no role in dose and treatment decisions in the trial. Of the 79 treatment cycles administered at 135-300 mg/m^2, only one (1.3%) cycle resulted in an ANC nadir < 500 cells/mm^3. At the MTD of 300 mg/m^2, only 1/35 (2.9%) cycles administered in 6 patients resulted in an ANC < 500 cells/mm^3. No patients experienced Grade 4 non-hematological toxicities. Peripheral neuropathy was absent at 200 mg/m^2 and only 1 patient manifested a Grade 3 sensory neuropathy at 300 mg/m^2. Other than this single episode, there were no other Grade 3 non-hematological toxicities at the MTD of 300 mg/m^2. Dose limiting toxicities at 375 mg/m^2 were sensory neuropathy, stomatitis and superficial keratitis; however, neither Grade 3 stomatitis nor superficial keratitis was observed at the 300 mg/m^2 dose level.

Of the total 19 enrolled and treated patients, 7 (37%) patients were either TAXOL or TAXOTERE resistant. Three (43%) of the 7 taxane resistant patients achieved stable disease and the remaining four progressed.

Thus, the Phase I study demonstrated that ABI-007 is tolerated at higher doses (300 mg/m^2) than TAXOL® (175 mg/m^2), administered with much faster infusion times (30 minutes), with no severe hypersensitivity or fluid retention reactions associated with its use, and without the need for premedication, or G-CSF support. Furthermore, standard tubing and I.V. bags may be used for the intravenous administration of ABI-007.

2. CA005-0: ABI-007 at 80 – 150 mg/m^2 q 1 week:

A Phase I clinical study to evaluate the safety/tolerability and antitumor effect of intravenously administered ABI-007 weekly monotherapy in patients with advanced non-hematologic malignancies. This study will determine the maximum tolerated dose of ABI-007 given weekly for the three weeks with repeated dosing every 4 Weeks (Day 1, Day 8, Day 15, rest).

Of the current 13 enrolled patients, preliminary data show that no dose limiting toxicities were reported in the three patients treated at the initial dosing level of 80 mg/m^2. Two patients in the 80 mg/m^2 dosing level reported achieving a stable disease and one patient reported progressive disease. Seven patients have currently been treated in the 100 mg/m^2 weekly dosing level with only one reported dose limiting toxicity, a Grade 4 neutropenia, recorded during the rest period of Course 2. Three patients in the 100 mg/m^2 dosing level have reported achieving a partial response (two of which are metastatic melanoma patients), three patients have reported progressive disease and one patient in the 100 mg/m^2 has not completed the restaging imaging at the time this protocol was written. Overall hematological toxicities are mild. Only one occurrence of peripheral neuropathy (Grade 1) has been reported to-date in the 125 mg/m^2 dosing level. Eight out of thirteen patients remain active in the study. Three patients have been dosed at the 125 mg/m^2 dosing level. One dose limiting toxicity has been reported early in Course 1. Four patients discontinued from the study due to disease progression and one withdrew from the study with stable disease status.

3. ABI-007 administered intra-arterially at 120 - 300 mg/m^2 q 4 weeks:

A phase I/II clinical study to evaluate the safety/tolerability, maximum tolerated dose and antitumor activity of intra-arterially administered ABI-007 in patients with either recurrent head and neck cancer or anal canal cancer. 43 patients were treated with ABI-007 every 4 Weeks for 3 cycles. Of these 43 patients, increasing dose levels from 120 to 300 mg/m^2 were studied in 18 patients and the remaining 25 patients initiated treatment at 250 mg/m^2. The dose limiting toxicity of ABI-007 was myelosupression consisting of Grade 4 neutropenia in 3 patients. Nonhematologic toxicities included total alopecia (30 patients), gastrointestinal toxicity (3 patients, Grade 2), skin toxicity (5 patients, Grade 2), neurologic toxicity (4 patients, Grade 2), ocular toxicity (1 patient, Grade 2), flu-like syndrome (7 patients, Grade 2; 1 patient, Grade 3). The maximum tolerated dose in a single administration was 270 mg/m^2. Most dose levels showed considerable antitumour activity (of the 29 assessable patients with advanced head and neck cancer, the combined complete and partial response rate was 75.8%. Of the 11 assessable patients with recurrent anal canal cancer, the combined complete and partial response rate was 63.6%).

Phase II Clinical Trials:

1. CA002-0LD: ABI-007 at 175 mg/m^2 q 3 weeks:

A multicenter Phase II clinical trial to determine the anti-tumor effect of ABI-007 monotherapy (175 mg/m^2) in patients with metastatic breast cancer has enrolled 43 patients. ABI-007 was administered over 30-45 minutes every three weeks without steroid premedication and without G-CSF. Preliminary data show a 51% response rate for 41 evaluable patients. Patients previously exposed to anthracycline had a 50% (11/22) response rate (CR = 14% and PR = 36%) and anthracycline-naive patients had a 50% (9/18) response rate (CR = 0% and PR = 50%). The

overall response rate of ABI-007 (51%) in this study was higher than the 28% response rate reported for TAXOL at an equi-dose (175 mg/m^2). In two patients with prior taxane exposure, stable disease was noted. The Phase II study of ABI-007 at 175 mg/m^2 confirmed that this nanoparticle formulation of paclitaxel can be administered safely (n=43 evaluable for toxicity) at this dose level, with absence of severe hypersensitivity without the need for premedication in any patients (0%), reduced myelosuppression (5% with ANC < 500/mm^3) when compared to TAXOL at equi-dose, and absence (0%) of any evidence of peripheral neuropathy ≥ Grade 3. Of the total 43 enrolled and treated patients, 2 (5%) were either TAXOL or TAXOTERE resistant. Both patients demonstrated stable disease.

2. CA002-0: ABI-007 at 300 mg/m^2 q 3 weeks:

A multicenter Phase II clinical trial to determine the anti-tumor effect of ABI-007 monotherapy (300 mg/m^2) in patients with metastatic breast cancer has enrolled 63 patients. ABI-007 was administered over 30-45 minutes every three weeks without steroid premedication and without G-CSF support. Preliminary data show a 61% response rate for 59 evaluable patients. Patients previously exposed to anthracycline had a 48% (14/29) response rate (CR = 3% and PR = 45%) and anthracycline-naive patients had a 76% (22/29) response rate (CR = 3% and PR = 72%). The overall response rate for ABI-007 (61%) was substantially higher than the 28% response rate reported for TAXOL (175 mg/m^2). In 7 patients with prior taxane exposure, the response rate was 43% (CR = 0%, PR = 43% (3/7), SD = 29% (2/7) and PD = 29% (2/7). In addition, this Phase II study of ABI-007 at 300 mg/m^2 confirmed that this nanoparticle formulation of paclitaxel can be administered safely (n=62 evaluable for toxicity) at this dose level, with no severe hypersensitivity (except rash, 2%) in the absence of premedication, a level of myelosuppression (14/62 or 23% with ANC < 500/mm^3) in the absence of G-CSF support approximating that for TAXOL at a dose of 175 mg/m^2, and peripheral neuropathy (6/62 or 10% [≥ Grade 3]). Analysis of the data suggested that ABI-007 showed efficacy in patients who had failed taxane therapy.

Of the total 63 enrolled and treated patients, 8 (13%) patients were either TAXOL or TAXOTERE resistant, of which 7 patients were evaluable. Three (43%) out of the 7 patients achieved a partial response (PR), 2 (29%) patients demonstrated stable disease (SD) and 2 (29%) progressed.

Current Phase III CA012-0:

This controlled, randomized, phase III, multicenter, open label study of ABI-007 and TAXOL will assess the efficacy and safety of ABI-007 in a larger population of patients with metastatic breast cancer, and aims to demonstrate the non-inferiority of ABI-007 to TAXOL.

Potential Risks of ABI-007:

Toxicities other than those noted in the aforementioned studies are not known. However, since ABI-007 is made with paclitaxel (the active component of TAXOL), risks should be similar to those of TAXOL. Please refer to the Clinical Investigator's Brochure for details of the Adverse Reactions in the overall Safety Database for ABI-007.

1.2. Rationale

ABI-007, a unique protein formulation of a non-crystalline, amorphous form of paclitaxel in nanoparticle has been developed to reduce the toxicities associated with TAXOL (and the Cremophor vehicle) while maintaining or improving the chemotherapeutic effect of the drug. The potential exists that enhanced efficacy could be seen in solid tumors as a consequence of (i) higher tolerated dose (260 mg/m^2), (ii) longer half-life, (iii) prolonged local tumor availability and/or (iv) sustained in-vivo release. Consequently, the Cremophor-free formulation of paclitaxel may offer an alternative to TAXOL if it shows equivalent level of anti-tumor activity against breast cancer. Since the active ingredient in the trial product is paclitaxel, there is little reason not to expect a similar level of anti-tumor activity.

The purpose of this Phase III trial is to conduct a comparative study of ABI-007 to TAXOL in an estimated population of 420 evaluable patients (approximately 460 enrolled) in order to determine the response rate in metastatic breast cancer patients who are eligible to receive paclitaxel in accordance with the Marketing Authorization in the country in which the study is being conducted, in a non-inferiority analysis at 80% power, where the 95% confidence interval in the response rate for ABI-007 (P_2) is no less than 75% of the TAXOL (P_1) response rate. In addition, an evaluation of the safety and tolerability of ABI-007 monotherapy compared to that of TAXOL will be assessed.

ABI-007 may have advantages compared to available taxanes with regards to reduced toxicity, potential enhanced efficacy, with ease of administration, shorter drug infusion time, and avoidance of hypersensitivity reactions attributable to the Cremophor component of the currently available TAXOL (paclitaxel) formulation.

2. OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objectives

The primary objectives of this study are to:

- To compare antitumor activity of ABI-007 with that of TAXOL in metastatic breast cancer patients; and,
- To evaluate the safety/tolerability of ABI-007 compared to that of TAXOL.

2.1.2. Secondary Objectives

The secondary objectives of this study are:

- To evaluate time to disease progression and survival;
- To evaluate changes from Baseline in Quality of Life (QOL); and,
- To determine the pharmacokinetics of ABI-007.

2.2. Study Endpoints

2.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint for comparison of ABI-007 and TAXOL is:

- Percentage of patients in ABI-007 and TAXOL arms who achieve complete or partial responses for target lesions after a minimum of two cycles of treatment.

2.2.2. Secondary Efficacy Endpoints

Secondary efficacy endpoints for comparison of ABI-007 and TAXOL include:

- Time to disease progression;
- Survival; and
- Quality of life evaluated by changes from Baseline in scores on the ECOG (Zubrod) performance status scale, EORTC QLQ-C30 and weight.

2.2.3. Safety Endpoints

The safety/tolerability endpoints for ABI-007 and TAXOL include the following:

- Adverse events (AEs) and serious adverse events (SAEs) that occur during treatment;
- Maximal degree of myelosuppression (nadir of white count);
- Changes from Baseline in CBC, platelet count, and chemistries;
- Physical examination, EKG, echocardiogram/MUGA (if clinically indicated), vital signs during study drug dosing.

The above safety endpoints will be tabulated for each study drug and a comparison made between the study drugs (ABI-007 and TAXOL).

2.2.4. Pharmacokinetic Endpoints

A subset of 12 patients undergoing treatment with ABI-007 will also have blood, urine, and feces collected to determine drug pharmacokinetics (PK), including elimination rate constant, half-life, volume of distribution, C_{max}, $T_{max,}$ AUC_{inf}, clearance, urinary clearance, and excretion.

