CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21660Orig1s037

Trade Name: ABRAXANE for Injectable Suspension 100 mg/vial

Generic or Proper Name: paclitaxel protein-bound particles for injectable suspension

Sponsor: Abraxis BioScience, LLC

Approval Date: September 6, 2013

Indication: For the first-line treatment of patients with metastatic adenocarcinoma of the pancreas, in combination with gemcitabine.

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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<u>APPROVAL LETTER</u>

Food and Drug Administration
Silver Spring MD 20993

NDA 21660/S-037

SUPPLEMENT APPROVAL

Abraxis BioScience, LLC, a wholly-owned subsidiary of Celgene Corporation
Attention: Deborah Tady, PharmD, RPh, MBA, RAC
Senior Director, Global Regulatory Affairs
9225 Indian Creek Parkway, Suite 900
Overland Park, KS 66210

Dear Dr. Tady:

Please refer to your Supplemental New Drug Application (sNDA) dated March 21, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ABRAXANE for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) (albumin-bound), 100 mg/vial.

We acknowledge receipt of your amendments dated May 21, 2013, June 6, 2013, June 17, 2013, June 19, 2013, June 28, 2013, July 12, 2013, August 9, 2013, August 13, 2013, September 3, 2013, September 4, 2013, and September 5, 2013.

This Prior Approval supplemental new drug application provides for a new indication for the first-line treatment of patients with metastatic adenocarcinoma of the pancreas, in combination with gemcitabine.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

Content of labeling must be identical to the enclosed labeling text for the package insert, text for the patient package insert, with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes with the revisions indicated above approved in this supplemental application, as well as annual reportable changes, and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND IMMEDIATE CONTAINER LABELS

Your March 21, 2013 and September 3, 2013, submissions contained proposed changes to the carton and container labels. The proposed changes are annual reportable changes which were not reviewed under the supplemental application for this NDA. Please submit the proposed carton and container labels changes in your next annual report in accordance with 21 CFR 314.81(b)(2)(iii).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form
FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)].
Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html;
instructions are provided on page 2 of the form. For more information about submission of
promotional materials to the Office of Prescription Drug Promotion (OPDP), see
http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA
(21 CFR 314.80 and 314.81).

If you have any questions, call Meredith Libeg, Regulatory Project Manager, at (301) 796-1721.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Division Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURES:
    Content of Labeling

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21660Orig1s037

<u>LABELING</u>

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ABRAXANE safely and effectively. See full prescribing information for ABRAXANE.

ABRAXANE® for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) (albumin-bound)
Initial U.S. Approval: 2005

WARNING: NEUTROPENIA
See full prescribing information for complete boxed warning.

- **Do not administer ABRAXANE therapy to patients with baseline neutrophil counts of less than 1,500 cells/mm³. (4)**
- **It is recommended that frequent peripheral blood cell counts be performed to monitor the occurrence of bone marrow suppression. (4, 5.1, 6.1, 6.2, 6.3)**

DO NOT SUBSTITUTE FOR OR WITH OTHER PACLITAXEL FORMULATIONS.

-------------------------- RECENT MAJOR CHANGES --------------------------
- Indications and Usage (1.3)   09/2013
- Dosage and Administration (2.3, 2.5)   09/2013
- Warnings and Precautions, Hematologic Effects (5.1), Nervous System (5.2), Sepsis (5.3), Pneumonitis (5.4)   09/2013

--------------------------- INDICATIONS AND USAGE ---------------------------
ABRAXANE is a microtubule inhibitor indicated for the treatment of:
- Metastatic breast cancer, after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated. (1.1)
- Locally advanced or metastatic non-small cell lung cancer (NSCLC), as first-line treatment in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy. (1.2)
- Metastatic adenocarcinoma of the pancreas as first-line treatment, in combination with gemcitabine. (1.3)

----------------------- DOSAGE AND ADMINISTRATION -----------------------
- Metastatic Breast Cancer: Recommended dosage of ABRAXANE is 260 mg/m² intravenously over 30 minutes every 3 weeks. (2.1)
- Non-Small Cell Lung Cancer: Recommended dosage of ABRAXANE is 100 mg/m² intravenously over 30 minutes on Days 1, 8, and 15 of each 21-day cycle; administer carboplatin on Day 1 of each 21-day cycle immediately after ABRAXANE. (2.2)
- Adenocarcinoma of the Pancreas: Recommended dosage of ABRAXANE is 125 mg/m² intravenously over 30-40 minutes on Days 1, 8 and 15 of each 28-day cycle; administer gemcitabine on Days 1, 8 and 15 of each 28-day cycle immediately after ABRAXANE. (2.3)
- No adjustment is necessary for patients with mild hepatic impairment. Withhold ABRAXANE if AST > 10 x ULN or bilirubin > 5 x ULN. Reduce starting dose in patients with moderate to severe hepatic impairment. (2.4)
- Dose Reductions: Dose reductions or discontinuation may be needed based on severe hematologic, neurologic, cutaneous, or gastrointestinal toxicities. (2.5)
- Use caution when handling cytotoxic drugs. Closely monitor the infusion site for extravasation and infiltration. No premedication is required prior to administration. (2.6)

-------------------- DOSAGE FORMS AND STRENGTHS --------------------
- For injectable suspension: lyophilized powder containing 100 mg of paclitaxel in single-use vial for reconstitution. (3)

----------------------------- CONTRAINDICATIONS -----------------------------
- Neutrophil counts of < 1,500 cells/mm³. (4)
- Severe hypersensitivity reaction to ABRAXANE. (4)

---------------------- WARNINGS AND PRECAUTIONS ----------------------
- ABRAXANE causes myelosuppression. Monitor CBC and withhold and/or reduce the dose as needed. (5.1)
- Sensory neuropathy occurs frequently and may require dose reduction or treatment interruption. (5.2)
- Sepsis occurred in patients with or without neutropenia who received ABRAXANE in combination with gemcitabine; interrupt ABRAXANE and gemcitabine until sepsis resolves, and if neutropenic, until neutrophils are at least 1500 cells/mm³, then resume treatment at reduced dose levels. (5.3)
- Pneumonitis occurred with the use of ABRAXANE in combination with gemcitabine; permanently discontinue treatment with ABRAXANE and gemcitabine. (5.4)
- Severe hypersensitivity reactions with fatal outcome have been reported. Do not re-challenge with this drug. (5.5)
- Exposure and toxicity of paclitaxel can be increased in patients with hepatic impairment; therefore administer with caution. (5.6)
- ABRAXANE contains albumin derived from human blood, which has a theoretical risk of viral transmission. (5.7)
- Fetal harm may occur when administered to a pregnant woman. Advise women of childbearing potential to avoid becoming pregnant while receiving ABRAXANE. (5.8)
- Advise men not to father a child while on ABRAXANE. (5.9)

------------------------------ ADVERSE REACTIONS ------------------------------
- The most common adverse reactions (≥ 20%) in metastatic breast cancer are alopecia, neutropenia, sensory neuropathy, abnormal ECG, fatigue/asthenia, myalgia/arthralgia, AST elevation, alkaline phosphatase elevation, anemia, nausea, infections, and diarrhea. (6.1)
- The most common adverse reactions (≥ 20%) in NSCLC are anemia, neutropenia, thrombocytopenia, alopecia, peripheral neuropathy, nausea, and fatigue. (6.2)
- The most common (≥ 20%) adverse reactions of ABRAXANE in adenocarcinoma of the pancreas are neutropenia, fatigue, peripheral neuropathy, nausea, alopecia, peripheral edema, diarrhea, pyrexia, vomiting, decreased appetite, rash, and dehydration. (6.3)

To report SUSPECTED ADVERSE REACTIONS, contact Celgene Corporation at 1-888-423-5436 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

------------------------------ DRUG INTERACTIONS ------------------------------
- Use caution when concomitantly administering ABRAXANE with inhibitors or inducers of either CYP2C8 or CYP3A4. (7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: September 2013

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the Full Prescribing Information are not listed.

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FULL PRESCRIBING INFORMATION
ABRAXANE® for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) (albumin-bound)

WARNING: NEUTROPENIA

- **Do not administer ABRAXANE therapy to patients who have baseline neutrophil counts of less than 1,500 cells/mm³. In order to monitor the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving ABRAXANE** *[see Contraindications (4), Warnings and Precautions (5.1) and Adverse Reactions (6.1, 6.2, 6.3)].*

- **Note: An albumin form of paclitaxel may substantially affect a drug's functional properties relative to those of drug in solution. DO NOT SUBSTITUTE FOR OR WITH OTHER PACLITAXEL FORMULATIONS.**

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1 INDICATIONS AND USAGE

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

1.2 Non-Small Cell Lung Cancer
ABRAXANE is indicated for the first-line treatment of locally advanced or metastatic non-small cell lung cancer, in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy.

1.3 Adenocarcinoma of the Pancreas
ABRAXANE is indicated for the first-line treatment of patients with metastatic adenocarcinoma of the pancreas, in combination with gemcitabine.

2 DOSAGE AND ADMINISTRATION

2.1 Metastatic Breast Cancer
After failure of combination chemotherapy for metastatic breast cancer or relapse within 6 months of adjuvant chemotherapy, the recommended regimen for ABRAXANE is 260 mg/m² administered intravenously over 30 minutes every 3 weeks.

2.2 Non-Small Cell Lung Cancer
The recommended dose of ABRAXANE is 100 mg/m² administered as an intravenous infusion over 30 minutes on Days 1, 8, and 15 of each 21-day cycle. Administer carboplatin on Day 1 of each 21 day cycle immediately after ABRAXANE *[see Clinical Studies (14.2)].*

2.3 Adenocarcinoma of the Pancreas
The recommended dose of ABRAXANE is 125 mg/m² administered as an intravenous infusion over 30-40 minutes on Days 1, 8 and 15 of each 28-day cycle. Administer gemcitabine immediately after ABRAXANE on Days 1, 8 and 15 of each 28-day cycle *[see Clinical Studies (14.3)].*

2.4 Dosage in Patients with Hepatic Impairment
No dose adjustment is necessary for patients with mild hepatic impairment. Patients with moderate and severe hepatic impairment treated with ABRAXANE may be at increased risk of toxicities known to paclitaxel. Withhold ABRAXANE if AST >10 x ULN or bilirubin > 5 x ULN. Recommendations for dosage adjustment for the first course of therapy are shown in Table 1.

For metastatic breast cancer, the dose of ABRAXANE can be increased from 130 mg/m² up to 200 mg/m² in patients with severe hepatic impairment in subsequent cycles based on individual tolerance.

For non-small cell lung cancer, reduce the dose of ABRAXANE to 50 mg/m² in patients with severe hepatic impairment. In subsequent cycles, the dose of ABRAXANE may be increased to 75 mg/m² as tolerated.

Monitor patients closely *[see Warnings and Precautions (5.6), Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)].*

Table 1: Recommendations for Starting Dose in Patients with Hepatic Impairment

	SGOT (AST) Levels		Bilirubin Levels	ABRAXANE Dose[a]		
				MBC	**NSCLC** [c]	**Pancreatic** [c] **Adenocarcinoma**
Mild	< 10 x ULN	AND	> ULN to ≤ 1.25 x ULN	260 mg/m^2	100 mg/m^2	125 mg/m^2
Moderate	< 10 x ULN	AND	1.26 to 2 x ULN	200 mg/m^2	75 mg/m^2	not recommended
Severe	< 10 x ULN	AND	2.01 to 5 x ULN	130 mg/m$^{2\ b}$	50 mg/m^2	not recommended
	> 10 x ULN	OR	> 5 x ULN	not recommended	not recommended	not recommended

MBC = Metastatic Breast Cancer; NSCLC = Non-Small Cell Lung Cancer.
[a] Dosage recommendations are for the first course of therapy. The need for further dose adjustments in subsequent courses should be based on individual tolerance.
[b] A dose increase to 200 mg/m^2 in subsequent courses should be considered based on individual tolerance.
[c] Patients with bilirubin levels above the upper limit of normal were excluded from clinical trials for pancreatic or lung cancer.

2.5   Dose Reduction/Discontinuation Recommendations

Metastatic Breast Cancer
Patients who experience severe neutropenia (neutrophil <500 cells/mm^3 for a week or longer) or severe sensory neuropathy during ABRAXANE therapy should have dosage reduced to 220 mg/m^2 for subsequent courses of ABRAXANE. For recurrence of severe neutropenia or severe sensory neuropathy, additional dose reduction should be made to 180 mg/m^2. For Grade 3 sensory neuropathy hold treatment until resolution to Grade 1 or 2, followed by a dose reduction for all subsequent courses of ABRAXANE *[see Contraindications (4), Warnings and Precautions (5.1, 5.2) and Adverse Reactions (6.1)]*.