3. STUDY DESIGN AND PLAN

3.1. Study Design

This is a controlled, randomized, multicenter, phase III, open label study to evaluate the safety/tolerability and anti-tumor effect of intravenously administered ABI-007 compared to that of TAXOL in patients with metastatic breast cancer. Patients who received anthracycline prior to study enrollment must have a four week interval between last dose of anthracycline and starting study drug. To ensure within-country balance in the number of patients between treatment groups

with respect to history of anthracycline use, the randomization schedule within each country participating will be stratified into two strata: *anthracycline treated and anthracycline naïve.* The study will consist of the following phases:

- Baseline (3 weeks pre-dose);
- Treatment (maximum 6 cycles);
- End of Study (EOS) after six cycles of treatment at Week 15/withdrawal. The primary efficacy endpoint is the percentage of patients in ABI-007 and TAXOL arms who achieve complete or partial responses for target lesions and can be established after a minimum of two cycles of treatment. Patients who complete 6 cycles of therapy and do not have progressive disease will be able to continue their arm of treatment (ABI-007 or TAXOL) at the investigator's discretion, provided the withdrawal criteria as defined in Section 3.3.4 have not been met;
- Follow Up 30 days (± 2 days) after last dose.

Patients will be randomized into one of two treatment arms. Treatment Arm A will be assigned for ABI-007 and Treatment Arm B will be assigned for the administration of TAXOL.

- Treatment Arm A (ABI-007): During the Treatment Phase, patients randomized to ABI-007 will receive cycles of 260 mg/m^2 ABI-007 administered over 30 minutes repeated every 3 weeks without any steroid premedication and without G-CSF prophylaxis (unless modified as described within section 3.4.1).
- Treatment Arm B (TAXOL): During the Treatment Phase, patients randomized to TAXOL will receive cycles of 175 mg/m^2 TAXOL administered over 3 hours repeated every 3 weeks with standard premedication as per the package insert for TAXOL authorized in the country in which the study is being conducted (Appendix D).

Patients will be treated on an outpatient basis to receive a maximum of six cycles of ABI-007 or TAXOL. Patients who complete 6 cycles of therapy and do not have progressive disease will be able to continue their arm of treatment (ABI-007 or TAXOL) at the investigator's discretion, provided the withdrawal criteria as defined in Section 3.3.4 have not been met. All patients who receive at least 1 dose of ABI-007 or TAXOL will be assessed by telephone once every month for the first three months after EOS and every three months thereafter to collect survival data.

Response will be determined according to the Response Evaluation Criteria in Solid Tumors [RECIST] guidelines[5] Tumors will be assessed in the study by imaging studies at Weeks 5, 9 and 15. This will allow assessment of response to ABI-007 and TAXOL following cycles 2, 3 and 5 of chemotherapy according to RECIST criteria, with confirmation of stable disease at least 6 weeks after the baseline imaging evaluation and confirmation of response to cycle 2 at week 9 and cycle 3 at week 15. Secondary analyses will include time to disease progression, changes in QOL and patient survival during treatment and post study.

Safety and tolerability will be monitored through adverse events, clinical laboratory values, physical examinations, vital signs during study drug dosing, EKGs, echocardiogram/MUGA (if clinically indicated), and % of patients with dose modifications, dose interruptions, and/or premature discontinuation of study drug. Pharmacokinetic data will be collected on twelve patients receiving ABI-007 enrolled at multiple sites in the study.

Patients will be considered responders if they achieve an objective complete or partial response for target lesions, after a minimum of two cycles (response confirmation can be reported as early as Week 9). Patients achieving stable disease will have confirmation of stable disease at least 6 weeks after the baseline imaging evaluation. Progressive disease after a minimum of two cycles of study drug will be the criteria for treatment failure and discontinuation from the study.

Secondarily, an Overall Response will be evaluated using the response from the target and non-target lesions.

Changes in tumor size will be evaluated by the following formula when determining complete or partial response:

[(Post value – Baseline value)/Baseline value] x 100

Changes in tumor size will be evaluated by the following formula when determining stable or progressive disease:

[(Post value – Smallest value since treatment started)/Smallest value since treatment started] x 100

Definitions for complete response, partial response, stable disease, and progressive disease as defined by the RECIST guidelines[5] are given in Table 3.1.

TABLE 3.1: RESPONSE CRITERIA (RECIST[5])

EVALUATION OF TARGET LESIONS	
Complete Response (CR):	Disappearance of all target lesions Duration of response is ≥ four weeks
Partial Response (PR):	At least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter Duration of response is ≥ four weeks
Stable Disease (SD):	Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter since the treatment started Duration of response is ≥ six weeks since baseline
Progressive Disease (PD):	At least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since the treatment started or the appearance of one or more new lesions

EVALUATION OF NON-TARGET LESIONS	
Complete Response (CR):	Disappearance of all non-target lesions
Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s)
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

Target lesions	**Non-Target lesions**	**New lesions**	**Overall response**
CR	CR	No	**CR**
CR	Incomplete response/SD	No	**PR**
PR	Non-PD	No	**PR**
SD	Non-PD	No	**SD**
PD	Any	Yes or No	**PD**
Any	PD	Yes or No	**PD**
Any	Any	Yes	**PD**

The investigator must have made a designation as to tumor response at Week 5 prior to continuation of study drug treatment and the investigator must have made a designation to toxicity grade prior to continuation of study drug administration.

A central image reader who is blinded to treatment administered will evaluate radiological evaluations of tumor size. Films or electronic copies will be forwarded to the central image reader in the United States and collected and archived in a centralized database. The reader will be the arbiter of response for the purposes of study evaluation, although clinical treatment will always be at the judgment and discretion of the local clinician.

Patients who are receiving anthracycline prior to study enrollment must have a four-week interval between last dose of anthracycline and starting study drug. Patients must initiate therapy within 21 days of the Baseline visit.

The current study is designed for approximately 210 (approximately 230 enrolled) evaluable patients per treatment arm with at least 100 patients per arm that have been treated with anthracycline. Patients that discontinue early from the study will not be replaced. An interim analysis for the purpose of re-estimating sample size will be performed after approximately 105 patients have been treated for a minimum of two treatment cycles in each treatment arm, and have undergone the necessary tumor evaluations for the assessment of protocol response.

This initial sample size will provide at least 80% power with a one-sided 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 percentage of TAXOL. We assume that the TAXOL response percentage is in the interval of 28% to 32% and that the ABI-007 response will demonstrate a relative improvement of 20% (i.e., 33.6% to 38.4%.) The re-estimated sample size will conform to the levels of power, alpha, and non-inferiority margin used to estimate the initial sample size.

A randomized controlled study was chosen to provide the least biased (especially treatment related bias) and most precise demonstration of efficacy of ABI-007.

Tumors (lesions) found at baseline will be classified as either target lesions or non-target lesions, as defined by the Response Evaluation Criteria in Solid Tumors guidelines[5]. A maximum of 5 target lesions per organ and 10 target lesions in total will be identified at baseline. Target lesions should be selected on the basis of their size (those with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). All other lesions will be identified as non-target lesions. All lesions will be followed throughout the study and any new lesions that develop while in the study will be recorded.

This multi-national study will be conducted globally, and will include sites in North America, Europe, Russia, and Ukraine. Multiple sites will be used to perform the pharmacokinetic sub-study.

3.2 Study Personnel

The multicenter clinical trial described in this protocol will be conducted in compliance with the Declaration of Helsinki, International Conference on Harmonization (ICH) guideline for Good Clinical Practice (GCP) and all current Food and Drug Administration (FDA) regulations. This clinical trial will be overseen and managed by American BioScience, Inc. (ABI), sponsor. ABI will be responsible for global project management, clinical monitoring in the United States and Canada, overall quality assurance, and final study report. ABI has delegated study conduct responsibilities to the following contract research organizations (CRO): ORION-United Kingdom, and PSI-Russia and the Ukraine. InGenium has been contracted for the responsibilities of data handling, statistical analyses and final statistical report. In addition, Drug Safety Solutions has been contracted for the purpose of providing a medical assessment and review of all serious adverse events. Drug Safety Solutions will be responsible for preparing any IND Safety Reports and CIOMS Reports accordingly for reportable serious adverse events.

3.3 Study Population

3.3.1 Inclusion Criteria

A patient will be eligible for inclusion in this study only if all of the following criteria are met:

1. Patient is female, non-pregnant and not lactating, and ≥ 18 years of age. If patient is of child-bearing potential, as evidenced by regular menstrual periods, she must have a negative serum pregnancy test (β-hCG) within 72-hours prior to first study drug administration and, if sexually active, agrees to utilize contraception considered adequate and appropriate by the investigator;
2. Patient has histologically or cytologically confirmed measurable metastatic breast cancer who 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 have 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 cancer, 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 liver metastases;
   - AST (SGOT), ALT (SGPT) ≤ 5.0 x upper limit of normal range (ULN), total bilirubin ≤ 26 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.

3.3.2 Exclusion Criteria

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

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.

3.3.3 Other Study Eligibility Criteria Consideration

In order to assess any potential impact on patient eligibility with regard to safety, the investigator must refer to the relevant document(s) for detailed information regarding warnings, precautions, contraindications, adverse events, and other significant data pertaining to the study drug being used in this study. Such documents may include, but are not limited to the Clinical Investigator's Brochure (CIB ABI-007), or equivalent document provided by ABI, and the TAXOL package insert (see Appendix D).

3.3.4 Withdrawal/Premature Discontinuation

A patient may voluntarily discontinue study participation at any time. The investigator may also, at his/her discretion, discontinue the patient's study participation at any time. In the event of premature discontinuation, the patient should return to the study site as soon as feasible to have the End of Study (EOS) assessments performed and the appropriate follow-up evaluations should occur (see sections 5.2.3 and 5.2.5). Patients must be withdrawn from this study if any of the following occurs:

- Progressive disease after a minimum of two treatment cycles with ABI-007 or TAXOL or after initial response followed by increasing tumor size;
- Development of unacceptable toxicity in the opinion of the investigator, as defined by the NCI Toxicity Criteria Scale (Appendix A);
- Patient refuses to continue therapy;
- If, following the 2nd dose reduction of ABI-007 to 180 mg/m^2 there is a recurrence of grade 4 neutropenia, or any other hematologic toxicity that is grade 3 or 4, or any Grade 3 or 4 non-myelosuppresive adverse event (excluding alopecia), unless at the discretion of the investigator there is evidence of continuing benefit to the patient;
- Refer to the TAXOL package insert for information regarding treatment discontinuation of Treatment Arm B;
- Initiation of further anti-cancer therapy; and/or,
- At the investigator's discretion.

Patients who are withdrawn from this study secondary to a laboratory toxicity or adverse event should be followed by the investigator until the abnormality is resolved or stabilized, the patient is lost to follow-up, or the event is otherwise explained.

3.4 Treatment During Study

3.4.1 Study Drug and Dosages

Treatment Arm A (ABI-007):

Patients will be treated on an outpatient basis. Patients randomized to Treatment Arm A will be dosed intravenously with 260 mg/m^2 ABI-007 administered over approximately 30 minutes without steroid premedication and without G-CSF prophylaxis (unless modified as described under herein). Cycles of therapy will be repeated at three-week intervals. A minimum of two cycles of therapy will be given to adequately assess the response to treatment and a maximum of six cycles will be administered. Patients who complete 6 cycles of therapy and do not have progressive disease will be able to continue treatment at three week intervals at the investigator's discretion, provided the withdrawal criteria as defined in Section 3.3.4 have not been met.

Dose Reductions:

Dose reductions will be permitted as outlined in the tables below. A maximum of two dose reductions will be allowed from the original 260 mg/m^2 dose to the following dose levels:

- 1st dose reduction: by 40 mg/m^2 to 220 mg/m^2

- 2nd dose reduction: by 40 mg/m^2 to 180 mg/m^2

Dose Delays:

All dosing visits must occur within ± 3 days of the planned visit date. If study drug dosing is not reinitiated within 5 weeks of the last dosing (i.e. 2 weeks after the next scheduled dosing date), the patient will not be included in the per-protocol population but may continue in the study, per the investigator's discretion, in the intent-to-treat population. In the event of any non-hematological 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, with the exception of dose reductions due to neurotoxicity (see Table 3.4.1.2).

Reinitiation of ABI-007 dosing after a Hematological Adverse Event:

ABI-007 dosing may not be reinitiated after any hematological adverse event, until absolute neutrophil counts are $\geq$1.5 x 10^9 cells/L and platelets have returned to $\geq$100 x 10^9 cells/L. Weekly monitoring of hematology labs will be analyzed if the ANC and/or platelet count drops below these criteria. Samples should be collected and sent to the central lab for analysis although the central lab results do not have to be available prior to dosing, as dosing may be determined by local lab results.

G-CSF/Dose Reductions for Hematologic Toxicity:

Table 3.4.1-1 provides a guideline for the use of G-CSF and for implementing dose reductions for hematologic toxicity.

TABLE 3.4.1-1: USE OF G-CSF AND DOSE REDUCTIONS FOR HEMATOLOGIC TOXICITY IN SUBJECTS RECEIVING ABI-007

Adverse Event	Occurrence	Action to be Taken
ANC < 0.5 x 10^9cells/L (nadir count) without neutropenic fever*	1st Occurrence	No action to be taken
	Recurrence	Dose reduction to next lower level
ANC < 0.5 x 10^9cells/L (nadir count) with neutropenic fever*	1st Occurrence	G-CSF rescue may be administered if neutropenic fever and/or sepsis occurs. For subsequent cycles, at the discretion of the investigator, either: (a) the same dose is maintained with prophylactic G-CSF, or (b) dose is reduced to the next lower level.
	Recurrence	Dose reduction to next lower level
Thrombocytopenia Grade 3 or Grade 4	1st Occurrence	Dose reduction to next lower level
	Recurrence	Dose reduction to next lower level

- Investigator may administer antibiotics as a prophylactic measure.

Dose Reductions for Non-hematologic Toxicity:

Table 3.4.1-2 provides a guideline for dose reductions for non-hematologic toxicity.

TABLE 3.4.1-2: DOSE REDUCTIONS FOR NON-HEMATOLOGIC TOXICITY

Adverse Event	Occurrence	Action to be Taken
Grade 3 or 4 Neurotoxicity	1st Occurrence	Dose reduction to next lower level
	Recurrence	Dose reduction to next lower level
Any other Grade 3 or 4 non-hematologic toxicity excluding alopecia	1st Occurrence	Dose reduction to next lower level
	Recurrence	Dose reduction to next lower level

Discontinuation from Study:

If a Grade 3 or 4 adverse event (excluding alopecia) recurs after the dose has been reduced to 180 mg/m^2, the patient will be discontinued from the study unless at the discretion of the investigator there is continuing benefit to the patient.

Treatment Arm B (TAXOL):

Patients randomized to Treatment Arm B will be dosed intravenously with 175 mg/m^2 TAXOL administered over approximately 3 hours. Cycles of therapy will be repeated at three-week intervals. A minimum of two cycles of therapy will be given to adequately assess the response to treatment and a maximum of six cycles will be administered. Patients who complete 6 cycles of therapy and do not have progressive disease will be able to continue treatment at three week intervals at the investigator's discretion, provided the withdrawal criteria as defined in Section 3.3.4 have not been met.

Dose adjustments for patients receiving TAXOL 175 mg/m^2 and experiencing adverse events or SAEs will be made according to the TAXOL package insert authorized in the country in which the study is being conducted (Appendix D).

3.4.2 Concomitant Medications and Non-Drug Therapies

Since ABI-007 is a formulation containing paclitaxel, the potential drug-drug interactions precautions contained in the TAXOL package insert will be applied to this study (See Appendix D for the US TAXOL package insert). Specifically, the metabolism of TAXOL is catalyzed by cytochrome P450 isozymes CYP2C8 and CYP3A4. Caution is recommended when administering TAXOL concomitantly with substrates or inhibitors of the cytochrome P450 isozymes CYP2C8 and CYP3A4. The TAXOL package insert also cautions for potential interactions between paclitaxel, a substrate of CYP3A4 and protease inhibitors (ritonavir, saquinavir, indinavir, and nelfinavir), which are substrates and/or inhibitors of CYP3A4 and have not been evaluated in clinical trials. Finally, the TAXOL package insert states that reports in the literature have suggested that plasma levels of doxorubicin (and its active metabolite doxorubicinol) may be increased when paclitaxel and doxorubicin are used in combination.

Patients must be made aware that the following medications are not allowed to be taken

concomitantly with ABI-007 monotherapy: ritonavir, saquinavir, indinavir, nelfinavir and doxorubicin, as well as any taxane, anthracycline, anti-cancer drug or other investigational study drug.

In the Phase I and Phase II clinical studies of ABI-007, no steroidal premedication for hypersensitivity reactions was necessary. No steroidal premedication is to be given to patients in Treatment Arm A, unless the Principal Investigator or designee deems it necessary. If the investigator chooses to premedicate with an anti-emetic/anti-nauseant to prevent nausea and vomiting, medications such as Kytril and Compazine are suggested.

Prior to administration of TAXOL, the Investigator should review the Dosage and Administration section of the TAXOL package insert authorized in the country in which the study is being conducted (Appendix D). All patients should be pre-medicated prior to TAXOL administration in order to prevent severe hypersensitivity reactions. For example, such pre-medication may consist of dexamethasone 20 mg PO administered approximately 12 and 6 hours before TAXOL; diphenhydramine (or its equivalent) 50 mg IV 30 to 60 minutes prior to TAXOL; and cimetidine (300 mg) or ranitidine (50 mg) IV 30 to 60 minutes prior to TAXOL.

Hypersensitivity to TAXOL has been attributed to Cremophor in the product, and is not therefore expected with ABI-007. However, if the patient experiences a typical TAXOL hypersensitivity reaction manifested by flushing, lower back pain, and chest tightness, they should have their infusion stopped immediately. At the discretion of the Principal Investigator or his designee, the patient may be rechallenged following adequate premedication with diphenhydramine 50 mg IV, cimetidine 300 mg IV, and dexamethasone 10-20 mg IV.

Growth factors may be used in Treatment Arm A (ABI-007) under circumstances described in Section 3.4.1 (Study Drug and Dosages). If indicated, growth factors may be used in Treatment Arm B (TAXOL) and should be administered as described in the TAXOL package insert authorized in the country in which the study is being conducted (Appendix D). If growth factors are administered, the product and dose must be documented on the concomitant medication case report form.

If a patient develops neutropenia after receiving study drug, investigator may administer antibiotics as a prophylactic measure. All medications administered to patient (e.g. growth factors, antibiotics, etc.) must be recorded on the concomitant medication case report form.

3.5 Pharmacokinetic Evaluations

Only patients in Treatment Arm A (ABI-007) will be included in the pharmacokinetic evaluations. PK studies will be conducted in the first treatment cycle only and will include 12 patients receiving ABI-007 from multiple sites in this study. These patients will be assigned directly to ABI-007 and not be included in the analyses of randomized patients.

For patients receiving ABI-007, whole blood samples (~5 ml) in EDTA containing tubes will be obtained during and after the 30 minute IV infusion at the following time points: 0, 15, 30 (end of infusion), 45 minutes; 1 hour, 1.25, 1.5, 2, 3, 4, 6, 9, 12, 15, 24, 36, 48, 60, and 72 hours post dose (n = 19 samples/dose). Urine samples collected following ABI-007 administration: pre-dose, 0-6,

6–12, 12–24, 24–48, 48-72, 72-96, and 96-120 hours post dose (n = 8 samples/dose).

All feces should be collected following ABI-007 administration from 0 - 5 days (120 hours); if the patient does not have a bowel movement on day 5, feces should be collected at the next bowel movement.

4. STUDY DRUG MANAGEMENT

4.1. Packaging, Labeling, and Storage of Study Drug

ABI-007 will be supplied by the sponsor, ABI, in single-use vials. Each single-use 50 mL vial will contain 100 mg paclitaxel and Human Albumin (HA) as a stabilizer. Each vial will be labeled according to country-specific regulatory requirements for labeling of investigational products. Unreconstituted ABI-007 should be stored at controlled room temperature (15°C -30°C or 59°F-86°F) and reconstituted ABI-007 must be refrigerated at 2°C-8°C (36°F-46°F) for a maximum of 8 hours. Both forms should be stored in an area free of environmental extremes and must be accessible only to study personnel.

ABI, the study sponsor, will provide TAXOL, which is to be supplied from the hospital pharmacy when possible; otherwise, TAXOL will be sent to study sites when ABI-007 is supplied. The hospital pharmacy will store TAXOL as per label instructions and must not, in any event, store TAXOL at temperatures greater than 25°C (77°F). In addition, the hospital pharmacy will retain the TAXOL vials in the original package to protect them from light. Once reconstituted, TAXOL should be stored at 25°C (77°F) for a maximum of 27 hours.

Temperature records for both ABI-007 and TAXOL must be made available to the American BioScience, Inc. or sponsor-nominated Contract Research Organization (CRO) monitoring teams for verification of proper study drug storage.

If storing reconstituted ABI-007 sample, some settling may occur. Ensure complete re-suspension by mild agitation prior to use.

Only completely unused study drug vials should be retained by the site until a representative from American BioScience, Inc. or sponsor-nominated CRO has completed an inventory. Partially used and completely used vials should be discarded according to the site's guidelines, and their disposition should be recorded on the Investigational Drug Accountability Record Form.

The investigator, or designee, shall record the dispensing of study drug to patients and any remaining study drug after dosing in a study drug accountability record. The study drug record will be made available to American BioScience, Inc. or authorized sponsor representative monitoring personnel for the purpose of accounting for the study drug supply. Inspections of the study drug supply for inventory purposes and assurance of proper storage will be conducted as necessary. Any significant discrepancy will be recorded, reported to American BioScience, Inc. or sponsor-nominated CRO and a plan for resolution will be documented.

Study drugs will not be loaned or dispensed by the investigator to another investigator or site not specified on the FDA Form-1572.

4.2. Receipt and Return of Study Drug

Upon receipt of the study drug supplies, the investigator or designee will conduct an inventory and sign both copies of the study drug receipt and forward one copy to the address indicated on the form. One copy of the receipt and the packing slip must be retained in the investigator's regulatory file records. In instances where the TAXOL is being provided by the hospital pharmacy, the investigator or designee will maintain detailed drug receipt and return records detailing TAXOL receipt.