Non-Small Cell Lung Cancer
- Do not administer ABRAXANE on Day 1 of a cycle until absolute neutrophil count (ANC) is at least 1500 cells/mm^3 and platelet count is at least 100,000 cells/mm^3 *[see Contraindications (4), Warnings and Precautions (5.1) and Adverse Reactions (6.2)]*.
- In patients who develop severe neutropenia or thrombocytopenia withhold treatment until counts recover to an absolute neutrophil count of at least 1500 cells/mm^3 and platelet count of at least 100,000 cells/mm^3 on Day 1 or to an absolute neutrophil count of at least 500 cells/mm^3 and platelet count of at least 50,000 cells/mm^3 on Days 8 or 15 of the cycle. Upon resumption of dosing, permanently reduce ABRAXANE and carboplatin doses as outlined in Table 2.
- Withhold ABRAXANE for Grade 3-4 peripheral neuropathy. Resume ABRAXANE and carboplatin at reduced doses (see Table 2) when peripheral neuropathy improves to Grade 1 or completely resolves *[see Warnings and Precautions (5.2) and Adverse Reactions (6.2)]*.

Table 2: Permanent Dose Reductions for Hematologic and Neurologic Adverse Drug Reactions in NSCLC

Adverse Drug Reaction	Occurrence	Weekly ABRAXANE Dose (mg/m^2)	Every 3-Week Carboplatin Dose (AUC mg•min/mL)
Neutropenic Fever (ANC less than 500/mm^3 with fever >38°C) OR Delay of next cycle by more than 7 days for ANC less than 1500/mm^3 OR ANC less than 500/mm^3 for more than 7 days	First	75	4.5
	Second	50	3
	Third	Discontinue Treatment	
Platelet count less than 50,000/mm^3	First	75	4.5
	Second	Discontinue Treatment	
Severe sensory Neuropathy – Grade 3 or 4	First	75	4.5
	Second	50	3
	Third	Discontinue Treatment	

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Adenocarcinoma of the Pancreas
Dose level reductions for patients with adenocarcinoma of the pancreas, as referenced in Tables 4 and 5, are provided in Table 3.

Table 3: Dose Level Reductions for Patients with Adenocarcinoma of the Pancreas

Dose Level	ABRAXANE (mg/m^2)	Gemcitabine (mg/m^2)
Full dose	125	1000
1st dose reduction	100	800
2nd dose reduction	75	600
If additional dose reduction required	Discontinue	Discontinue

Recommended dose modifications for neutropenia and thrombocytopenia for patients with adenocarcinoma of the pancreas are provided in Table 4.

Table 4: Dose Recommendation and Modifications for Neutropenia and/or Thrombocytopenia at the Start of a Cycle or within a Cycle for Patients with Adenocarcinoma of the Pancreas

Cycle Day	ANC (cells/mm^3)		Platelet count (cells/mm^3)	ABRAXANE / Gemcitabine
Day 1	< 1500	OR	< 100,000	Delay doses until recovery
Day 8	500 to < 1000	OR	50,000 to < 75,000	Reduce 1 dose level
	< 500	OR	< 50,000	Withhold doses
Day 15: IF Day 8 doses were reduced or given without modification:				
	500 to < 1000	OR	50,000 to < 75,000	Reduce 1 dose level from Day 8
	< 500	OR	< 50,000	Withhold doses
Day 15: IF Day 8 doses were withheld:				
	≥ 1000	OR	≥ 75,000	Reduce 1 dose level from Day 1
	500 to < 1000	OR	50,000 to < 75,000	Reduce 2 dose levels from Day 1
	< 500	OR	< 50,000	Withhold doses

Abbreviations: ANC = Absolute Neutrophil Count

Recommended dose modifications for other adverse drug reactions in patients with adenocarcinoma of the pancreas are provided in Table 5.

Table 5: Dose Modifications for Other Adverse Drug Reactions in Patients with Adenocarcinoma of the Pancreas

Adverse Drug Reaction	ABRAXANE	Gemcitabine
Febrile Neutropenia: Grade 3 or 4	Withhold until fever resolves and ANC ≥ 1500; resume at next lower dose level	
Peripheral Neuropathy: Grade 3 or 4	Withhold until improves to ≤ Grade 1; resume at next lower dose level	No dose reduction
Cutaneous Toxicity: Grade 2 or 3	Reduce to next lower dose level; discontinue treatment if toxicity persists	
Gastrointestinal Toxicity: Grade 3 mucositis or diarrhea	Withhold until improves to ≤ Grade 1; resume at next lower dose level	

2.6   Preparation and Administration Precautions
ABRAXANE is a cytotoxic drug and, as with other potentially toxic paclitaxel compounds, caution should be exercised in handling ABRAXANE. The use of gloves is recommended. If ABRAXANE (lyophilized cake or reconstituted suspension) contacts the skin, wash the skin immediately and thoroughly with soap and water. Following topical exposure to paclitaxel, events may include tingling, burning and redness. If ABRAXANE contacts mucous membranes, the membranes should be flushed thoroughly with water.

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Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration. Limiting the infusion of ABRAXANE to 30 minutes, as directed, reduces the likelihood of infusion-related reactions *[see Adverse Reactions (6.4)]*.

Premedication to prevent hypersensitivity reactions is generally not needed prior to the administration of ABRAXANE. Premedication may be needed in patients who have had prior hypersensitivity reactions to ABRAXANE. Patients who experience a severe hypersensitivity reaction to ABRAXANE should not be re-challenged with this drug [*see Warnings and Precautions (5.5)*].

2.7   Preparation for Intravenous Administration
ABRAXANE is supplied as a sterile lyophilized powder for reconstitution before use. **AVOID ERRORS, READ ENTIRE PREPARATION INSTRUCTIONS PRIOR TO RECONSTITUTION.**

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

Each mL of the reconstituted formulation will contain 5 mg/mL paclitaxel.

Calculate the exact total dosing volume of 5 mg/mL suspension required for the patient: Dosing volume (mL) = Total dose (mg)/5 (mg/mL).

The reconstituted suspension should be milky and homogenous without visible particulates. If particulates or settling are visible, the vial should be **gently** inverted again to ensure complete resuspension prior to use. Discard the reconstituted suspension if precipitates are observed. Discard any unused portion.

Inject the appropriate amount of reconstituted ABRAXANE into an empty, sterile intravenous bag [plasticized polyvinyl chloride (PVC) containers, PVC or non-PVC type intravenous bag]. The use of specialized DEHP-free solution containers or administration sets is not necessary to prepare or administer ABRAXANE infusions. The use of an in-line filter is not recommended.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

2.8   Stability
Unopened vials of ABRAXANE are stable until the date indicated on the package when stored between 20ºC to 25ºC (68ºF to 77ºF) in the original package. Neither freezing nor refrigeration adversely affects the stability of the product.

Stability of Reconstituted Suspension in the Vial
Reconstituted ABRAXANE in the vial should be used immediately, but may be refrigerated at 2ºC to 8ºC (36ºF to 46ºF) for a maximum of 8 hours if necessary. If not used immediately, each vial of reconstituted suspension should be replaced in the original carton to protect it from bright light. Discard any unused portion.

Stability of Reconstituted Suspension in the Infusion Bag
The suspension for infusion when prepared as recommended in an infusion bag should be used immediately but may be stored at ambient temperature (approximately 25ºC) and lighting conditions for up to 4 hours. Discard any unused portion.

3   DOSAGE FORMS AND STRENGTHS
For injectable suspension: lyophilized powder containing 100 mg of paclitaxel in single-use vial for reconstitution.

4   CONTRAINDICATIONS
- ABRAXANE should not be used in patients who have baseline neutrophil counts of < 1,500 cells/mm^3.
- Patients who experience a severe hypersensitivity reaction to ABRAXANE should not be rechallenged with the drug.

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5 WARNINGS AND PRECAUTIONS

5.1 Hematologic Effects
Bone marrow suppression (primarily neutropenia) is dose-dependent and a dose-limiting toxicity of ABRAXANE. In clinical studies, Grade 3-4 neutropenia occurred in 34% of patients with metastatic breast cancer (MBC), 47% of patients with non-small cell lung cancer (NSCLC), and 38% of patients with pancreatic cancer.

Monitor for myelotoxicity by performing complete blood cell counts frequently, including prior to dosing on Day 1 (for MBC) and Days 1, 8, and 15 (for NSCLC and for pancreatic cancer). Do not administer ABRAXANE to patients with baseline absolute neutrophil counts (ANC) of less than 1,500 cells/mm^3. In the case of severe neutropenia (<500 cells/mm^3 for seven days or more) during a course of ABRAXANE therapy, reduce the dose of ABRAXANE in subsequent courses in patients with either MBC or NSCLC.

In patients with MBC, resume treatment with every-3-week cycles of ABRAXANE after ANC recovers to a level >1,500 cells/mm^3 and platelets recover to a level >100,000 cells/mm^3.

In patients with NSCLC, resume treatment if recommended (see Dosage and Administration, Table 2) at permanently reduced doses for both weekly ABRAXANE and every-3-week carboplatin after ANC recovers to at least 1500 cells/mm^3 and platelet count of at least 100,000 cells/mm^3 on Day 1 or to an ANC of at least 500 cells/mm^3 and platelet count of at least 50,000 cells/mm^3 on Days 8 or 15 of the cycle *[see Dosage and Administration (2.5)]*.

In patients with adenocarcinoma of the pancreas, withhold ABRAXANE and gemcitabine if the ANC is less than 500 cells/mm^3 or platelets are less than 50,000 cells/mm^3 and delay initiation of the next cycle if the ANC is less than 1500 cells/mm^3 or platelet count is less than 100,000 cells/mm^3 on Day 1 of the cycle. Resume treatment with appropriate dose reduction if recommended *[see Dosage and Administration (2.5)]*.

5.2 Nervous System
Sensory neuropathy is dose- and schedule-dependent *[see Adverse Reactions (6.1, 6.2, 6.3)]*. The occurrence of Grade 1 or 2 sensory neuropathy does not generally require dose modification. If ≥ Grade 3 sensory neuropathy develops, withhold ABRAXANE treatment until resolution to Grade 1 or 2 for metastatic breast cancer or until resolution to ≤ Grade 1 for NSCLC and pancreatic cancer followed by a dose reduction for all subsequent courses of ABRAXANE *[see Dosage and Administration (2.5)]*.

5.3 Sepsis
Sepsis occurred in 5% of patients with or without neutropenia who received ABRAXANE in combination with gemcitabine. Biliary obstruction or presence of biliary stent were risk factors for severe or fatal sepsis. If a patient becomes febrile (regardless of ANC) initiate treatment with broad spectrum ant biotics. For febrile neutropenia, interrupt ABRAXANE and gemcitabine until fever resolves and ANC ≥ 1500, then resume treatment at reduced dose levels *[see Dosage and Administration (2.5)]*.

5.4 Pneumonitis
Pneumonitis, including some cases that were fatal, occurred in 4% of patients receiving ABRAXANE in combination with gemcitabine. Monitor patients for signs and symptoms of pneumonitis and interrupt ABRAXANE and gemcitabine during evaluation of suspected pneumonitis. After ruling out infectious etiology and upon making a diagnosis of pneumonitis, permanently discontinue treatment with ABRAXANE and gemcitabine.

5.5 Hypersensitivity
Severe and sometimes fatal hypersensitivity reactions, including anaphylactic reactions, have been reported. Patients who experience a severe hypersensitivity reaction to ABRAXANE should not be re-challenged with this drug.

5. 6 Hepatic Impairment
Because the exposure and toxicity of paclitaxel can be increased with hepatic impairment, administration of ABRAXANE in patients with hepatic impairment should be performed with caution. The starting dose should be reduced for patients with moderate or severe hepatic impairment *[see Dosage and Administration (2.4), Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

5.7 Albumin (Human)
ABRAXANE contains albumin (human), a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries a remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob Disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

5.8 Use in Pregnancy
ABRAXANE can cause fetal harm when administered to a pregnant woman. Administration of paclitaxel protein-bound particles to rats during pregnancy at doses lower than the maximum recommended human dose, based on body surface area, caused embryo-fetal toxicities, including intrauterine mortality, increased resorptions, reduced numbers of live fetuses, and malformations.

There are no adequate and well-controlled studies in pregnant women receiving ABRAXANE. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving ABRAXANE *[see Use in Specific Populations (8.1)]*.

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5.9 Use in Men

Men should be advised not to father a child while receiving ABRAXANE *[see Nonclinical Toxicology (13.1)]*.

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The most common adverse reactions (≥ 20%) with single-agent use of ABRAXANE in metastatic breast cancer are alopecia, neutropenia, sensory neuropathy, abnormal ECG, fatigue/asthenia, myalgia/arthralgia, AST elevation, alkaline phosphatase elevation, anemia, nausea, infections, and diarrhea *[see Adverse Reactions (6.1)]*.

The most common adverse reactions (≥ 20%) of ABRAXANE in combination with carboplatin for non-small cell lung cancer are anemia, neutropenia, thrombocytopenia, alopecia, peripheral neuropathy, nausea, and fatigue *[see Adverse Reactions (6.2)]* The most common serious adverse reactions of ABRAXANE in combination with carboplatin for non-small cell lung cancer are anemia (4%) and pneumonia (3%). The most common adverse reactions resulting in permanent discontinuation of ABRAXANE are neutropenia (3%), thrombocytopenia (3%), and peripheral neuropathy (1%). The most common adverse reactions resulting in dose reduction of ABRAXANE are neutropenia (24%), thrombocytopenia (13%), and anemia (6%). The most common adverse reactions leading to withholding or delay in ABRAXANE dosing are neutropenia (41%), thrombocytopenia (30%), and anemia (16%).