A representative from American BioScience, Inc. or sponsor-nominated CRO will inspect the study drug inventory, and will arrange for the return of any remaining unused study drug. No study drug may be returned without the representative from American BioScience, Inc. or sponsor-nominated CRO first inspecting the study drug inventory.

4.3. Study Medication Dispensing and Accountability

NOTE: It is not a requirement to use filter needles in the preparation of, or in-line filters during the administration of ABI-007. In any event, filters of pore-size less than 15 micrometers must not be used.

ABI-007 will be reconstituted by appropriate study personnel and administered to the patient in the study site setting at 3-week intervals. The investigator will calculate the body surface area (BSA) of the patient in order to determine the total amount (mg) of paclitaxel to be administered.

Reconstitution and use of ABI-007:

1. Calculate the patient's body surface area prior to each cycle by using the formula provided in the study manual. The upper limit for BSA is 2 m^2. When calculating the dose of ABI-007 to be administered, BSA=2 will be used for all BSAs>2.
2. Calculate the total dose (in mg) to be administered by:

   Total Dose (mg) = BSA x 260 mg/m^2
3. Calculate the total number of vials required by:

   $$\textbf{Total Number of Vials} = \frac{\textbf{Total Dose (mg)}}{\textbf{100 (mg/vial)}}$$

   Round up the number of vials to be reconstituted to the next higher whole number when a fractional number of vials is obtained by the above formula (e.g. if the total number of vials = 4.05 or 4.5, then 5 vials would be reconstituted).
4. Using sterile technique, prepare the vials for reconstitution.
5. Swab the rubber stoppers with alcohol.
6. Reconstitute each ABI-007 vial by using a 50 or 60 cc sterile syringe to inject 20 mL of 0.9% Sodium Chloride Injection, USP or equivalent into each vial over a period of not less than one minute (Note: Change the syringes after reconstituting every three vials.).

- **Slowly** inject the 20 mL of 0.9% Sodium Chloride Injection, USP, over a minimum of one minute, using the sterile syringe directing the solution flow onto the **inside wall** of the vial.
- **DO NOT INJECT** the 0.9% Sodium Chloride Injection, USP solution directly onto the lyophilized cake as this will result in foaming.
- Once the injection is complete, allow the vial to sit for a **minimum of five (5) minutes** to ensure proper wetting of the lyophilized cake/powder.
- **Gently** swirl and/or invert the vial **slowly** for at least **two (2) minutes** until complete dissolution of any cake/powder occurs. **Avoid** generation of foam.
- Each mL of reconstituted product will contain 5 mg of paclitaxel.

7. Calculate the exact total dosing volume of 5 mg/mL suspension required for the patient:

   Dosing volume (mL) = Total dose (mg) / 5 (mg/mL)

8. The reconstituted sample should be milky and homogeneous without visible particulates. If unsuspended powder is visible, the vial should be **gently** inverted again to ensure complete resuspension, prior to use.
9. Once the exact volume of reconstituted ABI-007 has been withdrawn from the vials, discard any excess solution left over in accordance with standard operating procedures.
10. Inject the calculated dosing volume of reconstituted ABI-007 suspension into an empty sterile, standard PVC IV bag using an injection port. Inject perpendicularly into the center of the injection port to avoid dislodging plastic material into the IV bag. Repeat steps 10 and 11 until the patient's entire required dose is injected into the IV bag.
11. Administer the calculated dosing volume of reconstituted ABI-007 suspension by IV infusion over 30 minutes. The use of in-line filters are not necessary. If used, in-line filters with pore sizes of < 15μ should not be used.
12. The reconstituted suspension should be used immediately. If not used immediately, reconstituted ABI-007 may be stored in a refrigerator for not more than 8 hours.
13. For TAXOL: See TAXOL package insert authorized in the country in which the study is being conducted (Appendix D) for section "Preparation for Intravenous Administration" and "Stability" of reconstituted TAXOL solution. For example, the US package insert states:
    - TAXOL must be diluted prior to infusion.
    - TAXOL should be diluted in 0.9% Sodium Chloride Injection, USP; or 5% Dextrose Injection, USP; or 5% Dextrose and 0.9% Sodium Chloride Injection, USP; or 5% Dextrose in Ringer's Injection to a final concentration of 0.3 to 1.2 mg/mL.
    - Upon preparation, solutions may show haziness, which is attributed to the formulation vehicle. No significant losses in potency have been noted following simulated delivery of the solution through IV tubing containing an in-line (0.22 micron) filter.
    - Use reconstituted TAXOL solution, stored at ambient temperature (25^{o}C) within 27 hours of reconstitution.

4.4. Treatment Adherence

Patients will be dosed at the study site in the presence of study personnel, and dosages will be delivered by intravenous infusion. Therefore, issues of patient treatment compliance are minimized for this study. The procedures outlined in Section 4.1 will be conducted to ensure drug accountability.

5. MEASUREMENTS AND EVALUATIONS

5.1. General Considerations

Informed consent will be obtained prior to any study procedures being performed, including the washout period for any patient who is engaged in the washout for the sole purpose of possible inclusion into this trial. Each participant will be given a copy of the signed informed consent form. The informed consent form must be approved by an Institutional Review Board or Ethics Committee (IRB/EC) and by an American BioScience, Inc. or sponsor-nominated CRO representative.

A complete medical history (including specific information regarding any prior anthracycline-related cardiac abnormality) and physical examination will be conducted on each patient for a review of systems and determination of any concurrent symptoms or conditions prior to the first dose of study drug.

Routine study evaluations will be conducted to monitor for existing adverse events and the development of new adverse events. Study site personnel will ask patients the following questions:

- Have you had any (other) medical problems since your last study visit?
- Have you taken any new medicines, other than those given to you for this study, since your last study visit?
- Have any new procedures been performed since your last study visit?

In addition, patients are to be encouraged to call the site to self-report any unexpected symptoms or problems they encounter between study visits.

Medical symptoms or conditions present at or before study drug administration that manifest with the same intensity or frequency subsequent to study drug administration do not need to be recorded as adverse events in the CRF. However, any pre-existing condition that presents with increased intensity or increased frequency following study drug administration, or any exacerbation of an event that is present at the time of study drug administration, should be considered an adverse event. All adverse events occurring from initial dosing through study end, inclusive, should be followed by the investigator until they are resolved or stabilized, the patient is lost to follow-up, or the event is otherwise explained. All adverse events must be completely and promptly recorded in the patient's source document (e.g., patient hospital records, patient clinic charts, and laboratory reports) and on the CRF (see Section 10.4). Note that individual signs/symptoms should not be recorded in the CRF as adverse events. If a unifying diagnosis is known, it is the diagnosis, which

should be recorded as the adverse event.

Clinically significant laboratory abnormalities present at the Baseline Visit will be recorded as pre-treatment signs and symptoms. After study treatment administration, Grade 1 and Grade 2 laboratory abnormalities will not be recorded as adverse events unless considered clinically significant by the investigator. All Grade 3 and Grade 4 laboratory abnormalities will be recorded as adverse events. Grade 4 laboratory abnormalities will be reported as serious *except* in those cases when the abnormality is associated with a clinical diagnosis that has already been recorded as a SAE. For example, if a Grade 4 elevated amylase occurs with the clinical diagnosis of pancreatitis for which the patient is hospitalized, the laboratory abnormality does not need to be recorded as a SAE because the clinical event will be recorded as a SAE.

Each investigator is responsible for assessing the clinical significance of all abnormal laboratory values using the NCI Toxicity Criteria Scale (provided in Appendix A), where applicable. It is also the responsibility of the investigator to assess the clinical significance of all abnormal laboratory values as defined by the list of normal values provided by the local and/or central laboratory. All abnormal laboratory tests that are judged to be at least possibly drug related, or clinically relevant abnormal laboratory tests of uncertain causality, must be repeated. Any abnormal values that persist should be followed at the discretion of the investigator. In some cases, significant changes within the range of normal values will require similar judgment.

All CBC, differential, platelet count, and serum chemistry evaluations will be performed by central laboratories. Results for Week 0 should be obtained from the central laboratory prior to initial dosing. For all subsequent visits, dosing may commence based upon acceptable local labs results; it is not a requirement that the results from the central labs be available prior to dosing. At weeks 3, 6, 9, 12, and 15, if time does not permit central lab results to be obtained prior to dosing, duplicate samples may be collected for analysis by local lab and all dosing decisions will based from local lab results; however samples must also be sent to central laboratory for evaluation. The lab tests (local and central) must be performed and evaluated within 72 hours prior to each dosing. Central laboratory evaluations should also occur at 14 days ($\pm$2 days) after each course, and at the EOS visit. Additional clinical laboratory tests should be performed as clinically indicated during the cycle of the study and sent to the central lab for analysis as an unscheduled visit. Any additional central laboratory tests that are not protocol-defined must be approved by American BioScience, Inc. or sponsor-nominated CRO Clinical Research Associate, Clinical Project Manager, or designee.

5.2. Time and Events Schedule

An overview of the schedule of study assessments is provided in Table 5.2.

TABLE 5.2: SCHEDULE OF ASSESSMENTS

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[j]	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 $\geq 1.5 \times 10^9$ cells/L and platelets have returned to $\geq 100 \times 10^9$ 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.

5.2.1 Baseline Evaluations

Baseline evaluations will be performed for all patients to determine study eligibility. These evaluations must be completed within 21 days of the initiation of study drug dosing. Any questions regarding patient eligibility should be directed to American BioScience, Inc. for written approval.

Patients who have received any anthracycline must have an interval of four weeks between the last dose of anthracycline and the first dose of study drug. Patients who have received an investigational drug must have a washout period of four weeks before the first dose of study drug is administered. The investigator will document the designated washout period in the patient's source documentation.

The following clinical evaluations will be performed at Baseline after informed consent has been obtained:

- Medical history (including specific information regarding any prior anthracycline-related cardiac abnormality);
- Prior medication evaluation (only medications taken within 30 days before the Baseline Visit will be recorded);
- Physical examination, weight;
- Vital signs;
- Echocardiogram/MUGA (if clinically indicated, see Table 5.2);
- 12 lead EKG;
- ECOG (Zubrod) performance status scale;
- European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 (Appendix G);
- Peripheral neuropathy assessment (physician and patient assessment);
- Chest X-ray, followed by CT scan of the thorax if any positive findings on the chest X-ray;
- Bone scan with X-rays of all areas of bone metastases identified from the bone scan;
- Imaging studies to determine the extent of the tumor [includes CT of head (only if symptomatic of brain metastasis) and CT of liver/abdomen];
- CBC, differential, platelet count panels, and clinical chemistries; and,
- Serum ß-hCG pregnancy test (for women of childbearing-potential only) will be conducted within **72-hours** of first study drug administration (negative results required for study drug administration).

The investigator will account for all patients who are screened for this study. Although CRFs will not be completed for patients who fail screening, source documents will be reviewed by the American BioScience, Inc., sponsor-nominated CRO study monitor, or independent study monitor for completion and accuracy. All appropriate CRF pages must be completed for enrolled patients.

5.2.2 Treatment Phase Evaluations

Following the Baseline visit, patients will return to the clinic within 21 days for Cycle 1 of study drug dosing. Subsequent cycles will be administered at 3-week intervals. Unless otherwise specified, all visits must occur within ± 3 days of the planned visit date. If study drug dosing is not reinitiated within five weeks (or two weeks after the next scheduled dosing date) of the last dosing, the subject will not be included in the per-protocol population, but may continue in the study, per the investigator's discretion, in the intent-to-treat population. Pharmacokinetic data will be collected on twelve patients receiving ABI-007 enrolled at multiple sites in the study.

If the investigator suspects a drug-related toxicity, an extra-unscheduled visit with additional laboratory tests may be performed. The clinic will be responsible for contacting the American BioScience, Inc. or sponsor-nominated CRO Project Manager, or designee, for approval of the additional central laboratory testing which is not protocol-specified.

Study drug must not be administered until the ANC has returned to $\geq 1.5 \times 10^9$ cells/L and platelets have returned to $\geq 100 \times 10^9$ 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 hematology labs will be conducted if the ANC and/or platelet count drops below these criteria.

The same mode of imaging must be used at Baseline and throughout the study. CT image preparation guidelines will be provided to sites by the central image reviewer and will follow the specifications provided in the RECIST guidelines[5]. CT imaging should include contrast and conventional CT should be performed with contiguous cuts of 10 mm or less in slice thickness. Spiral CT should be performed by use of a 5 mm contiguous reconstruction algorithm.

Vital signs during study drug dosing. For both ABI-007 and Taxol, vital signs will be taken at 15 and 1 minutes prior to dosing; during study drug dosing at 5 and 20 minutes after start of infusion and at the end of the infusion; if infusion continues to 40 minutes for ABI-007, then vital signs will be taken again 40 minutes after start of ABI-007 infusion. Post study drug administration, vital signs will be taken again at 15 and 30 minutes after the end of infusion.

5.2.2.1 Week 0/Cycle 1, Week 3/Cycle 2, Week 6/Cycle 3, Week 12/Cycle 5

The following evaluations will be performed prior to dosing:

- Concurrent medications evaluation;
- Concurrent procedures evaluation;
- Physical examination/vital signs;
- ECOG (Zubrod) scale;
- EORTC QLQ-C30 (Appendix G, cycle 3 only);
- Peripheral neuropathy assessment (physician and patient assessment);
- Adverse event evaluation;

- Assessment of toxicities;
- CBC, differential, platelet count, and clinical chemistry panel [perform and evaluate locally within 72 hours prior to dosing, duplicate samples should be sent to the central laboratory for analysis. Exception: For cycle 1 only, the labs may be performed and evaluated (by the central laboratory only) up to seven days prior to the first dose.

5.2.2.2 Week 2, Week 8, Week 11, Week 14, Week 17

The following evaluations will be performed at 14 days post dose (± 2 days):

- CBC, differential and platelet count (central laboratory only)

5.2.2.3 Week 5

The following evaluations will be performed:

- Chest X-ray (optional unless clinically indicated, if positive perform CT of Thorax);
- X-ray of positive bone scans;
- Imaging studies of tumor (limited to sites of pre-existing metastasis at baseline or to new sites suspected to contain metastasis);
- CBC, differential and platelet count (central laboratory only)

5.2.2.4 Week 9/Cycle 4

The following evaluations will be performed prior to dosing:

- Concurrent medications evaluation;
- Concurrent procedures evaluation;
- Physical examination/vital signs;
- ECOG (Zubrod) scale;
- EORTC QLQ-C30 (Appendix G);
- Peripheral neuropathy assessment (physician and patient assessment);
- Adverse event evaluation;
- Assessment of toxicities;
- Echocardiogram/MUGA (if clinically indicated);
- Chest X-ray (optional unless clinically indicated, if positive perform CT of Thorax);
- X-ray of positive bone scans;
- Imaging studies of tumor (limited to sites of pre-existing metastasis identified at baseline or to new sites suspected to contain metastasis);
- CBC, differential, platelet count, and clinical chemistry panel (perform and evaluate locally within 72 hours prior to dosing, duplicate samples should be sent to the central laboratory for analysis).

The same mode of imaging must be used at Baseline and throughout the study.

Changes in tumor size will be evaluated by the following formula when determining complete or partial response:

[(Post value – Baseline value)/Baseline value] x 100

Changes in tumor size will be evaluated by the following formula when determining stable or progressive disease:

[(Post value – Smallest value since treatment started)/Smallest value since treatment started] x 100

5.2.3 EOS Phase Evaluations (Week 15/Withdrawal)

An EOS evaluation should be performed at Week 15 for patients who complete the study and at least four weeks after initial dose for patients who withdraw early after cycle 2 (so that CR or PR could possibly be obtained). Confirmation for patients achieving stable disease will be performed at least 6 weeks after baseline. For subjects who withdraw before cycle 2 is administered, EOS assessments should be performed as soon as possible. EOS evaluations include (perform evaluations prior to dosing for subjects that are dosed at cycle 6):

- Concurrent medications evaluation;
- Concurrent procedures evaluation;
- Physical examination/vital signs (collect vital signs at the time points detailed in section 5.2.2 for patients who complete the study, collect once only for patients who are withdrawn);
- ECOG (Zubrod) scale;
- EORTC QLQ-C30 (Appendix G);
- Peripheral neuropathy assessment (physician and patient assessment);
- Adverse event evaluation;
- Assessment of toxicities;
- Echocardiogram/MUGA (if clinically indicated);
- Chest X-ray (if positive perform CT of Thorax);
- X-ray of positive bone scans;
- Imaging studies of tumor (must include CT of Liver/Abdomen in addition to sites of pre-existing metastasis or new sites suspected to contain metastasis);
- CBC, differential, platelet count, and clinical chemistry panel (perform and evaluate locally within 72 hours prior to dosing, duplicate samples should be sent to the central laboratory for analysis);
- Serum ß-hCG pregnancy test (for women of childbearing-potential only).

The investigator must follow all SAEs observed during the study until these events have resolved or stabilized, the patient is lost to follow-up, or the events are otherwise explained. The investigator should report these SAEs in accordance with the procedures described in section 10.4. Clinical laboratory tests may be repeated during the post-treatment period if clinically indicated.

5.2.4 Continued Therapy after Week 15/Cycle 6

Only patients who complete 6 cycles of therapy and do not have progressive disease will be able to continue their arm of treatment (ABI-007 or TAXOL). This will be at the investigator's discretion, provided the withdrawal criteria as defined in Section 3.3.4 have not been met.

Patients will receive continued therapy at three week intervals, starting at week 18 and will receive ABI-007 or TAXOL as specified in Section 3.4.1. Restaging and disease evaluation should be performed after the completion of every second cycle of treatment beyond Cycle 6, i.e., Week 23 – Cycle 8, Week 29 – Cycle 10. In addition, the following evaluations will be performed prior to dosing at each cycle:

- Concomitant medication
- Physical examination
- Adverse event evaluation;
- Assessment of Toxicities;
- CBC, differential, platelet count, and clinical chemistry panel (central lab required and local lab as needed for dosing decisions).

Patients will be withdrawn from continued treatment if one or more of the criteria for withdrawal, specified in Section 3.3.4, have been met. When a patient is withdrawn from continued therapy, they will undergo follow-up evaluations 30 days ± 2 days after final study drug administration and every three months thereafter by phone as specified in Section 5.2.5 month for the first three months after completion/withdrawal from this study and every three months thereafter by phone as specified in Section 5.2.5.

5.2.5 Follow-up Evaluations

Follow-up evaluations should occur 30 days ± 2 days of final study drug administration and include the following assessments:

- Concomitant medication evaluation;
- Concomitant procedure evaluation;
- Physical examination/vital signs;
- ECOG (Zubrod) scale;
- EORTC QLQ-C30 (Appendix G);
- Peripheral neuropathy assessment (physician and patient assessment);
- Adverse event evaluation;
- Assessment of toxicities;
- Echocardiogram/MUGA (if clinically indicated);
- CBC, differential, platelet count, and clinical chemistries;
- 12 Lead EKG.

Patient status will continue 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. Patients should supply their Social Security Number and the names and addresses of three contact people whom the site may contact to assist the site in conducting the Phone Follow-Up evaluations. In the event that the patient cannot be reached by telephone, post-study survival data may also be obtained by patient visits to the site or source documents from other doctor visits.

5.2.6 Pharmacokinetic Evaluations

A subset of 12 patients undergoing treatment with ABI-007 will also have blood, urine, and feces collected to determine drug pharmacokinetics (PK), including elimination rate constant, half-life, volume of distribution, C_{max}, $T_{max,}$ AUC_{inf}, clearance, urinary clearance, and excretion. Multiple sites may be used to perform the pharmacokinetic sub-study.

For patients receiving ABI-007, whole blood samples (~5 ml) in EDTA containing tubes will be obtained during and after the 30 minute IV infusion at the following time points: 0, 15, 30 (end of infusion), 45 minutes; 1 hour, 1.25, 1.5, 2, 3, 4, 6, 9, 12, 15, 24, 36, 48, 60, and 72 hours post dose (n = 19 samples/dose). Urine samples collected following ABI-007 administration: pre-dose, 0-6, 6–12, 12–24, 24– 48, 48-72, 72-96, and 96-120 hours post dose (n = 8 samples/dose). All feces should be collected following ABI-007 administration from 0 - 5 days (120 hours); if the patient does not have a bowel movement on day 5, feces should be collected at the next bowel movement.

6. ADVERSE EVENT MANAGEMENT GUIDELINES

The adverse event management guidelines are intended to ensure the safety of each patient while attempting to characterize the safety and tolerability of the test products. Questions regarding toxicity management should be directed to American BioScience, Inc. (refer to Appendix B for guidelines for reporting AEs).

Adverse events occurring during the study will be graded according to the NCI Toxicity Criteria Scale (provided in Appendix A), where applicable. Adverse events that are not included on the toxicity scale will be designated as Grade 1 = mild, Grade 2 = moderate, Grade 3 = severe, and Grade 4 = life-threatening.

The investigator should evaluate all adverse events and should make an immediate effort to determine their etiology. Adverse events that are determined *not* to be possibly, probably, or definitely related to study drug may not require further evaluation.

Study medications may be interrupted for an adverse event at the discretion of the investigator. Patients requiring toxicity management should be assessed and evaluated at least weekly as indicated by the severity of the event.

7. DATA MONITORING COMMITTEE

The Data Monitoring Committee (DMC) will be established with responsibilities for safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the trial, and for monitoring the overall conduct of the clinical trial. The DMC will provide recommendations about stopping or continuing the trial. To contribute to enhancing the integrity of the trial, the DMC may also formulate recommendations relating to the management of participants, improving adherence to protocol-specified regimens and retention of participants, and the procedures for data management and quality control.

While it is not anticipated that the DMC will provide recommendations for early termination due to overwhelming evidence of benefit or lack of benefit, the committee will have access to interim efficacy as well as safety data to enable them to make a judgment about the emerging benefit-to-risk profile, in the event that important adverse events are identified during the review of safety data.

The DMC will be advisory to the clinical trial leadership group. This leadership group will be responsible to promptly review the DMC recommendations, to decide whether to continue or terminate the trial, and to determine whether amendments to the protocol or changes in study conduct are required.

It is assumed that the DMC will meet on one or two occasions. The first review is expected to occur after completion of enrollment of 105 evaluable patients into each treatment arm of the trial. A second review, if necessary, will occur mid way between the first review and the planned time of trial completion.

The DMC is an independent multidisciplinary group consisting of a biostatistician and clinicians that, collectively, has experience in the management of breast cancer patients and in the conduct and monitoring of randomized clinical trials.