In a randomized open-label trial of ABRAXANE in combination with gemcitabine for pancreatic adenocarcinoma [*see Clinical Studies (14.3)]*, the most common (≥ 20%) selected (with a ≥ 5% higher incidence) adverse reactions of ABRAXANE are neutropenia, fatigue, peripheral neuropathy, nausea, alopecia, peripheral edema, diarrhea, pyrexia, vomiting, decreased appetite, rash, and dehydration. The most common serious adverse reactions of ABRAXANE (with a ≥ 1% higher incidence) are pyrexia (6%), dehydration (5%), pneumonia (4%) and vomiting (4%). The most common adverse reactions resulting in permanent discontinuation of ABRAXANE are peripheral neuropathy (8%), fatigue (4%) and thrombocytopenia (2%). The most common adverse reactions resulting in dose reduction of ABRAXANE are neutropenia (10%) and peripheral neuropathy (6%). The most common adverse reactions leading to withholding or delay in ABRAXANE dosing are neutropenia (16%), thrombocytopenia (12%), fatigue (8%), peripheral neuropathy (15%), anemia (5%) and diarrhea (5%).

6.1 Clinical Trials Experience in Metastatic Breast Cancer

Table 6 shows the frequency of important adverse events in the randomized comparative trial for the patients who received either single-agent ABRAXANE or paclitaxel injection for the treatment of metastatic breast cancer.

Table 6: Frequency[a] of Important Treatment Emergent Adverse Events in the Randomized Metastatic Breast Cancer Study on an Every-3-Weeks Schedule

	Percent of Patients	
	ABRAXANE **260 mg/m^2 over 30 min** **(n=229)**	**Paclitaxel Injection** **175 mg/m^2 over 3 h[b]** **(n=225)**
Bone Marrow		
Neutropenia $< 2.0 \times 10^9$/L $< 0.5 \times 10^9$/L	80 9	82 22
Thrombocytopenia $< 100 \times 10^9$/L $< 50 \times 10^9$/L	2 <1	3 <1
Anemia < 11 g/dL < 8 g/dL	33 1	25 <1
Infections	24	20
Febrile Neutropenia	2	1
Neutropenic Sepsis	<1	<1
Bleeding	2	2
Hypersensitivity Reaction[c]		
All	4	12
Severe[d]	0	2
Cardiovascular		
Vital Sign Changes During Administration		
Bradycardia	<1	<1
Hypotension	5	5
Severe Cardiovascular Events[d]	3	4
Abnormal ECG		
All Patients	60	52
Patients with Normal Baseline	35	30

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	Percent of Patients	
	ABRAXANE 260 mg/m^2 over 30 min (n=229)	Paclitaxel Injection 175 mg/m^2 over 3 h[b] (n=225)
Respiratory		
Cough	7	6
Dyspnea	12	9
Sensory Neuropathy		
Any Symptoms	71	56
Severe Symptoms[d]	10	2
Myalgia / Arthralgia		
Any Symptoms	44	49
Severe Symptoms[d]	8	4
Asthenia		
Any Symptoms	47	39
Severe Symptoms[d]	8	3
Fluid Retention/Edema		
Any Symptoms	10	8
Severe Symptoms[d]	0	<1
Gastrointestinal		
Nausea		
Any Symptoms	30	22
Severe Symptoms[d]	3	<1
Vomiting		
Any Symptoms	18	10
Severe Symptoms[d]	4	1
Diarrhea		
Any Symptoms	27	15
Severe Symptoms[d]	<1	1
Mucositis		
Any Symptoms	7	6
Severe Symptoms[d]	<1	0
Alopecia	90	94
Hepatic (Patients with Normal Baseline)		
Bilirubin Elevations	7	7
Alkaline Phosphatase Elevations	36	31
AST (SGOT) Elevations	39	32
Injection Site Reaction	<1	1

[a] Based on worst grade by NCI Common Terminology Criteria for Adverse Events (CTCAE) version 2.
[b] Paclitaxel injection patients received premedication.
[c] Includes treatment-related events related to hypersensitivity (e.g., flushing, dyspnea, chest pain, hypotension) that began on a day of dosing.
[d] Severe events are defined as at least grade 3 toxicity.

Adverse Event Experiences by Body System

Hematologic Disorders
Neutropenia was dose dependent and reversible. Among patients with metastatic breast cancer in the randomized trial, neutrophil counts declined below 500 cells/mm^3 (Grade 4) in 9% of the patients treated with a dose of 260 mg/m^2 compared to 22% in patients receiving paclitaxel injection at a dose of 175 mg/m^2. Pancytopenia has been observed in clinical trials.

Infections
Infectious episodes were reported in 24% of the patients treated with ABRAXANE. Oral candidiasis, respiratory tract infections and pneumonia were the most frequently reported infectious complications.

Hypersensitivity Reactions (HSRs)
Grade 1 or 2 HSRs occurred on the day of ABRAXANE administration and consisted of dyspnea (1%) and flushing, hypotension, chest pain, and arrhythmia (all <1%). The use of ABRAXANE in patients previously exhibiting hypersensitivity to paclitaxel injection or human albumin has not been studied.

Cardiovascular
Hypotension, during the 30-minute infusion, occurred in 5% of patients. Bradycardia, during the 30-minute infusion, occurred in <1% of patients. These vital sign changes most often caused no symptoms and required neither specific therapy nor treatment discontinuation.

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Severe cardiovascular events possibly related to single-agent ABRAXANE occurred in approximately 3% of patients. These events included cardiac ischemia/infarction, chest pain, cardiac arrest, supraventricular tachycardia, edema, thrombosis, pulmonary thromboembolism, pulmonary emboli, and hypertension. Cases of cerebrovascular attacks (strokes) and transient ischemic attacks have been reported.

Electrocardiogram (ECG) abnormalities were common among patients at baseline. ECG abnormalities on study did not usually result in symptoms, were not dose-limiting, and required no intervention. ECG abnormalities were noted in 60% of patients. Among patients with a normal ECG prior to study entry, 35% of all patients developed an abnormal tracing while on study. The most frequently reported ECG modifications were non-specific repolarization abnormalities, sinus bradycardia, and sinus tachycardia.

Respiratory
Dyspnea (12%), cough (7%), and pneumothorax (<1%) were reported after treatment with ABRAXANE.

Neurologic
The frequency and severity of sensory neuropathy increased with cumulative dose. Sensory neuropathy was the cause of ABRAXANE discontinuation in 7/229 (3%) patients. Twenty-four patients (10%) treated with ABRAXANE developed Grade 3 peripheral neuropathy; of these patients, 14 had documented improvement after a median of 22 days; 10 patients resumed treatment at a reduced dose of ABRAXANE and 2 discontinued due to peripheral neuropathy. Of the 10 patients without documented improvement, 4 discontinued the study due to peripheral neuropathy.

No Grade 4 sensory neuropathies were reported. Only one incident of motor neuropathy (Grade 2) was observed in either arm of the controlled trial.

Vision Disorders
Ocular/visual disturbances occurred in 13% of all patients (n=366) treated with ABRAXANE and 1% were severe. The severe cases (keratitis and blurred vision) were reported in patients who received higher doses than those recommended (300 or 375 mg/m^2). These effects generally have been reversible.

Arthralgia/Myalgia
The symptoms were usually transient, occurred two or three days after ABRAXANE administration, and resolved within a few days.

Hepatic
Grade 3 or 4 elevations in GGT were reported for 14% of patients treated with ABRAXANE and 10% of patients treated with paclitaxel injection in the randomized trial.

Renal
Overall 11% of patients experienced creatinine elevation, 1% severe. No discontinuations, dose reductions, or dose delays were caused by renal toxicities.

Other Clinical Events
Nail changes (changes in pigmentation or discoloration of nail bed) have been reported. Edema occurred in 10% of patients; no patients had severe edema. Dehydration and pyrexia were also reported.

6.2   Clinical Trials Experience in Non-Small Cell Lung Cancer

Adverse reactions were assessed in 514 ABRAXANE/carboplatin-treated patients and 524 paclitaxel injection/carboplatin-treated patients receiving first-line systemic treatment for locally advanced (stage IIIB) or metastatic (IV) non-small cell lung cancer (NSCLC) in a multicenter, randomized, open-label trial. ABRAXANE was administered as an intravenous infusion over 30 minutes at a dose of 100 mg/m^2 on Days 1, 8, and 15 of each 21-day cycle. Paclitaxel injection was administered as an intravenous infusion over 3 hours at a dose of 200 mg/m^2, following premedication. In both treatment arms carboplatin at a dose of AUC = 6 mg•min/mL was administered intravenously on Day 1 of each 21-day cycle after completion of ABRAXANE/paclitaxel infusion.
The differences in paclitaxel dose and schedule between the two arms limit direct comparison of dose- and schedule-dependent adverse reactions. Among patients evaluable for adverse reactions, the median age was 60 years, 75% were men, 81% were White, 49% had adenocarcinoma, 43% had squamous cell lung cancer, 76% were ECOG PS 1. Patients in both treatment arms received a median of 6 cycles of treatment.

The following common (≥ 10% incidence) adverse reactions were observed at a similar incidence in ABRAXANE plus carboplatin-treated and paclitaxel injection plus carboplatin-treated patients: alopecia 56%, nausea 27%, fatigue 25%, decreased appetite 17%, asthenia 16%, constipation 16%, diarrhea 15%, vomiting 12%, dyspnea 12%, and rash 10% (incidence rates are for the ABRAXANE plus carboplatin treatment group).

Table 7 provides the frequency and severity laboratory-detected abnormalities which occurred with a difference of ≥ 5% for all grades (1-4) or ≥ 2% for Grade 3-4 toxicity between ABRAXANE plus carboplatin-treated patients or paclitaxel injection plus carboplatin-treated patients.

Table 7: Selected Hematologic Laboratory-Detected Abnormalities With a Difference of ≥ 5% for grades (1-4) or ≥ 2% for Grade 3-4 Toxicity Between Treatment Groups

	ABRAXANE (100 mg/m^{2} weekly) plus carboplatin		Paclitaxel Injection (200 mg/m^{2} every 3 weeks) plus carboplatin	
	Grades 1-4 (%)	Grade 3-4 (%)	Grades 1-4 (%)	Grade 3-4 (%)
Anemia[1,2]	98	28	91	7
Neutropenia[1,3]	85	47	83	58
Thrombocytopenia[1,3]	68	18	55	9

[1] 508 patients assessed in ABRAXANE/carboplatin-treated group
[2] 514 patients assessed in paclitaxel injection/carboplatin-treated group
[3] 513 patients assessed in paclitaxel injection/carboplatin-treated group

Table 8 provides the frequency and severity of adverse reactions, which occurred with a difference of ≥ 5% for all grades (1-4) or ≥ 2% for Grade 3-4 between either treatment group for the 514 ABRAXANE plus carboplatin-treated patients compared with the 524 patients who received paclitaxel injection plus carboplatin.

Table 8: Selected Adverse Reactions with a Difference of ≥5% for All Grade Toxicity or ≥2% for Grade 3-4 Toxicity Between Treatment Groups

System Organ Class	MedDRA v 12.1 Preferred Term	ABRAXANE (100 mg/m^{2} weekly) + carboplatin (N=514)		Paclitaxel Injection (200 mg/m^{2} every 3 weeks) + carboplatin (N=524)	
		Grade 1-4 Toxicity (%)	Grade 3-4 Toxicity (%)	Grades 1-4 Toxicity (%)	Grade 3-4 Toxicity (%)
Nervous system disorders	Peripheral neuropathy[a]	48	3	64	12
General disorders and administration site conditions	Edema peripheral	10	0	4	<1
Respiratory thoracic and mediastinal disorders	Epistaxis	7	0	2	0
Musculoskeletal and connective tissue disorders	Arthralgia	13	<1	25	2
	Myalgia	10	<1	19	2

[a] Peripheral neuropathy is defined by the MedDRA Version 14.0 SMQ neuropathy (broad scope).

For the ABRAXANE plus carboplatin treated group, 17/514 (3%) patients developed Grade 3 peripheral neuropathy and no patients developed Grade 4 peripheral neuropathy. Grade 3 neuropathy improved to Grade 1 or resolved in 10/17 patients (59%) following interruption or discontinuation of ABRAXANE.

6.3   Clinical Trials Experience in Adenocarcinoma of the Pancreas
Adverse reactions were assessed in 421 patients who received ABRAXANE plus gemcitabine and 402 patients who received gemcitabine for the first-line systemic treatment of metastatic adenocarcinoma of the pancreas in a multicenter, multinational, randomized, controlled, open-label trial. Patients received a median treatment duration of 3.9 months in the ABRAXANE/gemcitabine group and 2.8 months in the gemcitabine group. For the treated population, the median relative dose intensity for gemcitabine was 75% in the ABRAXANE/gemcitabine group and 85% in the gemcitabine group. The median relative dose intensity of ABRAXANE was 81%.

Table 9 provides the frequency and severity of laboratory-detected abnormalities which occurred at a higher incidence for Grades 1-4 (≥ 5%) or for Grade 3-4 (≥ 2%) toxicity in ABRAXANE plus gemcitabine-treated patients.

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Table 9: Selected Hematologic Laboratory-Detected Abnormalities with a Higher Incidence (≥ 5% for Grades 1-4 or ≥ 2% for Grades 3-4 Events) in the ABRAXANE/Gemcitabine Arm

	ABRAXANE(125 mg/m^2)/ Gemcitabine[d]		Gemcitabine	
	Grades 1-4 (%)	Grade 3-4 (%)	Grades 1-4 (%)	Grade 3-4 (%)
Neutropenia[a,b]	73	38	58	27
Thrombocytopenia[b,c]	74	13	70	9

[a] 405 patients assessed in ABRAXANE/gemcitabine-treated group
[b] 388 patients assessed in gemcitabine-treated group
[c] 404 patients assessed in ABRAXANE/gemcitabine-treated group
[d] Neutrophil growth factors were administered to 26% of patients in the ABRAXANE/gemcitabine group.

Table 10 provides the frequency and severity of adverse reactions which occurred with a difference of ≥ 5% for all grades or ≥ 2% for Grade 3 or higher in the ABRAXANE plus gemcitabine-treated group compared to the gemcitabine group.

Table 10: Selected Adverse Reactions with a Higher Incidence (≥5% for All Grade Toxicity or ≥2% for Grade 3 or Higher Toxicity) in the ABRAXANE/Gemcitabine Arm

System Organ Class	Adverse Reaction	ABRAXANE (125 mg/m^2) and gemcitabine (N=421)		Gemcitabine (N=402)	
		All Grades	Grade 3 or Higher	All Grades	Grade 3 or Higher
General disorders and administration site conditions	Fatigue	248 (59%)	77 (18%)	183 (46%)	37 (9%)
	Peripheral edema	194 (46%)	13 (3%)	122 (30%)	12 (3%)
	Pyrexia	171 (41%)	12 (3%)	114 (28%)	4 (1%)
	Asthenia	79 (19%)	29 (7%)	54 (13%)	17 (4%)
	Mucositis	42 (10%)	6 (1%)	16 (4%)	1 (<1%)
Gastrointestinal disorders	Nausea	228 (54%)	27 (6%)	192 (48%)	14 (3%)
	Diarrhea	184 (44%)	26 (6%)	95 (24%)	6 (1%)
	Vomiting	151 (36%)	25 (6%)	113 (28%)	15 (4%)
Skin and subcutaneous tissue disorders	Alopecia	212 (50%)	6 (1%)	21 (5%)	0
	Rash	128 (30%)	8 (2%)	45 (11%)	2 (<1%)
Nervous system disorders	Peripheral neuropathy[a]	227 (54%)	70 (17%)	51 (13%)	3 (1%)
	Dysgeusia	68 (16%)	0	33 (8%)	0
	Headache	60 (14%)	1 (<1%)	38 (9%)	1 (<1%)
Metabolism and nutrition disorders	Decreased appetite	152 (36%)	23 (5%)	104 (26%)	8 (2%)
	Dehydration	87 (21%)	31 (7%)	45 (11%)	10 (2%)
	Hypokalemia	52 (12%)	18 (4%)	28 (7%)	6 (1%)
Respiratory, thoracic and mediastinal disorders	Cough	72 (17%)	0	30 (7%)	0
	Epistaxis	64 (15%)	1 (<1%)	14 (3%)	1 (<1%)
Infections and infestations	Urinary tract infections [b]	47 (11%)	10 (2%)	20 (5%)	1 (<1%)
Musculoskeletal and connective tissue disorders	Pain in extremity	48 (11%)	3 (1%)	24 (6%)	3 (1%)
	Arthralgia	47 (11%)	3 (1%)	13 (3%)	1 (<1%)
	Myalgia	44 (10%)	4 (1%)	15 (4%)	0

Table 10: Selected Adverse Reactions with a Higher Incidence (≥5% for All Grade Toxicity or ≥2% for Grade 3 or Higher Toxicity) in the ABRAXANE/Gemcitabine Arm (continued)

System Organ Class	Adverse Reaction	ABRAXANE (125 mg/m^2) and gemcitabine (N=421)		Gemcitabine (N=402)	
		All Grades	Grade 3 or Higher	All Grades	Grade 3 or Higher
Psychiatric disorders	Depression	51 (12%)	1 (<1%)	24 (6%)	0

a   Peripheral neuropathy is defined by the MedDRA Version 15.0 Standard MedDRA Query neuropathy (broad scope).
b   Urinary tract infections includes the preferred terms of: urinary tract infection, cystitis, urosepsis, urinary tract infection bacterial, and urinary tract infection enterococccal.

Additional clinically relevant adverse reactions that were reported in < 10% of the patients with adenocarcinoma of the pancreas who received ABRAXANE/gemcitabine included:

Infections & infestations: oral candidiasis, pneumonia
Vascular disorders: hypertension
Cardiac disorders: tachycardia, congestive cardiac failure
Eye disorders: cystoid macular edema

Peripheral Neuropathy
Grade 3 peripheral neuropathy occurred in 17% of patients who received ABRAXANE/gemcitibine compared to 1% of patients who received gemcitabine only; no patients developed grade 4 peripheral neuropathy. The median time to first occurrence of Grade 3 peripheral neuropathy in the ABRAXANE arm was 140 days. Upon suspension of ABRAXANE dosing, the median time to improvement from Grade 3 peripheral neuropathy to ≤ Grade 1 was 29 days. Of ABRAXANE-treated patients with Grade 3 peripheral neuropathy, 44% resumed ABRAXANE at a reduced dose.

Sepsis
Sepsis occurred in 5% of patients who received ABRAXANE/gemcitabine compared to 2% of patients who received gemcitabine alone. Sepsis occurred both in patients with and without neutropenia. Risk factors for sepsis included biliary obstruction or presence of biliary stent.

Pneumonitis
Pneumonitis occurred in 4% of patients who received ABRAXANE/gemcitabine compared to 1% of patients who received gemcitabine alone. Two of 17 patients in the ABRAXANE arm with pneumonitis died.

6.4   Post-Marketing Experience with ABRAXANE and other Paclitaxel Formulations
Unless otherwise noted, the following discussion refers to the adverse reactions that have been identified during post-approval use of ABRAXANE. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. In some instances, severe events observed with paclitaxel injection may be expected to occur with ABRAXANE.

Hypersensitivity Reactions
Severe and sometimes fatal hypersensitivity reactions have been reported with ABRAXANE. The use of ABRAXANE in patients previously exhibiting hypersensitivity to paclitaxel injection or human a bumin has not been studied.

Cardiovascular
There have been reports of congestive heart failure and left ventricular dysfunction with ABRAXANE. Most of the individuals were previously exposed to cardiotoxic drugs, such as anthracyclines, or had underlying cardiac history.

Respiratory
There have been reports of pneumonitis, interstitial pneumonia and pulmonary embolism in patients receiving ABRAXANE and reports of radiation pneumonitis in patients receiving concurrent radiotherapy. Reports of lung fibrosis have been received as part of the continuing surveillance of paclitaxel injection safety and may also be observed with ABRAXANE.

Neurologic
Cranial nerve palsies and vocal cord paresis have been reported, as well as autonomic neuropathy resulting in paralytic ileus.

Vision Disorders
Reports in the literature of abnormal visual evoked potentials in patients treated with paclitaxel injection suggest persistent optic nerve damage. These may also be observed with ABRAXANE.

Reduced visual acuity due to cystoid macular edema (CME) has been reported during treatment with ABRAXANE as well as with other taxanes. After cessation of treatment, CME improves and visual acuity may return to baseline.

Hepatic
Reports of hepatic necrosis and hepatic encephalopathy leading to death have been received as part of the continuing surveillance of paclitaxel injection safety and may occur following ABRAXANE treatment.

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Gastrointestinal (GI)
There have been reports of intestinal obstruction, intestinal perforation, pancreatitis, and ischemic colitis following ABRAXANE treatment. There have been reports of neutropenic enterocolitis (typhlitis), despite the coadministration of G-CSF, occurring in patients treated with paclitaxel injection alone and in combination with other chemotherapeutic agents.

Injection Site Reaction
There have been reports of extravasation of ABRAXANE. Given the possibility of extravasation, it is advisable to monitor closely the ABRAXANE infusion site for poss ble infiltration during drug administration.

Severe events such as phlebitis, cellulitis, induration, necrosis, and fibrosis have been reported as part of the continuing surveillance of paclitaxel injection safety. In some cases the onset of the injection site reaction in paclitaxel injection patients either occurred during a prolonged infusion or was delayed by a week to ten days. Recurrence of skin reactions at a site of previous extravasation following administration of paclitaxel injection at a different site, i.e., "recall", has been reported.

Other Clinical Events
Skin reactions including generalized or maculopapular rash, erythema, and pruritus have been observed with ABRAXANE. There have been case reports of photosensitivity reactions, radiation recall phenomenon, and in some patients previously exposed to capecitabine, reports of palmar-plantar erythrodysesthesia. Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported.

There have been reports of conjunctivitis, cellulitis, and increased lacrimation with paclitaxel injection.

6.5   Accidental Exposure
No reports of accidental exposure to ABRAXANE have been received. However, upon inhalation of paclitaxel, dyspnea, chest pain, burning eyes, sore throat, and nausea have been reported. Following topical exposure, events have included tingling, burning, and redness.

7   DRUG INTERACTIONS
The metabolism of paclitaxel is catalyzed by CYP2C8 and CYP3A4. In the absence of formal clinical drug interaction studies, caution should be exercised when administering ABRAXANE concomitantly with medicines known to inhibit (e.g., ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir) or induce (e.g., rifampicin, carbamazepine, phenytoin, efavirenz, and nevirapine) either CYP2C8 or CYP3A4.

8   USE IN SPECIFIC POPULATIONS

8.1   Pregnancy
Pregnancy Category D *[see Warnings and Precautions (5.9)]*.

There are no adequate and well-controlled studies in pregnant women using ABRAXANE. Based on its mechanism of action and findings in animals, ABRAXANE can cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving ABRAXANE.

Administration of paclitaxel protein-bound particles to rats during pregnancy, on gestation days 7 to 17 at doses of 6 mg/m^2 (approximately 2% of the daily maximum recommended human dose on a mg/m^2 basis) caused embryofetal toxicities, as indicated by intrauterine mortality, increased resorptions (up to 5-fold), reduced numbers of litters and live fetuses, reduction in fetal body weight and increase in fetal anomalies. Fetal anomalies included soft tissue and skeletal malformations, such as eye bulge, folded retina, microphthalmia, and dilation of brain ventricles. A lower incidence of soft tissue and skeletal malformations were also exhibited at 3 mg/m^2 (approximately 1% of the daily maximum recommended human dose on a mg/m^2 basis).

8.3   Nursing Mothers
It is not known whether paclitaxel is excreted in human milk. Paclitaxel and/or its metabolites were excreted into the milk of lactating rats. Because many drugs are excreted in human mi k and because of the potential for serious adverse reactions in nursing infants, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother**.**

8.4   Pediatric Use
The safety and effectiveness of ABRAXANE in pediatric patients have not been evaluated.

8.5   Geriatric Use
Of the 229 patients in the randomized study who received ABRAXANE for the treatment of metastatic breast cancer, 13% were at least 65 years of age and < 2% were 75 years or older. No toxicities occurred notably more frequently among patients who received ABRAXANE.

Of the 514 patients in the randomized study who received ABRAXANE and carboplatin for the first-line treatment of non-small cell lung cancer, 31% were 65 years or older and 3.5% were 75 years or older. Myelosuppression, peripheral neuropathy, and arthralgia were more frequent in patients 65 years or older compared to patients younger than 65 years old. No overall difference in effectiveness, as measured by response rates, was observed between patients 65 years or older compared to patients younger than 65 years old.

Of the 431 patients in the randomized study who received ABRAXANE and gemcitabine for the first-line treatment of pancreatic adenocarcinoma, 41% were 65 years or older and 10% were 75 years or older. No overall differences in effectiveness were observed between patients who were 65 years of age or older and younger patients. Diarrhea, decreased appetite, dehydration and epistaxis were more frequent in patients 65 years or older compared with patients younger than 65 years old. Clinical studies of ABRAXANE did not include sufficient number of patients with pancreatic cancer who were 75 years and older to determine whether they respond differently from younger patients.

8.6 Patients with Hepatic Impairment
Because the exposure and toxicity of paclitaxel can be increased in patients with hepatic impairment, the administration of ABRAXANE should be performed with caution in patients with hepatic impairment *[see Dosage and Administration (2.4), Warnings and Precautions (5.6) and Clinical Pharmacology (12.3)]*. Abraxane has not been studied in combination with gemcitabine for the treatment of pancreatic cancer in patients with a bilirubin greater than the upper limit of normal.

8.7 Patients with Renal Impairment
The use of ABRAXANE has not been studied in patients with renal impairment.

10 OVERDOSAGE
There is no known antidote for ABRAXANE overdosage. The primary anticipated complications of overdosage would consist of bone marrow suppression, sensory neurotoxicity, and mucositis.

11 DESCRIPTION
ABRAXANE for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) (a bumin-bound) is an a bumin-bound form of paclitaxel with a mean particle size of approximately 130 nanometers. Paclitaxel exists in the particles in a non-crystalline, amorphous state. ABRAXANE is supplied as a white to yellow, sterile, lyophilized powder for reconstitution with 20 mL of 0.9% Sodium Chloride Injection, USP prior to intravenous infusion. Each single-use vial contains 100 mg of paclitaxel (bound to human albumin) and approximately 900 mg of human albumin (containing sodium caprylate and sodium acetyltryptophanate). Each milliliter (mL) of reconstituted suspension contains 5 mg paclitaxel. ABRAXANE is free of solvents.