The DMC membership has been restricted to individuals free of apparent significant conflicts of interest. The source of these conflicts may be financial, scientific or regulatory in nature. Thus, neither study investigators nor individuals employed by the sponsor, nor individuals who might have regulatory responsibilities for the trial products, are members of the DMC.

8. DATA COLLECTION AND HANDLING PROCEDURES

All data will be recorded on the Case Report Forms (CRFs) provided by American BioScience. Inc.. Data on the CRFs must be marked or printed legibly in black ink. Data errors on the CRFs should be corrected by drawing a line through the error, and the correction should be initialed and dated by the appropriate study site personnel. Corrections should also be explained where necessary. Missing values should be distinguished from a value of zero, or characteristic absent. Any information requested that is not obtained as specified in the protocol should be verified unknown by initialing and dating. Patients will not be identified by name on any of the case report forms, rather, they will be identified by initials and an assigned identification number.

The investigator will allow representatives of the sponsor, CROs conducting the study, regulatory agencies, and their designees to inspect all study documents (including, but not limited to, consent forms, study drug accountability forms, IRB/EC approvals) and pertinent hospital or clinic records for confirmation of data throughout and after completion of the study. Monitoring visits will be conducted approximately every 4 to 6 weeks, or more frequently, as needed, during the course of the study. Sites that experience particularly high enrollment may have more frequent monitoring visits scheduled in order to obtain information in a timely manner. A monitoring visit will be scheduled upon enrollment and first study drug dosing of the first patient at a study site to verify that the sites are adhering to the protocol and all regulatory requirements. One hundred percent review of source documentation of key efficacy and safety data will be conducted at each monitoring visit for verification that all information recorded in the CRF accurately reflects the data recorded in the patient's source document.

All data verification, using hospital or clinic records, will be performed respecting patient confidentiality. A copy of the original CRF and any CRF updates will remain at the investigational site upon final query resolution.

The “Subject Assessment of Peripheral Neuropathy (FACT),” CRF pages 13, 23, 31, 43, 53, 66, 74, and 88 is to be completed by the patient and the answers recorded directly on the CRF. The site personnel are to complete the header information and the date of assessment.

Each CRF must be filled in completely and neatly with a black-inked ballpoint pen. At the admission visit, the Principal Investigator must sign off on the Subject Eligibility CRF. The final authorization of the CRF data is the End of Study Record form. This form must be signed and dated by the Principal Investigator to signify that he/she has reviewed the CRF booklet, including all laboratory and safety assessments, and that all of the data therein is complete and accurate. Data collected on the CA012-0 CRF will be double data entered into a validated database by inGenium Research, Inc, a data management and statistical CRO delegated by American BioScience, Inc.

Once the CRFs are received by inGenium Research, Inc., the data will be validated to ensure that the forms were completed properly and that all data is in range, per the validation specifications. Any data that is flagged from the validation process will be processed as a data query for resolution to be compared against source documentation. Data updates that result from queries will not be applied to the CRF copy at the site; rather the site will maintain the query resolution report with the subject’s clinical trial file, in the form of a Data Clarification Form (DCF). An electronic audit trail will document any changes to original data entered in the clinical database versus query resolution data entered at a later time. Investigators will sign-off on all data changes that occur on a DCF after the data has been collected from the trial site in the form of a CRF.

Each page of the CRF is logged in and double data entered by inGenium Research, Inc.

A Master Log will be maintained at inGenium of all CRF pages received and entered in the clinical trial database.

Data entered will be validated on two levels, electronic and manual. Electronic range and

consistency checks are applied to non-text fields to ensure internal consistency among data collected within any one CRF and across CRFs. Errors detected during validation are corrected by one of two methods, in-house convention and investigator query. Errors can be corrected in-house if there is only one possible correct response. Other errors are corrected through the process of sending queries to clinical trial sites. The corrected file and documentation of validation steps are retained as an integral part of the clinical trial record.

All data modifications to the database are recorded electronically to provide an electronic audit trail. A Data History table in the clinical trial database records the following information for all data changes:

- User ID who made the change
- CRF ID for CRF that was changed
- Data field on CRF that was changed
- Old value and new value in the data field
- Date of change
- Stated reason for change

9. STATISTICAL METHODS

9.1. Analyses of Data

9.1.1. Patient Characteristics and Accountability

Patient characteristics, including disease duration and severity at baseline, demographics, and relevant medical history, will be summarized for the purposes of (I) characterizing the patient population; and (II) establishing baseline comparability between the randomized treatment groups. Appropriate analysis-of-variance and categorical analysis methods will be used for the treatment group comparisons of these results. Descriptive summaries, including mean, standard deviation, frequency distributions, etc., as appropriate, will be presented for each randomized group.

Enrollment rates will be tabulated by study site. Patients who fail to meet all eligibility criteria will be listed with the unmet criteria. Patients who discontinue from the study prematurely will be listed with the reason for premature discontinuation, and reasons will be tabulated for all patients.

Patients who are withdrawn from this study secondary to a laboratory toxicity or adverse event should be followed by the investigator until the abnormality is resolved or stabilized, the patient is lost to follow-up, or the event is otherwise explained.

9.1.2. Efficacy Analyses

9.1.2.1 Primary

The null hypothesis is that ABI-007 patients have a response percentage that is no larger than 75% of the response percentage of TAXOL. Response is defined as the percent of patients with

metastatic breast cancer, who achieve complete or partial response for target lesions after at least two cycles of treatment. Response will be determined according to Response Evaluation Criteria in Solid Tumors guidelines[5]. Complete response is defined as disappearance of all clinical evidence (confirmed radiologically or by physical examination) of visible tumor. Partial response 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 ≥ four weeks.

The null hypothesis will be rejected if the lower bound of the 95% exact binomial confidence interval based on the difference in unadjusted response percentages ($p_A - 0.75p_T$) is positive (non-inferiority alternative). p_A is the observed percentage of patients treated with ABI-007 who achieve complete or partial response and p_T is the observed percentage of patients treated with TAXOL who achieve complete or partial response.

Descriptive results including counts and percentages and confidence bounds will be presented by treatment group for each country.

9.1.2.2 Secondary

If we reject the null hypothesis, we will construct a 95% 'superiority' confidence interval for the difference ($p_A - p_T$).

Other secondary analyses will include treatment group comparisons of the following:

- Time to disease progression (defined as at least a 20% increase in the sum of the longest diameter, taking as reference the smallest sum of the longest diameter recorded since the treatment started, the appearance of one or more new lesions, or the unequivocal progression of existing non-target lesions)
- Patient survival
- Percentage of patients who achieve complete or partial response for the Overall response after a minimum of two cycles of treatment
- Percentage of patients who achieve complete or partial response or stable disease for the Overall response after a minimum of two cycles of treatment
- The distribution of target lesion response and overall response at each time point where response is evaluated (weeks 5, 9, and 15)
- Factors that may influence response, including the following:
  - prior treatment for breast cancer in the adjuvant and metastatic setting
  - histology and stage at diagnosis
  - number of metastatic sites (≤ 1, ≥ 2)
  - interval from breast cancer diagnosis to most recent recurrence (< 1 year, ≥ 1 year)
  - current site(s) of relapse (visceral, bone/soft tissue)
  - hormone receptor status
- Quality of life evaluated by changes from Baseline in scores on the ECOG (Zubrod) performance status scale, EORTC QLQ-C30 and weight

Each of the secondary endpoints will be estimated and compared descriptively between treatments.

9.1.3. Populations in Analyses

The primary analysis will be based on the intent-to-treat (ITT) population. This includes all patients who were randomized and received at least one dose of ABI-007 or TAXOL after randomization. The ITT population will be the primary population for all secondary and safety analyses.

We will analyze the primary outcome variable for two other populations defined as follows:

- the all-randomized (AR) population: includes all patients who are randomized even if they are not treated or have no treatment evaluations;
- the per-protocol (PP) population: includes all patients from the ITT population that were evaluated for a response after receiving 2 cycles of study drug and have no major protocol violations;

9.1.4. Safety and Tolerance Analysis

Patients are followed in the ITT population from study drug initiation through 30 days after permanent discontinuation from the treatment regimen. Only patients with clear documentation that no study drug was administered may be excluded from the ITT population.

Safety will be evaluated by rates of premature discontinuation, adverse events, clinical laboratory measurements, prompted reporting of peripheral neuropathy by patients, EKG, echocardiogram/MUGA (if clinically indicated), physical examination (including vital signs, body weight, etc.), and % of patients with dose modifications and dose interruptions.

Incidence of treatment-emergent adverse events will be summarized for each treatment group by body system and MedDRA coding dictionary term. Treatment-emergent adverse events are defined to be adverse events that begin or worsen in severity after the start of study drug. Incidence of treatment-emergent adverse events will also be summarized by intensity and relationship to study drug. Incidence of SAEs will also be summarized. Listings will be made for subjects that discontinued due to an adverse event and for subjects with SAEs. SAEs will be described by narrative. No statistical testing will be performed on adverse events.

Safety laboratory (chemistry, hematology) mean changes from baseline to 3, 6, 9, 12, and 15 Weeks, and final evaluation will be analyzed, comparing treatments, using an ANOVA with treatment as the factor. To test for changes from baseline within treatments, a paired t-test will be performed at each evaluation. Laboratory shifts from baseline to final evaluation will be summarized for both treatment groups using normal ranges to define categories (low, normal, and high). Potentially clinically significant values that occur after the start of treatment will be listed. Each laboratory result will be flagged in data listings as low (L, L1, L2, L3, L4), high (H, H1, H2, H3, H4), or normal (N) based on the laboratory's normal range and the NCI Toxicity Criteria Scale (Appendix A).

The evaluation of peripheral neuropathy events will be captured according to protocol in adverse events and SAEs reported by investigators and investigative staff. Patient self-evaluations will be obtained at Baseline, prior to each treatment cycle, and at the Follow-up visit.

All prior and concomitant medications will be coded to therapeutic drug classes and generic drug names using the World Health Organization (WHO) Drug Classification. Prior and concomitant medication usage will be summarized by therapeutic drug class and generic drug names for each treatment group. The number of patients taking any medication will also be given.

9.1.5. Pharmacokinetic Analyses

A subset of 12 patients undergoing treatment with ABI-007 will also have blood, urine, and feces collected to determine drug pharmacokinetics (PK), including elimination rate constant, half-life, volume of distribution, C_{max}, $T_{max,}$ AUC_{inf}, clearance, urinary clearance, and excretion. Multiple sites will be used to perform the pharmacokinetic sub-study.

For patients receiving ABI-007, whole blood samples (~5 ml) in EDTA containing tubes will be obtained during and after the 30 minute IV infusion at the following time points: 0, 15, 30 (end of infusion), 45 minutes; 1 hour, 1.25, 1.5, 2, 3, 4, 6, 9, 12, 15, 24, 36, 48, 60, and 72 hours post dose (n = 19 samples/dose). Urine samples collected following ABI-007 administration: pre-dose, 0-6, 6–12, 12–24, 24– 48, 48-72, 72-96, and 96-120 hours post dose (n = 8 samples/dose). All Feces should be collected following ABI-007 administration from 0 - 5 days (120 hours); if the patient does not have a bowel movement on day 5, feces should be collected at the next bowel movement.