The active agent in ABRAXANE is paclitaxel, a microtubule inhibitor. The chemical name for paclitaxel is 5β,20-Epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine.

Paclitaxel has the following structural formula:
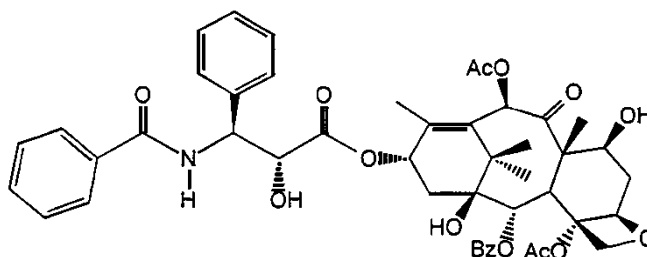
Paclitaxel is a white to off-white crystalline powder with the empirical formula $C_{47}H_{51}NO_{14}$ and a molecular weight of 853.91. It is highly lipophilic, insoluble in water, and melts at approximately 216°C to 217°C.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
ABRAXANE is a microtubule inh bitor that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. Paclitaxel induces abnormal arrays or "bundles" of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

12.3 Pharmacokinetics

Absorption
The pharmacokinetics of total paclitaxel following 30 and 180-minute infusions of ABRAXANE at dose levels of 80 to 375 mg/m^2 were determined in clinical studies. Dose levels of mg/m^2 refer to mg of paclitaxel in ABRAXANE. Following intravenous administration of ABRAXANE, paclitaxel plasma concentrations declined in a biphasic manner, the initial rapid decline representing distribution to the peripheral compartment and the slower second phase representing drug elimination. The terminal half-life was approximately 27 hours.

The drug exposure (AUCs) was dose proportional over 80 to 375 mg/m^2 and the pharmacokinetics of paclitaxel were independent of the duration of ABRAXANE administration. At the dose of 260 mg/m^2 for metastatic breast cancer, the mean maximum

concentration of paclitaxel, which occurred at the end of the infusion, was 18,741 ng/mL. The mean total clearance was 15 L/hr/m^2. The mean volume of distribution was 632 L/m^2 indicating extensive extravascular distribution and/or tissue binding of paclitaxel.

The pharmacokinetic data of 260 mg/m^2 ABRAXANE administered over a 30-minute infusion was compared to the pharmacokinetics of 175 mg/m^2 paclitaxel injection over a 3-hour infusion. The clearance was larger (43%) and the volume of distribution was also higher (53%) for ABRAXANE than for paclitaxel injection. Differences in the maximum concentration (C_{max}) and dose-corrected C_{max} reflected differences in total dose and rate of infusion. There were no differences in terminal half-lives.

Distribution
In vitro studies of binding to human serum proteins, using paclitaxel concentrations ranging from 0.1 to 50 μg/mL, indicated that between 89% to 98% of drug is bound; the presence of cimetidine, ranitidine, dexamethasone, or diphenhydramine did not affect protein binding of paclitaxel.

Metabolism
In vitro studies with human liver microsomes and tissue slices showed that paclitaxel was metabolized primarily to 6α-hydroxypaclitaxel by CYP2C8; and to two minor metabolites, 3'-*p*-hydroxypaclitaxel and 6α, 3'-*p*-dihydroxypaclitaxel, by CYP3A4. *In vitro*, the metabolism of paclitaxel to 6α-hydroxypaclitaxel was inhibited by a number of agents (ketoconazole, verapamil, diazepam, quinidine, dexamethasone, cyclosporin, teniposide, etoposide, and vincristine), but the concentrations used exceeded those found *in vivo* following normal therapeutic doses. Testosterone, 17α-ethinyl estradiol, retinoic acid, and quercetin, a specific inhibitor of CYP2C8, also inhibited the formation of 6α-hydroxypaclitaxel *in vitro*. The pharmacokinetics of paclitaxel may also be altered *in vivo* as a result of interactions with compounds that are substrates, inducers, or inh bitors of CYP2C8 and/or CYP3A4 *[see Drug Interactions (7)]*.

Excretion
After a 30-minute infusion of 260 mg/m^2 doses of ABRAXANE, the mean values for cumulative urinary recovery of unchanged drug (4%) indicated extensive non-renal clearance. Less than 1% of the total administered dose was excreted in urine as the metabolites 6α-hydroxypaclitaxel and 3'-*p*-hydroxypaclitaxel.

Fecal excretion was approximately 20% of the total dose administered.

Effect of Hepatic Impairment
The pharmacokinetic profile of ABRAXANE administered as a 30-minute infusion was evaluated in 15 out of 30 solid tumor patients with mild to severe hepatic impairment defined by serum bilirubin levels and AST levels. Patients with AST > 10 x ULN or bilirubin > 5 x ULN were not enrolled. ABRAXANE doses were assigned based on the degree of hepatic impairment as described:
- Mild (bilirubin > ULN to ≤ 1.25 x ULN and AST > ULN and < 10 x ULN): 260 mg/m^2
- Moderate (bilirubin 1.26 to 2 x ULN and AST > ULN and < 10 x ULN): 200 mg/m^2
- Severe (bilirubin 2.01 to 5 x ULN and AST > ULN and < 10 x ULN): 130 mg/m^2

The 260 mg/m^2 dose for mild hepatic impairment and the 200 mg/m^2 dose for moderate hepatic impairment resulted in paclitaxel exposures within the range seen in patients with normal hepatic function (mean AUC$_{0-∞}$ = 14,789 ± 6,703 hr*ng/mL). The 130 mg/m^2 dose in patients with severe hepatic impairment resulted in lower paclitaxel exposures than those seen in normal subjects. In addition, patients with severe hepatic impairment had higher mean cycle 1 absolute neutrophil count (ANC) nadir values than those with mild and moderate hepatic impairment. Table 11 summarizes the AUC values observed in the study. The 200 mg/m^2 dose has not been evaluated in patients with severe hepatic impairment, but it is predicted to adjust the paclitaxel AUC to the range observed in patients with normal hepatic function. There are no data for patients with AST >10 x ULN or bilirubin >5 x ULN *[see Dosage and Administration (2.4) and Use in Specific Populations (8.6)]*.

Table 11: Exposure (AUC$_{0-∞}$) of ABRAXANE Administered Intravenously over 30 Minutes in Patients with Hepatic Impairment

	Mild (n=5)	Moderate (n=5)	Severe[a] (n=5)
Dose	**260 mg/m^2**	**200 mg/m^2**	**130 mg/m^2**
AUC$_{inf}$ (hr*ng/mL)			
Mean ± SD	17434 ± 11454	14159 ± 13346	9187 ± 6475
Median (range)	13755 (7618, 35262)	7866 (5919, 37613)	6134 (5627, 20684)

[a] bilirubin 2.01 to 5 x ULN and AST > ULN and < 10 x ULN

Effect of Renal Impairment
The effect of renal impairment on the disposition of ABRAXANE has not been studied *[see Use in Specific Populations (8.7)]*.

Pharmacokinetic Interactions between and ABRAXANE and Carboplatin
Administration of carboplatin immediately after the completion of the ABRAXANE infusion to patients with NSCLC did not cause clinically meaningful changes in paclitaxel exposure. The observed mean AUC$_{inf}$ of free carboplatin was approximately 23% higher than the targeted value (6 min*mg/mL), but its mean half-life and clearance were consistent with those reported in the absence of paclitaxel.

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Pharmacokinetic Interactions between and ABRAXANE and Gemcitabine
Pharmacokinetic interactions between ABRAXANE and gemcitabine have not been studied in humans.

13   NONCLINICAL TOXICOLOGY

13.1   Carcinogenesis, Mutagenesis, Impairment of Fertility
The carcinogenic potential of ABRAXANE has not been studied.

Paclitaxel was clastogenic *in vitro* (chromosome aberrations in human lymphocytes) and *in vivo* (micronucleus test in mice). ABRAXANE was not mutagenic in the Ames test or the CHO/HGPRT gene mutation assay.

Administration of paclitaxel protein-bound particles to male rats at 42 mg/m^2 on a weekly basis (approximately 16% of the daily maximum recommended human exposure on a body surface area basis) for 11 weeks prior to mating with untreated female rats resulted in significantly reduced fertility accompanied by decreased pregnancy rates and increased loss of embryos in mated females. A low incidence of skeletal and soft tissue fetal anomalies was also observed at doses of 3 and 12 mg/m^2/week in this study (approximately 1 to 5% of the daily maximum recommended human exposure on a mg/m^2 basis). Testicular atrophy/degeneration was observed in single-dose toxicology studies in rodents administered paclitaxel protein-bound particles at doses lower than the recommended human dose; doses were 54 mg/m^2 in rodents and 175 mg/m^2 in dogs.

14   CLINICAL STUDIES

14.1   Metastatic Breast Cancer
Data from 106 patients accrued in two single arm open label studies and from 460 patients enrolled in a randomized comparative study were available to support the use of ABRAXANE in metastatic breast cancer.

Single Arm Open Label Studies
In one study, ABRAXANE was administered as a 30-minute infusion at a dose of 175 mg/m^2 to 43 patients with metastatic breast cancer. The second trial utilized a dose of 300 mg/m^2 as a 30-minute infusion in 63 patients with metastatic breast cancer. Cycles were administered at 3-week intervals. Objective responses were observed in both studies.

Randomized Comparative Study
This multicenter trial was conducted in 460 patients with metastatic breast cancer. Patients were randomized to receive ABRAXANE at a dose of 260 mg/m^2 given as a 30-minute infusion, or paclitaxel injection at 175 mg/m^2 given as a 3-hour infusion. Sixty-four percent of patients had impaired performance status (ECOG 1 or 2) at study entry; 79% had visceral metastases; and 76% had > 3 sites of metastases. Fourteen percent of the patients had not received prior chemotherapy; 27% had received chemotherapy in the adjuvant setting, 40% in the metastatic setting and 19% in both metastatic and adjuvant settings. Fifty-nine percent received study drug as second or greater than second-line therapy. Seventy-seven percent of the patients had been previously exposed to anthracyclines.

In this trial, patients in the ABRAXANE treatment arm had a statistically significantly higher reconciled target lesion response rate (the trial primary endpoint) of 21.5% (95% CI: 16.2% to 26.7%), compared to 11.1% (95% CI: 6.9% to 15.1%) for patients in the paclitaxel injection treatment arm. See Table 12. There was no statistically significant difference in overall survival between the two study arms.

Table 12: Efficacy Results from Randomized Metastatic Breast Cancer Trial

		ABRAXANE 260 mg/m^2	Paclitaxel Injection 175 mg/m^2
Reconciled Target Lesion Response Rate (primary endpoint)[a]			
All randomized patients	Response Rate [95% CI]	50/233 (21.5%) [16.19% – 26.73%]	25/227 (11.1%) [6.94% – 15.09%]
	p-value[b]	0.003	
Patients who had failed combination chemotherapy or relapsed within 6 months of adjuvant chemotherapy[c]	Response Rate [95% CI]	20/129 (15.5%) [9.26% – 21.75%]	12/143 (8.4%) [3.85% – 12.94%]

[a] Reconciled Target Lesion Response Rate (TLRR) was the prospectively defined protocol specific endpoint, based on independent radiologic assessment of tumor responses reconciled with investigator responses (which also included clinical information) for the first 6 cycles of therapy. The reconciled TLRR was lower than the investigator Reported Response Rates, which are based on all cycles of therapy.
[b] From Cochran-Mantel-Haenszel test stratified by 1st line vs. > 1st line therapy.
[c] Prior therapy included an anthracycline unless clinically contraindicated.

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14.2 Non-Small Cell Lung Cancer

A multicenter, randomized, open-label study was conducted in 1052 chemonaive patients with Stage IIIb/IV non-small cell lung cancer to compare ABRAXANE in combination with carboplatin to paclitaxel injection in combination with carboplatin as first-line treatment in patients with advanced non-small cell lung cancer. ABRAXANE was administered as an intravenous infusion over 30 minutes at a dose of 100 mg/m^2 on Days 1, 8, and 15 of each 21-day cycle. Paclitaxel injection was administered as an intravenous infusion over 3 hours at a dose of 200 mg/m^2, following premedication. In both treatment arms carboplatin at a dose of AUC = 6 mg•min/mL was administered intravenously on Day 1 of each 21-day cycle after completion of ABRAXANE/paclitaxel infusion. Treatment was administered until disease progression or development of an unacceptable toxicity. The major efficacy outcome measure was overall response rate as determined by a central independent review committee using RECIST guidelines (Version 1.0).

In the intent-to-treat (all-randomized) population, the median age was 60 years, 75% were men, 81% were White, 49% had adenocarcinoma, 43% had squamous cell lung cancer, 76% were ECOG PS 1, and 73% were current or former smokers. Patients received a median of 6 cycles of treatment in both study arms.

Patients in the ABRAXANE/carboplatin arm had a statistically significantly higher overall response rate compared to patients in the paclitaxel injection/carboplatin arm [(33% versus 25%) see Table 13]. There was no statistically significant difference in overall survival between the two study arms.