Pharmacokinetic (PK) parameters to be determined include all volumes of distribution, elimination rate constant, half-life, C_{max}, T_{max}, AUC_{inf}, clearance and urinary clearance. Disposition and metabolism of paclitaxel in patients receiving ABI-007 will be assessed. The PK parameters for the individual data sets will be determined by non-compartmental analysis. Plots of individual patient whole-blood concentration versus time profiles will be evaluated. Mean whole-blood concentration versus time plots for all dose levels (semi-log plot) will be analyzed. A listing of PK parameters by patient number (with whole-blood clearance and volume of distribution expressed based on per m^2 body surface area and per kg body weight) will be generated.

9.2. Sample Size and Power

Phase III data on TAXOL at a dose of 175 mg/m^2 (TAXOL package insert – Appendix D) administered over 3 hours showed a response rate of 28% in patients previously exposed to 1 or 2 prior chemotherapeutic regimens (67% exposed to anthracyclines: N=471). Another Phase II study with TAXOL (+G-CSF) at a dose of 200 mg/m^2, administered over 24 hours (TAXOL package insert – Appendix D) showed a response rate of 30% (with a 95% CI of 15% to 50%) in 30 extensively pretreated patients who had failed anthracycline treatment and were exposed to at least 1 or 2 prior chemotherapeutic regimens.

The current study is designed for approximately 210 (approximately 230 enrolled) evaluable patients per treatment arm with at least 100 patients per arm that have been treated with anthracycline. The required sample size was estimated in the absence of any efficacy results from a controlled trial between ABI-007 and TAXOL. An interim analysis for the purpose of re-estimating sample size will be performed after approximately 105 patients have been treated for a minimum of two treatment cycles in each treatment arm, and have undergone the necessary tumor evaluations

for the assessment of protocol response.

The initial sample size will provide at least 80% power with a one-sided 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 percentage of TAXOL. We assume that the TAXOL response percentage is in the interval of 28% to 32% and that the ABI-007 response will demonstrate a relative improvement of 20% (i.e., 33.6% to 38.4%).

9.3. Interim Analyses

An interim analysis for the purpose of re-estimating sample size will be performed after approximately 105 patients have been treated for a minimum of two treatment cycles in each treatment arm, and have undergone the necessary tumor evaluations for the assessment of protocol response. Sample size re-estimation will be based on the group sequential two-sample proportion test of Cui, Hung and Wang[6].

10. ADVERSE EVENT AND SERIOUS ADVERSE EVENT REPORTING

One of the primary objectives of this study is to assess the safety of ABI-007 as compared to that of TAXOL; therefore, the investigator is responsible for recording adverse events observed during the study period, starting at initial dosing and ending 30 days after the patient discontinues the study drug. In addition, certain adverse events as described in Section 10.2 are classified as "serious" and must be reported promptly to American BioScience, Inc. The investigator should report and follow all adverse events, regardless of causality, occurring from initial dosing through study end, inclusive. The investigator should follow adverse events until they are resolved or stabilized, the patient is lost to follow-up, or the event is otherwise explained. Events occurring 30 days prior to study drug administration should be recorded as pre-treatment signs and symptoms. Patients will be instructed to phone into the site to self-report any unexpected symptom or problem between visits to be recorded as adverse events. When a diagnosis for the reported signs or symptoms is known, the investigator should report the diagnosis as the adverse event, not the symptoms.

Clinically significant laboratory abnormalities present at the Baseline visit will be recorded as pre-treatment signs and symptoms. After study treatment administration, Grade 1 and Grade 2 laboratory abnormalities will not be recorded as adverse events unless considered clinically significant by the investigator. All Grade 3 and Grade 4 laboratory abnormalities will be recorded as adverse events. Grade 4 laboratory abnormalities will be reported as serious *except* in those cases when the abnormality is associated with a clinical diagnosis that has already been recorded as a SAE. The investigator must follow all SAEs observed during the study, until these events have resolved or stabilized, the patient is lost to follow-up, or the events are otherwise explained.

Refer to Appendix B, Guidelines for Reporting Adverse Drug Reactions for more detail.

10.1 Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have a causal relationship with study treatment. Therefore, an adverse event can be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered to be related to the medicinal product.

An adverse event includes:

- an exacerbation of a pre-existing illness;
- an increase in frequency or intensity of a pre-existing episodic event or condition;
- a condition detected or diagnosed after study drug administration even though it may have been present prior to the start of the study;
- continuous persistent disease or symptoms present at Baseline that worsen following the start of the study.

An adverse event does not include:

- medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, or transfusion); the condition that leads to the procedure is an adverse event. [Procedures that occur during the trial should be recorded on the Concurrent Procedure CRF];
- pre-existing diseases, conditions, or laboratory abnormalities present or detected at the start of the study that do not worsen;
- situations where an untoward medical occurrence has not occurred (e.g., hospitalizations for cosmetic or elective surgery or social/convenience admissions);
- the disease being studied or signs/symptoms associated with the disease unless more severe than expected for the patient's conditions;
- overdose of study drug without any clinical signs or symptoms.

10.2 Definition of a Serious Adverse Event

A serious adverse event (SAE) is defined as any untoward medical occurrence at any dose that:

- is fatal;
- is life-threatening (defined as an immediate risk of death from the event as it occurred);
- results in persistent or significant disability or incapacity;
- requires in-patient hospitalization or prolongation of existing hospitalization. (Exception: Hospitalization for elective treatment of a pre-existing condition that did not worsen during the study is *not* considered an adverse event. NOTE: Complications that occur during hospitalization are adverse events and if a complication prolongs hospitalization, then the event is serious);
- is a congenital anomaly/birth defect in the offspring of a patient who received medication;

- though not included in the above definitions, may jeopardize the patient or may require intervention to prevent one of the outcomes listed above unless clearly related to current disease.

Grade 4 laboratory abnormalities will be reported as SAEs *except* in those cases when the abnormality is associated with a clinical diagnosis, which is already a documented SAE.

The investigator should exercise medical and scientific judgment when deciding whether expedited reporting is appropriate in other situations not strictly meeting the criteria outlined above. Examples of important medical events which may meet the definition of a SAE include: intensive treatment in an emergency room or at home for allergic bronchospasm, certain laboratory abnormalities (e.g., blood dyscrasias), convulsions that do not result in hospitalizations, or development of drug dependency or drug abuse. If there is any question, please consult the relevant Medical Monitor.

10.3 Lack of Efficacy as an Adverse Event or Serious Adverse Event

"Lack of efficacy" is not considered an adverse event. The signs and symptoms or clinical sequelae resulting from lack of efficacy should be reported if they fulfill the adverse event or SAE definitions.

10.4 Recording and Documenting Adverse Events and Serious Adverse Events

Patients will be instructed to phone into the site to self-report any unexpected symptom or problem between visits to be recorded as adverse advents. The investigator or designee must completely and promptly record each adverse event in the source documentation and in the appropriate CRF, regardless of relationship to study drug as determined by the investigator. The investigator should attempt, if possible, to establish a diagnosis based on the patient's signs and symptoms. When a diagnosis for the reported signs or symptoms is known, the investigator should report the diagnosis as the adverse event, not the symptoms. The Principal Investigator must assess causality for any patient treated at his/her site, or by the sub-investigator for patient(s) treated and under the direct care of said sub-investigator.

At each visit, after the patient has had an opportunity to spontaneously mention any problems, the investigator should inquire about adverse events by asking the following standard questions:

- Have you had any (other) medical problems since your last clinic visit?
- Have you taken any new medicines, other than those given to you in this study, since your last visit/assessment?
- Have any new procedures been performed since your last study visit?

In addition, patients are to be encouraged to call the site to self-report any unexpected symptoms or problems they encounter between office visits.

The investigator should follow all adverse events observed during the study until they are resolved or stabilized, the patient is lost to follow-up, or the events are otherwise explained. The investigator

should report SAEs according to the procedures described in Section 10.5.

All SAEs related to study drug should be reported to the IRB/EC within 10 working days of their occurrence except for Grade 4 myelosuppression. (See Appendix B for Guidelines for reporting Adverse Events).

10.5 Investigator Reporting of a Serious Adverse Event

All SAEs occurring at any site in all participating countries must be reported promptly to American BioScience, Inc. after the investigator recognizes/classifies the event as a SAE. The specific reporting time frame depends on the type of SAE. For life-threatening or fatal events, the investigator must report initial information on the SAE within 24 hours by phone or fax (preferably); at a minimum, a description of the event and the investigator's judgment of causality must be provided at the time of the initial report. If a SAE is reported by phone or by e-mail, the investigator must fax a completed SAE report form to American BioScience, Inc. within 24 hours. For an event that is not life-threatening or fatal, the investigator must fax a completed SAEs report form within 48 hours after he/she recognizes/classifies the event as a SAE.

For any questions regarding reporting requirements of a SAE contact one of the following individuals:

SAE COORDINATOR

[redacted]

SAFETY REVIEWER

[redacted]

10.6 Additional Investigator Responsibilities on Follow-up of Serious Adverse Events

The investigator and supporting personnel responsible for patient care should institute any supplemental investigations of SAEs based on their clinical judgment of likely causative factors. This may include extra clinical laboratory tests, physical examinations or consulting an appropriate specialist. ABI, through the designated Project Manager (ABI-US, PSI, ORION) / Study Monitor may also request the investigator to conduct supplemental assessments. The results of any additional assessments conducted must be reported to American BioScience, Inc. If a patient dies during participation in the study and an autopsy is performed, a copy of the report must be submitted to American BioScience, Inc. If a patient dies during the follow-up period, the event causing the death will be reported as a SAE. [Preferable causality as documented on Death Certificate, i.e., Primary Cause, Secondary Cause, should be specified].

10.7 IRB/EC Notification of Serious Adverse Events

The investigator is responsible for promptly notifying the IRB/EC of all SAEs, including any follow-up information, occurring at his/her site and any SAE regulatory reports and Investigational New Drug Safety Reports that he/she receives from American BioScience, Inc.

10.8 Sponsor Notification of Post-Study Serious Adverse Events

The investigator should notify American BioScience, Inc. of any death or SAE occurring after a patient has withdrawn from the study, when such death or SAE may reasonably be related to the medication used in the study. However, investigators are not obligated to actively seek adverse events in former study participants. If a patient dies during the study follow-up period, the adverse event should be captured as a SAE.

10.9 Regulatory Aspects of Serious Adverse Events Reporting

In agreeing to the provisions of this protocol, the investigator accepts all legal responsibilities for prompt notification of SAEs to American BioScience, Inc.

11. ETHICAL, LEGAL, AND ADMINISTRATIVE ASPECTS

11.1. Ethics

11.1.1. Institutional Review Board/Ethics Committee Approval

Before study initiation, this protocol and informed consent form will be submitted for review and approval to the IRB/EC charged with this responsibility. In addition, any form of proposed advertising and advertising text for patient recruitment must be reviewed and approved by American BioScience, Inc. prior to submission to the IRB/EC. The investigator will forward to American BioScience, Inc. or sponsor-nominated CRO a copy of the IRB/EC's approval of this protocol, any amendments, informed consent form, and any modifications to the informed consent, based on the FDA regulations set forth in Part 56 of Title 21 of the *Code of Federal Regulations,* as well as those of the applicable regulatory bodies in all other participating countries outside of the U.S. In addition, the investigator will be responsible for forwarding to American BioScience, Inc. or sponsor-nominated CRO a description of the IRB/EC board members (including profession and affiliation) or a US Department of Health and Human Services (DHHS) General Assurance number and expiration date. If neither of these is available, the chairperson must submit a statement indicating that the members of the board responsible for the review meet FDA and other appropriate regulatory requirements. In addition, the labeling for all approved study drugs should be submitted to the IRB/EC for informational purposes.

Clinical supplies will not be shipped to the clinical site until IRB/EC approval is obtained for the protocol. Any existing amendments, informed consent, and photocopies of the approved documents must be received by American BioScience, Inc. or sponsor-nominated CRO prior to drug shipment.

11.1.2. Ethical Conduct of the Study

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), Guidelines of the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use, and in full compliance with the World Medical Association Declaration of Helsinki (see Appendix C) and its most recent amendments.

11.1.3. Informed Consent

Written informed consent of the patient to participate in the study must be obtained and documented by the investigator in accordance with the FDA Regulations set forth in Part 50 of Title 21 of the *Code of Federal Regulations* as well as the applicable regulatory bodies in all other participating countries outside the United States.

The investigator must provide the patient with a copy of the consent form, which is in a language understandable to the patient. Written consent should be obtained before any protocol-required procedures are performed, including any procedure not part of normal patient care (e.g., withdrawal of current medications).

Once the participating site has formulated a draft informed consent, it must be forwarded to the American BioScience, Inc. or other sponsor-nominated CRO Project Manager for approval prior to submission to the corresponding IRB/EC. A copy of the signed informed consent will be given to the patient or their legal representative and a copy must be retained in the investigator's study records.

11.2. Disclosure of Data

11.2.1. Confidentiality

The investigator and any other study personnel involved in this study shall not disclose, or use for any purposes (other than for the performance of this study), any data, records, or other information (hereinafter collectively "information") disclosed to the investigator or other study personnel. Such information shall remain the confidential and proprietary property of ABI, and shall be disclosed only to the investigator or other designated study personnel. The obligation of non-disclosure shall not apply to the following:

- relevant disclosure to potential study participants for the purpose of obtaining informed consent;
- information after such time that it is or becomes publicly available through no fault of the investigator or other study personnel; and,
- information after such time that it is disclosed to the investigator by a third party entitled to disclose such information.

11.2.2. Publication

Data from any individual center must not be published or presented until the complete multicenter

study has been published or presented in full. Any subsequent publications should refer to the published multicenter findings.

The investigator(s) shall have the right, consistent with academic standards and with due regard to the protection of ABI's Confidential Information and Intellectual Property, to publish or present the results of work performed in accordance with the study; provided that any proposed publication or presentation is first reviewed and approved in writing by ABI. ABI shall complete its review within 60 days after receipt of the proposed publication or presentation. Upon ABI's request, proposed publication or presentation will be delayed up to 60 additional days to enable ABI to secure adequate intellectual property protection of property of ABI that would be affected by such proposed publication or presentation. If ABI believes in good faith that any proposed publication or presentation contains any Confidential Information and/or Intellectual Property, ABI shall have the right to remove references to any such Confidential Information and/or Intellectual Property.

11.3. Investigator Documentation

11.3.1. FDA Form-1572

The investigator must provide ABI with a fully executed FDA Form-1572 and all updates, on a new fully executed FDA Form-1572.

11.3.2. Curriculum Vitae

The investigator must provide American BioScience, Inc. with his/her current dated curriculum vitae and a current dated curriculum vitae for each sub-investigator listed on FDA Form-1572 and equivalent forms required by the applicable regulatory bodies in all other participating countries outside the United States. Current dated curriculum vitae is defined as updated within two years.

11.3.3. Laboratory Certification and Normal Ranges

The investigator will indicate on the FDA Form 1572 the name and location of the central laboratory and/or any local laboratories that will be used for laboratory assessments. The investigator will provide a copy of all clinical laboratory certifications, certification numbers, dates of certifications, and a list of the normal ranges for all laboratory tests for all facilities listed. Central laboratories will be delineated to each site dependent on site location. Updated versions of these documents must be provided to American BioScience, Inc. or sponsor-nominated CRO as appropriate. In the event the clinical laboratory is changed during the study, American BioScience, Inc. will be promptly notified, and the FDA Form-1572 will be updated. Appropriate documentation will be submitted to American BioScience, Inc. to verify the certification of the new laboratory.

All radiology facilities being utilized outside the investigative site must be pre-approved by ABI.

WorldCare has been delineated as the Central Imager for this study. WorldCare will have the responsibility of determining the protocol tumor response.

11.4. Records Retention

In accordance with applicable regulatory requirements, following closure of the study, the investigator will maintain a copy of all site study records in a safe and secure location. ABI will inform the investigator of the time period for retaining these records in order to comply with applicable regulatory requirements.

Completed original CRFs, which are dated and signed by the investigator, and any resolved query reports will be retained by ABI. A copy of each completed CRF and each signed resolved query report must be retained at the investigational site.

ABI reserves the right to terminate the study for refusal of the investigator and/or investigational site to comply with any requirements stated in this study protocol.

11.5. Protocol Deviations

Neither the investigator nor the sponsor is permitted to deviate from the protocol without proper FDA notification and notification to other applicable authorities in countries outside the US. Apart from the regulatory requirements, it is vital to the success of the study that the investigator adheres to the details of the protocol and thus holds to a minimum the number of cases, which may be later classified as "incomplete," "unusable," or "not evaluable."

12. TERMINATION OF STUDY

ABI reserves the right to discontinue this study at any time.

13. INVESTIGATOR'S PROTOCOL AGREEMENT

The investigator must sign the Investigator’s Protocol Agreement. The original must be kept on file at American BioScience, Inc. or sponsor-nominated CRO and the investigator must retain a copy. The completed Investigator's Protocol Agreement signifies agreement to comply with all procedures outlined by this protocol by the investigator. An Investigator’s Protocol Agreement must be signed if and when a protocol amendment is issued by American BioScience, Inc.

14. REFERENCES

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4. Nabholtz JM, Gelmon K, Bontenbal M, Spielmann M, Catimel G, Conte P, et al: Multicenter, Randomized Comparative Study of Two Doses of Paclitaxel in Patients with Metastatic Breast Cancer. J Clin Oncol., 14(6): 1858-1867, 1996.

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15. APPENDICES

Appendix A NCI Toxicity Criteria Scale
Appendix B Guidelines for Reporting of Adverse Drug Reactions (ADRs)
Appendix C World Medical Association Declaration of Helsinki
Appendix D Taxol® Package Insert (US, UK and Russia)
Appendix E Taxotere™ Package Insert
Appendix F ECOG (Zubrod) Performance Status Scale
Appendix G EORTC QLQ-C30
Appendix H Data Monitoring Committee: Composition and Function

Appendix A NCI Toxicity Criteria Scale

Appendix B Guidelines for Reporting of Adverse Drug Reactions (ADRs)

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Appendix H Data Monitoring Committee: Composition and Function

The Data Monitoring Committee (DMC) will be established with responsibilities for safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the trial, and for monitoring the overall conduct of the clinical trial. The DMC will provide recommendations about stopping or continuing the trial. To contribute to enhancing the integrity of the trial, the DMC may also formulate recommendations relating to the management of participants, improving adherence to protocol-specified regimens and retention of participants, and the procedures for data management and quality control.

While it is not anticipated that the DMC will provide recommendations for early termination due to overwhelming evidence of benefit or lack of benefit, the committee will have access to interim efficacy as well as safety data to enable them to make a judgment about the emerging benefit-to-risk profile, in the event that important adverse events are identified during the review of safety data.

The DMC will be advisory to the clinical trial leadership group. This leadership group will be responsible to promptly review the DMC recommendations, to decide whether to continue or terminate the trial, and to determine whether amendments to the protocol or changes in study conduct are required.

It is assumed that the DMC will meet on one or two occasions. The first review is expected to occur after completion of enrollment of 105 evaluable patients into each treatment arm of the trial. A second review, if necessary, will occur mid way between the first review and the planned time of trial completion.

The DMC is an independent multidisciplinary group consisting of a biostatistician and clinicians that, collectively, has experience in the management of breast cancer patients and in the conduct and monitoring of randomized clinical trials.

The DMC membership has been restricted to individuals free of apparent significant conflicts of interest. The source of these conflicts may be financial, scientific or regulatory in nature. Thus, neither study investigators nor individuals employed by the sponsor, nor individuals who might have regulatory responsibilities for the trial products, are members of the DMC.

A safety information packet will be provided prior to the review by the independent project manager. This packet will contain safety information and subject narratives for all deaths reported. The tables will consist of safety data grouped according to treatment (TAXOL or ABI-007).

The safety information packet will contain the following:

1. Demographics;
2. Subject Study Status;
3. Laboratory Values – abnormal values;
4. Vital Signs – abnormal values;
5. Deaths;

6. Reports of peripheral neuropathy;
7. Adverse Events: SAEs and discontinuations due to adverse events;
8. Adverse Events: incidence rates by body system;
9. Physical Exam;
10. Subject Listings.

The independent project manager at inGenium Research, Inc. will mail the safety information packet directly to the DMC members.

The plan for the review of safety data is described as follows:

1. Two weeks before the review meeting, the independent project manager at inGenium Research, Inc. will send a SIP to each DMC member.
2. One week before the review meeting, the independent project manager and the DMC members will have a conference call. During this teleconference, DMC members will determine if any additional information is needed for the scheduled meeting.
3. At the review meeting itself, the committee members will receive any information requested at the previous teleconference. They will also have access to subject listings and will retain the option to further query the data. Following the examination of all safety information, the committee will prepare two documents:
   - A brief synopsis will state that the committee has performed the review and give a conclusion and recommendation from a pre-specified list without providing any details.
   - A more detailed report will reiterate the conclusion and recommendation, providing actual data to justify the decisions.

The pre-specified conclusions and recommendations are as follows:

CONCLUSIONS:

I. No concerns have been identified.
II. Observations are identified that are not serious within the ABI-007 treated group.
III. Observations are identified that are serious and anticipated within the ABI-007 treated group.
IV. Observations are identified that are serious, unanticipated, and likely to be treatment-related within the ABI-007 treated group.

RECOMMENDATIONS:

I. No action recommended at this time.
II. Specific event monitoring recommended.
III. Modification of subject eligibility criteria recommended.
IV. Modification of ABI-007 treatment recommended (may be recommended only if Conclusion Option III or IV is chosen).

For any of the four conclusions, the DMC chair will provide a copy of the written synopsis including the conclusion and recommendation reached during the meeting to ABI within 24 hours. ABI in turn will forward a copy of this synopsis to the appropriate regulatory authorities. The detailed DMC report will be completed within ten working days of the meeting. The DMC chair,

who will not release the document unless the regulatory authority specifically requests it after seeing the synopsis, will retain this report. In this case, the DMC chair will send the report to ABI for appropriate distribution.

If the committee chooses Conclusion IV, identifying adverse events that are serious and unanticipated within the ABI-007 treated group, the committee chair will contact the medical monitor at American BioScience, Inc. within 24 hours. During this telephone call the chair will identify the serious, unanticipated observations that led to Conclusion IV and report the proportions of ABI-007 and TAXOL treated subjects who experienced these event(s). ABI will report this information to the FDA using the IND safety reporting regulations identified in 21 CRF 312.32 within ten working days and other regulatory agencies as appropriate. If the event is death, or otherwise life threatening, ABI will make a phone report to the FDA Reviewing Division within three working days and follow this up with a written report within ten working days. The written report will identify the event, its relevance to this investigation, and any action to be taken by American BioScience, Inc.

COMMUNICATION SCHEMA FOR SAFETY REVIEW