Table 13: Efficacy Results from Randomized Non-Small Cell Lung Cancer Trial (Intent-to-Treat Population)

	ABRAXANE (100 mg/m^2 weekly) + carboplatin (N=521)	Paclitaxel Injection (200 mg/m^2 every 3 weeks) + carboplatin (N=531)
Overall Response Rate (ORR)		
Confirmed complete or partial overall response, n (%)	170 (33%)	132 (25%)
95% CI	28.6, 36.7	21.2, 28.5
P-value (Chi-Square test)	0.005	
Median DoR in months (95% CI)	6.9 (5.6, 8.0)	6.0 (5.6, 7.1)
Overall Response Rate by Histology		
Carcinoma/Adenocarcinoma	66/254 (26%)	71/264 (27%)
Squamous Cell Carcinoma	94/229 (41%)	54/221 (24%)
Large Cell Carcinoma	3/9 (33%)	2/13 (15%)
Other	7/29 (24%)	5/33 (15%)

CI = confidence interval; DoR= Duration of response

14.3 Adenocarcinoma of the Pancreas

A multicenter, multinational, randomized, open-label study was conducted in 861 patients comparing ABRAXANE plus gemcitabine versus gemcitabine monotherapy as first-line treatment of metastatic adenocarcinoma of the pancreas. Key eligibility criteria were Karnofsky Performance Status (KPS) ≥70, normal bilirubin level, transaminase levels ≤ 2.5 times the upper limit of normal (ULN) or ≤ 5 times the ULN for patients with liver metastasis, no prior cytotoxic chemotherapy in the adjuvant setting or for metastatic disease, no ongoing active infection requiring systemic therapy, and no history of interstitial lung disease. Patients with rapid decline in KPS (≥10%) or serum albumin (≥20%) during the 14 day screening period prior to study randomization were ineligible.

A total of 861 patients were randomized (1:1) to the ABRAXANE/gemcitabine arm (N=431) or to the gemcitabine arm (N=430).

Randomization was stratified by geographic region (Australia, Western Europe, Eastern Europe, or North America), KPS (70 to 80 versus 90 to 100), and presence of liver metastasis (yes versus no). Patients randomized to ABRAXANE/gemcitabine received ABRAXANE 125 mg/m^2 as an intravenous infusion over 30-40 minutes followed by gemcitabine 1000 mg/m^2 as an intravenous infusion over 30-40 minutes on Days 1, 8, and 15 of each 28-day cycle. Patients randomized to gemcitabine received 1000 mg/m^2 as an intravenous infusion over 30-40 minutes weekly for 7 weeks followed by a 1-week rest period in Cycle 1 then as 1000 mg/m^2 on Days 1, 8 and 15 of each subsequent 28-day cycle. Patients in both arms received treatment until disease progression or unacceptable toxicity. The major efficacy outcome measure was overall survival (OS). Additional outcome measures were progression-free survival (PFS) and overall response rate (ORR), both assessed by independent, central, blinded radiological review using RECIST (version 1.0).

In the intent to treat (all randomized) population, the median age was 63 years (range 27-88 years) with 42% ≥ 65 years of age; 58% were men; 93% were White and KPS was 90-100 in 60%. Disease characteristics included 46% of patients with 3 or more metastatic sites; 84% of patients had liver metastasis; and the location of the primary pancreatic lesion was in the head of pancreas (43%), body (31%), or tail (25%).

Results for overall survival, progression-free survival, and overall response rate are shown in Table 14.

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Table 14: Efficacy Results from Randomized Study in Patients with Adenocarcinoma of the Pancreas (ITT Population)

	ABRAXANE(125 mg/m^2) and gemcitabine (N = 431)	Gemcitabine (N = 430)
Overall Survival		
Number of deaths, n (%)	333 (77)	359 (83)
Median Overall Survival (months)	**8.5**	**6.7**
95% CI	7.9, 9.5	6.0, 7.2
HR (95% CI) [a]	0.72 (0.62, 0.83)	
P-value [b]	<0.0001	
Progression-free Survival [c]		
Death or progression, n (%)	277 (64)	265 (62)
Median Progression-free Survival (months)	**5.5**	**3.7**
95% CI	4.5, 5.9	3.6, 4.0
HR (95% CI) [a]	0.69 (0.58, 0.82)	
P-value [b]	<0.0001	
Overall Response Rate [c]		
Confirmed complete or partial overall response, n (%)	**99 (23)**	**31 (7)**
95% CI	19.1, 27.2	5.0, 10.1
P-value [d]	<0.0001	

CI = confidence interval, HR = hazard ratio of ABRAXANE plus gemcitabine / gemcitabine, ITT = intent-to-treat population.
[a] Stratified Cox proportional hazard model.
[b] Stratified log-rank test stratified by geographic region (North America versus Others), Karnofsky performance score (70 to 80 versus 90 to 100), and presence of liver metastasis (yes versus no).
[c] Based on Independent Radiological Reviewer Assessment.
[d] Chi-square test.

In exploratory analyses conducted in clinically relevant subgroups with a sufficient number of subjects, the treatment effects on overall survival were similar to that observed in the overall study population.

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Figure 1: Kaplan-Meier Curve of Overall Survival (Intent-to-treat Population)
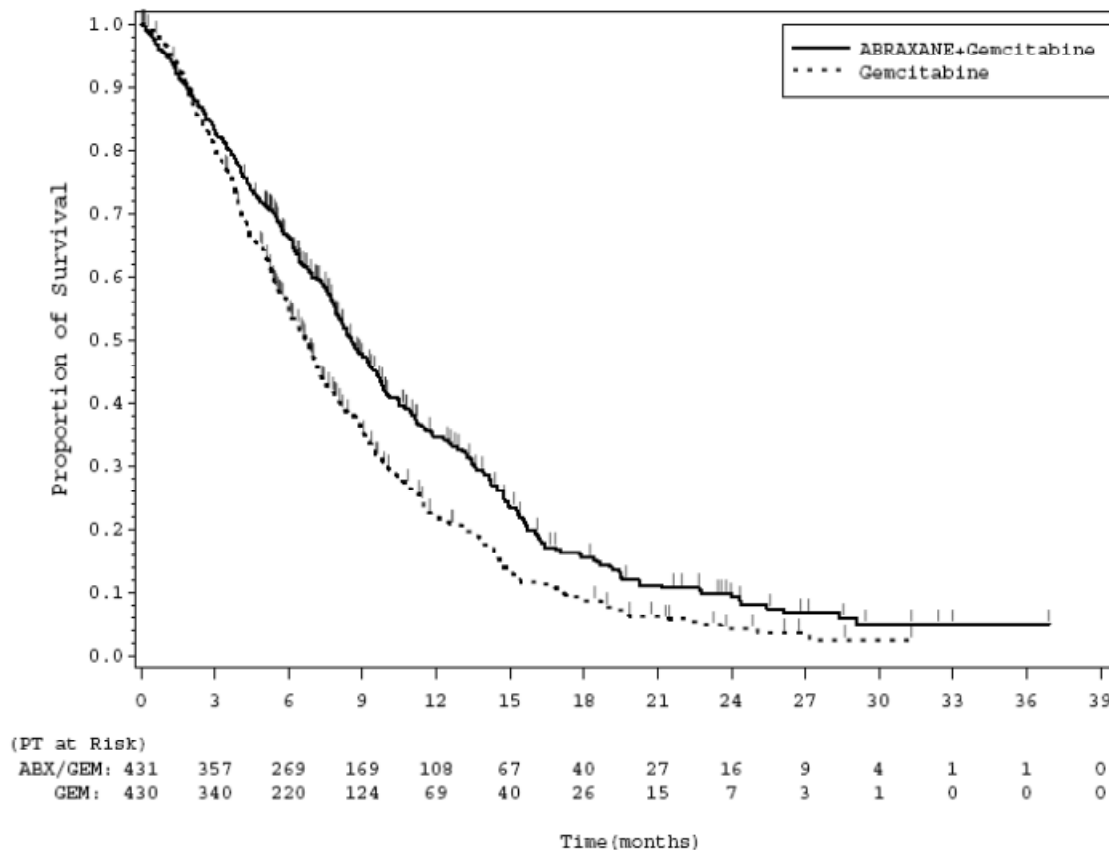
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4. Polovich, M., White, J. M., & Kelleher, L.O. (eds.) 2005. Chemotherapy and biotherapy guidelines and recommendations for practice (2nd. ed.) Pittsburgh, PA: Oncology Nursing Society.

16   HOW SUPPLIED/STORAGE AND HANDLING

16.1   How Supplied
Product No.: 103450
NDC No.: 68817-134-50   100 mg of paclitaxel in a single-use vial, individually packaged in a carton.

16.2   Storage
Store the vials in original cartons at 20°C to 25°C (68°F to 77°F). Retain in the original package to protect from bright light.

16.3   Handling and Disposal
Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published *[see References (15)]*. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

17   PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling

- ABRAXANE injection may cause fetal harm. Advise patients to avoid becoming pregnant while receiving this drug. Women of childbearing potential should use effective contraceptives while receiving ABRAXANE *[see Warnings and Precautions (5.8) and Use in Specific Populations (8.1)]*.
- Advise men not to father a child while receiving ABRAXANE *[see Warnings and Precautions (5.9)]*.
- Patients must be informed of the risk of low blood cell counts and severe and life-threatening infections and instructed to contact their physician immediately for fever or evidence of infection. *[see Warnings and Precautions (5.1), (5.3)]*.
- Patients should be instructed to contact their physician for persistent vomiting, diarrhea, or signs of dehydration.
- Patients must be informed that sensory neuropathy occurs frequently with ABRAXANE and patients should advise their physicians of numbness, tingling, pain or weakness involving the extremities *[see Warnings and Precautions (5.2)]*.
- Explain to patients that alopecia, fatigue/asthenia, and myalgia/arthralgia occur frequently with ABRAXANE
- Instruct patients to contact their physician for signs of an allergic reaction, which could be severe and sometimes fatal. *[see Warnings and Precautions (5.5)]*.
- Instruct patients to contact their physician immediately for sudden onset of dry persistent cough, or shortness of breath *[see Warnings and Precautions (5.4)]*.

Manufactured for: Celgene Corporation
                         Summit, NJ 07901

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U.S. Patent Numbers: See www.celgene.com.

ABRPI.006/PPI.006 09/13

Patient Information

ABRAXANE® (ah-BRAKS-ane)
(paclitaxel protein-bound particles for injectable suspension)
(albumin-bound)

Read this Patient Information before you start receiving ABRAXANE and before each infusion. This information does not take the place of talking with your doctor about your medical condition or your treatment.

What is ABRAXANE?

ABRAXANE is a prescription medicine used to treat:

- advanced breast cancer in people who have already received certain other medicines for their cancer.
- advanced non-small cell lung cancer, in combination with carboplatin in people who cannot be treated with surgery or radiation.
- and advanced pancreatic cancer, when used in combination with gemcitabine as the first medicine for advanced pancreatic cancer.

It is not known if ABRAXANE is safe or effective in children.

Who should not receive ABRAXANE?

Do not receive ABRAXANE if:

- your white blood cell count is below 1,500 cells/ mm^3.
- you have had a severe allergic reaction to ABRAXANE.

What should I tell my doctor before receiving ABRAXANE?
Before you receive ABRAXANE, tell your doctor if you:

- have liver or kidney problems.
- have any other medical conditions.
- are a man planning to father a child. You should not father a child during your treatment with ABRAXANE. ABRAXANE can harm the unborn baby of your partner. Talk to your doctor if this is a concern to you.
- are pregnant or plan to become pregnant. ABRAXANE can harm your unborn baby. You should not become pregnant while receiving ABRAXANE. Women who may become pregnant should use effective birth control (contraception). Talk to your doctor about the best way to prevent pregnancy while receiving ABRAXANE.
- are breastfeeding or plan to breastfeed. It is not known if ABRAXANE passes into your breast milk. You and your doctor should decide if you will receive ABRAXANE or breastfeed.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list to show your doctor and pharmacist when you get a new medicine.

How will I receive ABRAXANE?
- Your doctor will prescribe ABRAXANE in an amount that is right for you.
- Premedication to prevent allergic reactions is generally not needed to receive ABRAXANE. Premedication may be needed if you have had an allergic reaction to ABRAXANE. In case of severe allergic reaction, ABRAXANE should not be used again.
- ABRAXANE will be given to you by intravenous infusion into your vein.
- Your doctor should do regular blood tests while you receive ABRAXANE.

What are the possible side effects of ABRAXANE?

ABRAXANE may cause serious side effects, including:
- decreased blood cell counts. ABRAXANE can cause a severe decrease in neutrophils (a type of white blood cells important in fighting against bacterial infections) and platelets (important for clotting and to control bleeding). Your doctor will check your blood cell count during your treatment with ABRAXANE and after you have stopped your treatment.
- numbness, tingling, pain, or weakness in your hands or feet (neuropathy).
- severe infection (sepsis). If you receive ABRAXANE in combination with gemcitabine, infections can be severe and lead to death. Tell your doctor right away if you have a fever (temperature of greater than 100.4° F) or develop signs of infection.
- lung or breathing problems. If you receive Abraxane in combination with gemcitabine, lung or breathing problems may be severe and can lead to death. Tell your doctor right away if you have a sudden onset of persistent dry cough or shortness of breath.
- allergic reactions. Allergic reactions to ABRAXANE may be severe and can lead to death.

The most common side effects of ABRAXANE include:
- hair loss
- numbness, tingling, pain, or weakness in the hands or feet
- abnormal heart beat
- tiredness
- joint and muscle pain
- changes in your liver function tests
- rash
- low red blood cell count (anemia). Red blood cells carry oxygen to your body tissues. Tell your doctor if you feel weak, tired or short of breath.
- nausea and vomiting
- infections. If you have a fever (temperature of greater than 100.4° F) or other signs of infection, tell your doctor right away.

- Diarrhea
- Loss of body fluid (dehydration)
- Swelling in the hands or feet

These are not all the possible side effects of ABRAXANE. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of ABRAXANE.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet.

This Patient Information leaflet summarizes the important information about ABRAXANE. If you would like more information, talk to your doctor. You can ask your doctor or pharmacist for information about ABRAXANE that is written for health professionals.

For more information, call 1-888-423-5436.

What are the ingredients in ABRAXANE?

Active ingredient: paclitaxel (bound to human albumin).

Other ingredient: human albumin (containing sodium caprylate and sodium acetyltryptophanate).

This Patient Information has been approved by the U.S. Food and Drug Administration.

Revised: September 2013

Manufactured for: Celgene Corporation
                     Summit, NJ 07901

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U.S. Patent Numbers: See www.celgene.com.

ABRPPI.006 09/13

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21660Orig1s037

<u>SUMMARY REVIEW</u>

Division Director Summary Review

Date	September 6, 2013
From	Patricia Keegan, M.D.
Subject	Division Director Summary Review
NDA Supplement #	N 21660/S-037
Applicant Name	Abraxis Bioscience LLC, a wholly owned subsidiary of Celgene Corporation
Date of Submission	March 21, 2013
PDUFA Goal Date	September 21, 2013
Proprietary Name / Established (USAN) Name	Abraxane for Injectable Suspension/ paclitaxel protein-bound particles for injectable suspension (albumin-bound)
Dosage Forms / Strength	Lyophilized Powder for Injectable Suspension/ 100mg paclitaxel in single-dose vials
Proposed Indication(s)	"ABRAXANE is indicated for the first-line treatment of patients with _____ (b) (4) metastatic adenocarcinoma of the pancreas, in combination with gemcitabine."
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	Names of discipline reviewers
Regulatory Project Manager Review	Meredith Libeg
Medical Officer Review	Abhilasha Nair
Statistical Review	Yuan-Li Shen
CMC ONDQA Review	Sue Ching Lin
Nonclinical Pharmacology/Toxicology Review	Margaret Brower
Clinical Pharmacology Review	Stacy Shord
OPDP Consult Review	Marybeth Toscano
Patient Labeling Consult Review	Nathan P. Caulk
CDTL Review	Steven Lemery

OND=Office of New Drugs
CMC=Chemistry, Manufacturing, and Controls
ONDQA=Office of New Drug Quality Assurance
OPDP=Office of Prescription Drug Promotion
CDTL=Cross-Discipline Team Leader

Division Director Summary Review

1. Introduction

This efficacy supplement for Abraxane (paclitaxel protein-bound particles for injectable suspension (albumin-bound); Abraxis Biosciences, Inc.) was reviewed under the provisions of section 505(b)(2) of the Food, Drug, and Cosmetic Act since the original approval of Abraxane (NDA 021660) relied on FDA's prior finding of safety and effectiveness for the listed drug, Taxol® (paclitaxel; Bristol Myers Squibb). The supplement was submitted to support a new indication for the first-line treatment of metastatic pancreatic cancer, which is not an approved indication for the listed drug, Taxol. The major efficacy trial supporting this indication is Study CA-046, a single, multicenter, randomized trial designed to demonstrate that the addition of Abraxane to gemcitabine improves survival as compared to single agent gemcitabine.

Study CA-046 met its primary endpoint, demonstrating a statistically robust increase in overall survival [HR 0.72 ((95% CI=0.62,0.83); p-value < 0.0001] with an increase in the estimated median survival time of 1.8 months, based on the estimated median survival times of 8.5 months and 6.7 months in the Abraxane/gemcitabine and gemcitabine alone arms, respectively. In addition, the trial demonstrated a significant improvement in progression-free survival (PFS) based on independent review [HR 0.69 (95% CI=0.58, 0.82) p-value <0.0001] with median PFS times of 5.5 months and 3.7 months in the Abraxane/gemcitabine and gemcitabine alone arms, respectively. The objective response rate with the combination was also significantly higher (23% vs. 7%, p-value <0.0001) as compared to gemcitabine alone.

Safety was evaluated in the 421 patients in the Abraxane/gemcitabine arm, which was compared with adverse reactions in 402 patients who received gemcitabine alone in Study CA-046. In this trial, the most common ($\geq 20\%$) adverse reactions of Abraxane were neutropenia, fatigue, peripheral neuropathy, nausea, alopecia, peripheral edema, diarrhea, pyrexia, vomiting, decreased appetite, rash, and dehydration. The most common serious adverse reactions of Abraxane were pyrexia (6%), dehydration (5%), pneumonia (4%) and vomiting (4%).There incidence of the following Grade 3-4 adverse reactions: neutropenia (38% vs. 27%), thrombocytopenia (13% vs. 9%), fatigue (18% vs. 9%), peripheral neuropathy (17% vs. 1%). dehydration (7% vs. 2%), sepsis (5% vs. 2%), and drug-induced pneumonitis (4% vs. 1%) were also higher in the Abraxane/gemcitabine arm.   The most common adverse reactions resulting in permanent discontinuation of Abraxane were peripheral neuropathy (8%), fatigue (4%) and thrombocytopenia (2%).

Clinically significant toxicities which were first observed in this trial, which will be added to the Warnings and Precautions section of the product labeling, are sepsis and drug-induced pneumonitis. Sepsis occurred in 5% of patients who received Abraxane/gemcitabine compared to 2% of patients who received gemcitabine alone. Sepsis occurred in patients with and in patients without neutropenia. Risk factors for sepsis included biliary obstruction or presence

of biliary stent. Pneumonitis occurred in 4% of patients who received Abraxane/gemcitabine compared to 1% of patients who received gemcitabine alone. Two of 17 cases of pneumonitis in the Abraxane-containing arm were fatal. In addition, although peripheral neuropathy has been identified in previous trials of Abraxane, there was a marked increase in the incidence of Grade 3 peripheral neuropathy (17% vs. 1%) in the Abraxane/gemcitabine arm as compared to gemcitabine alone arm.

Major issues considered during this review were the impact of protocol modifications to increase the sample size during the conduct of the trial on the demonstration of efficacy and whether the benefits of the 1.8-month improvement in median survival, supported by the significant improvements in progression-free survival and objective response rates, outweighed the risks from the addition of Abraxane to gemcitabine.

2.   Background

Proposed Indication

> "ABRAXANE is indicated for the first-line treatment of patients with ⬛⬛⬛⬛ (b) (4) ⬛⬛⬛⬛ (b) (4) metastatic adenocarcinoma of the pancreas, in combination with gemcitabine"

Available Therapy for Proposed Indication

Based on the Surveillance and Epidemiology and End Results (SEER) epidemiologic data, an estimated 45,220 men and women (approximately equal incidence) will be diagnosed with pancreatic cancer.[1] Pancreatic cancer has a slight male predominance and with a higher incidence in Blacks and a lower incidence in Asians than in Whites. The median age at diagnosis for cancer of the pancreas is 71 years of age and, at diagnosis, approximately 27% of patients have regional disease (involved regional nodes) and 53% have metastatic disease. The prognoses in these patients is poor with 5-year relative survival rates of 9% for patients diagnosed with regional disease and 2% for patients diagnosed with metastatic disease.

There are four drugs which are currently FDA-approved for the treatment of pancreatic cancer; these are fluorouracil injection, erlotinib, gemcitabine, and mitomycin C injection. While the benefits of fluorouracil injection and mitomycin C injection are not well described, both gemcitabine and erlotinib have been shown to improved overall survival.

Gemzar (gemcitabine; Eli Lilly & Co) was approved on May 15, 1996 for the first-line treatment for patients with locally advanced (nonresectable Stage II or Stage III) or metastatic (Stage IV) adenocarcinoma of the pancreas and for patients with pancreatic cancer previously treated with 5-FU.

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[1] http://seer.cancer.gov/statfacts/html/pancreas.html (accessed on September 4, 2013).

Data from two clinical trials evaluated the use of Gemzar in patients with locally advanced or metastatic pancreatic cancer. The first trial was a randomized (1:1), multicenter trial comparing the safety and efficacy of single-agent gemcitabine to 5-fluorouracil (5-FU) in 126 patients who had received no prior chemotherapy. The second trial was a single-arm trial of gemcitabine conducted in 63 patients with pancreatic cancer previously treated with 5-FU or a 5-FU-containing regimen. In both studies, the first cycle of Gemzar was administered intravenously at a dose of 1000 mg/m2 over 30 minutes once weekly for up to 7 weeks (or until toxicity necessitated holding a dose) followed by a week of rest from treatment with Gemzar. Subsequent cycles consisted of injections once weekly for 3 consecutive weeks out of every 4 weeks.

The primary efficacy parameter in these studies was "clinical benefit response", which is a measure of clinical improvement based on analgesic consumption, pain intensity, performance status and weight change. Definitions for improvement in these variables were formulated prospectively during the design of the two trials. A patient was considered a clinical benefit responder if either:

i) The patient showed a ≥50% reduction in pain intensity (Memorial Pain Assessment Card) or analgesic consumption, or a twenty-point or greater improvement in performance status (Karnofsky Performance Scale) for a period of at least four consecutive weeks, without showing any sustained worsening in any of the other parameters. Sustained worsening was defined as four consecutive weeks with either any increase in pain intensity or analgesic consumption or a 20 point decrease in performance status occurring during the first 12 weeks of therapy.
OR:

ii) The patient was stable on all of the aforementioned parameters, and showed a marked, sustained weight gain (≥ 7% increase maintained for ≥ 4 weeks) not due to fluid accumulation.

In the first trial, the clinical benefit response rate was improved (22% vs. 4.8%; p=0.004) in patients randomized to gemcitabine compared to those randomized to 5-flourouracil; in addition, survival was significantly longer (p=0.0009) with median survivals of 5.7 months vs. 4.2 months and time-to-disease progression was significantly longer (p=0.0013) with median TTP times of 2.1 months vs. 0.9 months, in the gemcitabine and 5-flourouracil arms, respectively. In the second trial, the clinical benefit response rate was 27%.

Tarceva (erlotinib; OSI Pharmaceuticals, Inc.) received approval on November 2, 2005 for the use of Tarceva (erlotinib) tablets, in combination with gemcitabine, for the first-line treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer.

The efficacy and safety of TARCEVA in combination with gemcitabine as a first-line treatment was assessed in a randomized, double blind, placebo-controlled trial in 569 patients with locally advanced, unresectable or metastatic pancreatic cancer. Patients were randomized 1:1 to receive TARCEVA (100 mg or 150 mg) or placebo once daily in combination with gemcitabine at the approved dose and schedule for this indication. The primary endpoint of this trial was overall survival and secondary endpoints included response rate, progression-free

survival (PFS). A total of 285 patients were randomized to receive gemcitabine plus erlotinib (261 patients in the 100 mg cohort and 24 patients in the 150 mg cohort) and 284 patients were randomized to receive gemcitabine plus placebo (260 patients in the 100 mg cohort and 24 patients in the 150 mg cohort). Efficacy analyses were conducted in patients in the 100 mg erlotinib/placebo cohort. The trial demonstrated a statistically significant improvement in survival [HR 0.81 (95% CI: 0.68, 0.97), p=0.028], with median survival of 6.4 months and 6.0 months in the erlotinib plus gemcitabine and gemcitabine alone arms, respectively. The trial also demonstrated a significant improvement in progression-free survival [HR 0.76 (95% CI: 0.64, 0.92); p=0.006] with median PFS times of 3.8 and 3.5 months, respectively however the objective response rates were similar (8.6% and 7.9%) in the two arms.

In addition to the FDA-approved drugs discussed above, the combination chemotherapy regimen of FOLFIRINOX is recommended by the NCCN for the treatment of good performance status patients with metastatic pancreatic cancer, based on the published results by Conroy, et al.[2] In this trial, 342 patients with metastatic pancreatic cancer and an Eastern Cooperative Oncology Group performance status score of 0 or 1 were randomized to receive FOLFIRINOX (oxaliplatin, 85 mg^2 body-surface area; irinotecan, 180 mg^2; leucovorin, 400 mg^2; and fluorouracil, 400 mg^2 given as a bolus followed by 2400 mg^2 given as a 46-hour continuous infusion, every 2 weeks) or gemcitabine at the approved dose and schedule for pancreatic cancer.

As reported by Conroy, the trial demonstrated a statistically significant improvement in the primary endpoint of overall survival [HR 0.57 (95% CI 0.45, 0.73); p<0.001) with median survival times of 11.1 months in the FOLFIRINOX arm and 6.8 months in the gemcitabine arm. The trial also demonstrated a significant improvement in progression-free survival (HR 0.47 (95% CI: 0.37, 0.59); p<0.001) with median PFS times of 6.4 months and 3.3 months in the FOLFIRINOX and gemcitabine arms, respectively and a significant improvement in overall response rate (31.6% vs. 9.4%) for FOLFIRINOX.

Regulatory History for NDA 21660

January 7, 2005: Abraxane (paclitaxel protein-bound particles, for injection) (albumin-bound) was approved for "the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated."

This application was approved under the provisions of 505(b)(2) of the Food, Drug, and Cosmetic Act, relying on FDA's prior finding of safety and effectiveness for the listed drug, Taxol, for the same indication. Safety and demonstration of clinical activity were primarily supported by a single randomized (1:1) trial conducted in 460 patients with metastatic breast cancer. The trial was designed to establish that single agent Abraxane, dosed at 260 mg/m^2 as a 30 minute intravenous infusion, preserved at least 75% of the treatment effect on overall response rate observed in patients receiving Taxol at a dose of 175 mg/m^2 as a 3-hour intravenous infusion. The trial demonstrated superior overall

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[2] Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. NEJM. 2011 364(19):1817-25.

response rate (21.5% vs. 11.1%, p<0.003 stratified CMH test) for Abraxane-treated patients. The application was approved with post-marketing commitments to provide mature overall survival results, as follows: "Survival data and analysis results should be submitted from randomized study CA012-0 when 80% of the patients have died. Data should be available for submission approximately June 2005."

February 15, 2007: An efficacy supplement with clinical data (SE8) was submitted fulfilling the post-marketing commitment to an analysis of overall survival. At the time of the analysis, 74% of the patients in the Abraxane arm and 77% of the patients in the Taxol arm had died. There was no statistically significant different in overall survival between the two arms [HR 0.90 (95% CI: 0.73, 1.12), p=0.35]. Product labeling was amended to include a statement that there was no statistically significant different in overall survival between the two arms for the major efficacy trial.

October 11, 2012: Approval was granted for a new indication for first-line treatment of locally advanced or metastatic non-small cell lung cancer, in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy. Safety and confirmation of activity were established in a single, multicenter, open-label, randomized (1:1) trial (CA031) conducted in 1052 patients with stage IIIB or IV non-small cell lung cancer (NSCLC). Patients received Abraxane 100 mg/m^2 as an intravenous infusion over 30 minutes on Days 1, 8, and 15 of each 21-day cycle or paclitaxel injection 200 mg/m^2 as an intravenous infusion over 3 hours. Both treatment arms received carboplatin at an AUC of 6 mg•min/mL intravenously on Day 1 of each 21-day cycle, following the paclitaxel infusion.

The trial demonstrated superior overall response rate for the Abraxane-containing arm, as determined by an independent review committee masked to treatment assignment, the primary objective of the trial. The odds ratio for comparison of the overall response rate was 1.31 (overall response rates were 33% and 25%, p= 0.005, Chi square test). Responses appeared to be equally durable in both treatment arms with median durations of response were 9.6 and 9.5 months in the Abraxane- and paclitaxel injection-containing arms, respectively. The trial failed to meet the two key secondary objectives of demonstration of superior progression-free survival [HR 0.93 (95% CI: 0.79, 1.09); p= 0.38, unstratified log-rank test] and superior overall survival [HR 0.93 (95% CI: 0.81, 1.08); p=0.34, unstratified log-rank test] for the Abraxane-containing arm.

Regulatory History for NDA 21660/S037

The clinical development program for Abraxane for the treatment of metastatic pancreatic cancer was initiation under IND 55, 974 and was completed under IND 115027, an IND limited to the development program for pancreatic cancer.

September 9, 2008: A pre-sNDA meeting was held to discuss (b) (4) CA-046 (b) (4) for Abraxane in combination with gemcitabine for the first-line treatment metastatic pancreatic cancer (supported by CA-046) (b) (4)

With regard to Study CA-046, FDA agreed that the study endpoints, general design (randomized trial), and control arm (gemcitabine at the approved dose for this indication), were acceptable.

August 4, 2011: A Type C meeting was held to discuss the acceptability of submission of the results of CA-046 based on positive results on a surrogate endpoint under the provisions of 21 CFR 314 Subpart H. FDA advised that the study be completed as planned, with the NDA submission based on evidence of improvement in overall survival. FDA also initially advised that drug-drug interaction studies be conducted, however during the meeting, FDA agreed that non-clinical data and data regarding the metabolic pathways for gemcitabine and paclitaxel could be used to address this issue without the need for additional pharmacokinetic data.

October 16, 2012: Advice/information request letter responding to Abraxis' questions regarding content/format of the proposed sNDA. FDA confirmed general agreement with the proposed approach; however FDA requested additional detail on case narratives and a side-by-side format of safety data, where data would be segregated by dose and schedule of Abraxane and by indication.

November 8, 2012: Teleconference between FDA and Abraxis in which Abraxis summarized the top-line results of CA-046.

January 3, 2013: Advice information letter responding to Abraxis' follow-up questions on the content and format of the proposed sNDA. FDA again re-iterated the need to provide integrated safety data across indications for the combination use of Abraxane and gemcitabine, stated the need to submit narratives for all drop-outs, regardless of the reason for treatment discontinuation prior to disease progression. FDA agreed to the proposal for STDM submission but requested specific flags in the dataset.

January 15, 2013: Type B, pre-sNDA meeting. FDA agreed that the results of CA-040 and CA-046 would be adequate to support the submission and filing of a supplement, FDA requested that exploratory efficacy analyses based on SPARC expression be conducted and identified no additional requests for the content/format of the proposed supplement.

3. CMC

I concur with the conclusions reached by the quality reviewer that there are no outstanding CMC issues that preclude approval. No modification to chemistry, manufacturing, and controls for paclitaxel protein-bound particles for injectable suspension (albumin-bound) were contained in this supplement. The quality reviewer found the request for categorical exclusion from the preparation of an environmental assessment under 21 CFR 25.31(b), to be acceptable. Minor revisions to product labeling (Description; Dosage Forms and Strengths) were requested by the quality reviewer for consistency with current CDER policies.

4. Nonclinical Pharmacology/Toxicology

Not applicable.

5. Clinical Pharmacology

I concur with the conclusions reached by the clinical pharmacology reviewer that there are no outstanding clinical pharmacology issues that preclude approval. No clinical pharmacokinetic data were obtained in Protocols CA-040 and CA-046. The proposed dose of Abraxane 125 mg/m^2 as an intravenous infusion over 30-40 minutes on days 1, 8, and 15 of each 28-day treatment cycle, in combination with gemcitabine 1,000 mg/m^2, is based on tolerability in Studies CA-040 and CA-046.

The clinical pharmacology reviewer evaluated proposed revisions to Sections 2.4 (Dosage and Administration) and 7 (Drug Interactions) of the product labeling.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

I concur with the conclusions reached by the clinical and statistical reviewers that there are no outstanding issues that preclude approval.

Clinical data supporting this application were derived primarily from two trials, Study CA-040, a dose-finding study of the combination of Abraxane and gemcitabine, which supports the dose used in the major efficacy study, and Study CA-046, the major efficacy trial. The "recommended phase 2" dose determined in Study CA-040 was employed in Study CA-046, however the need for multiple protocol revisions to modify dosing and dose adjustments for toxicity in Study CA-046 suggests that an optimal dosing regimen was not determined prior to the initiation of Study CA-046.

Study CA-046

Protocol History
The major efficacy trial, Study CA-046, was modified six times during the conduct of the study; a detailed listing of these amendments are provided in the clinical and statistical reviews. The most significant amendment potentially affecting the study results was Amendment 4, which increased the sample size and altered the timing of the final efficacy analysis, as summarized below.

Amendment 4 (9/30/2010)
- Revised the sample size to 842 patients and modified the timing of the final analysis of survival to occur after "at least" 608 deaths, in order to allow for an increase in statistical power from 80% to 90%.
- Revised the monitoring plan to state that that baseline and follow-up PET scans would not be obtained in patients enrolled after the date of this amendment and no follow-up PET scans would be obtained in patients enrolled prior to this amendment.

Given the possibility that this modification of the trial may have been informed, the FDA statistician confirmed that the clinical trial would have met the primary endpoint if analyzed at the sample size and number of deaths identified in the original protocol.

Trial Design

The trial was designed as a multicenter, multinational, randomized, open-label study designed to compare two treatment arms and establish the clinical benefits and risks of the addition of Abraxane to the approved dose and schedule of gemcitabine for this indication. Randomization was stratified by geographic region (Australia, Western Europe, Eastern Europe, or North America), KPS (70 to 80 versus 90 to 100), and presence of liver metastasis (yes versus no).

The primary objective of study CA046 was the overall survival (OS). The secondary efficacy objectives were objectives were to evaluate the progression free survival (PFS) and objective response rate (ORR).

Key eligibility criteria included Karnofsky Performance Status (KPS) ≥70, normal bilirubin level, transaminase levels ≤ 2.5 times the upper limit of normal (ULN) or ≤ 5 times the ULN for patients with liver metastasis, no prior cytotoxic chemotherapy in the adjuvant setting or for metastatic disease, no ongoing active infection requiring systemic therapy, and no history of interstitial lung disease. Patients with rapid decline in KPS (≥10%) or serum albumin (≥20%) during the 14 day screening period prior to study randomization were ineligible.

Patients equally allocated to the following two treatment arms
- Abraxane 125 mg/m^2 as an intravenous infusion over 30-40 minutes followed by gemcitabine 1000 mg/m^2 as an intravenous infusion over 30-40 minutes on Days 1, 8, and 15 of each 28-day cycle.
- Gemcitabine received 1000 mg/m^2 as an intravenous infusion over 30-40 minutes weekly for 7 weeks followed by a 1-week rest period in Cycle 1 then as 1000 mg/m^2 on Days 1, 8 and 15 of each subsequent 28-day cycle.

Patients in both arms received treatment until disease progression or unacceptable toxicity.

In the final analysis plan, the planned sample size was 842 patients, equally allocated to the two treatment arms. The assumptions for this sample size were a 30% improvement in overall survival (HR = 0.769) for Abraxane plus gemcitabine compared to gemcitabine, allowing 90% power to reject the null hypothesis at a two-sided type I error of 0.049 at the time of the final analysis conducted on at least 608 events (deaths) in the intent-to-treat population.

One planned interim analysis for futility was to be conducted after 200 patients had been enrolled and followed for 6 months. An alpha spending function was to be utilized to preserve the overall study-wise Type 1 error at 0.050, with allocation of alpha of 0.001 and 0.049 at the interim and final analyses, respectively.

The key secondary efficacy endpoints were progression-free survival and overall survival. The analysis plan stated that, to control the overall family-wise Type I error rate at two-sided alpha of 0.050 for these two secondary efficacy endpoints. Progression-free survival was to be tested first at an alpha of 0.05. Comparison of the objective tumor response rate would be tested at an alpha of 0.05 only if the comparison for progression-free survival was significant.

Demographics
The first patient was enrolled on May 8, 2009; the last patient was randomized on April 17, 2012. A total of 861 patients were randomized (1:1) to receive either Abraxane plus gemcitabine (N=431) or to the gemcitabine alone (N=430) across 151 sites participating clinical sites in 11 countries. All patients were enrolled from one of four regions (North America, Western Europe, Eastern Europe and Australia); 63% of the study population was enrolled in the US or Canada.

In the intent to treat (all randomized) population, the median age was 63 years (range 27-88 years) with 42% ≥ 65 years of age; 58% were men; 93% were White and KPS was 90-100 in 60%. Disease characteristics included 46% of patients with 3 or more metastatic sites; 84% of patients had liver metastasis; and the location of the primary pancreatic lesion was in the head of pancreas (43%), body (31%), or tail (25%).

Efficacy Results

Results for overall survival, progression-free survival, and overall response rate are shown in the table below, abstracted from the product labeling.

Key Efficacy Results of Study CA-046

|	Abraxane plus Gemcitabine (N = 431)	Gemcitabine (N = 430)
Overall Survival		
Number of deaths, n (%)	333 (77)	359 (83)
Median Overall Survival (months)	8.5	6.7
95% CI	7.9, 9.5	6.0, 7.2
HR (95% CI) [a]	0.72 (0.62, 0.83)	
P-value[b]	<0.0001	
Progression-free Survival[c]		
Death or progression, n (%)	277 (64)	265 (62)
Median Progression-free Survival (months)	5.5	3.7
95% CI	4.5, 5.9	3.6, 4.0
HR (95% CI) [a]	0.69 (0.58, 0.82)	
P-value[b]	<0.0001	
Overall Response Rate[c]		
Confirmed complete or partial responses, n (rate %)	99 (23%)	31 (7%)
95% CI	19, 27	5.0, 10
P-value [d]	<0.0001	

[a] Stratified Cox proportional hazard model.
[b] Stratified log-rank test stratified by geographic region (North America versus Others), Karnofsky performance score (70 to 80 versus 90 to 100), and presence of liver metastasis (yes versus no).
[c] Based on Independent Radiological Reviewer Assessment.
[d] Chi-square test.

Kaplan-Meier Curve of Overall Survival (Intent-to-treat Population)
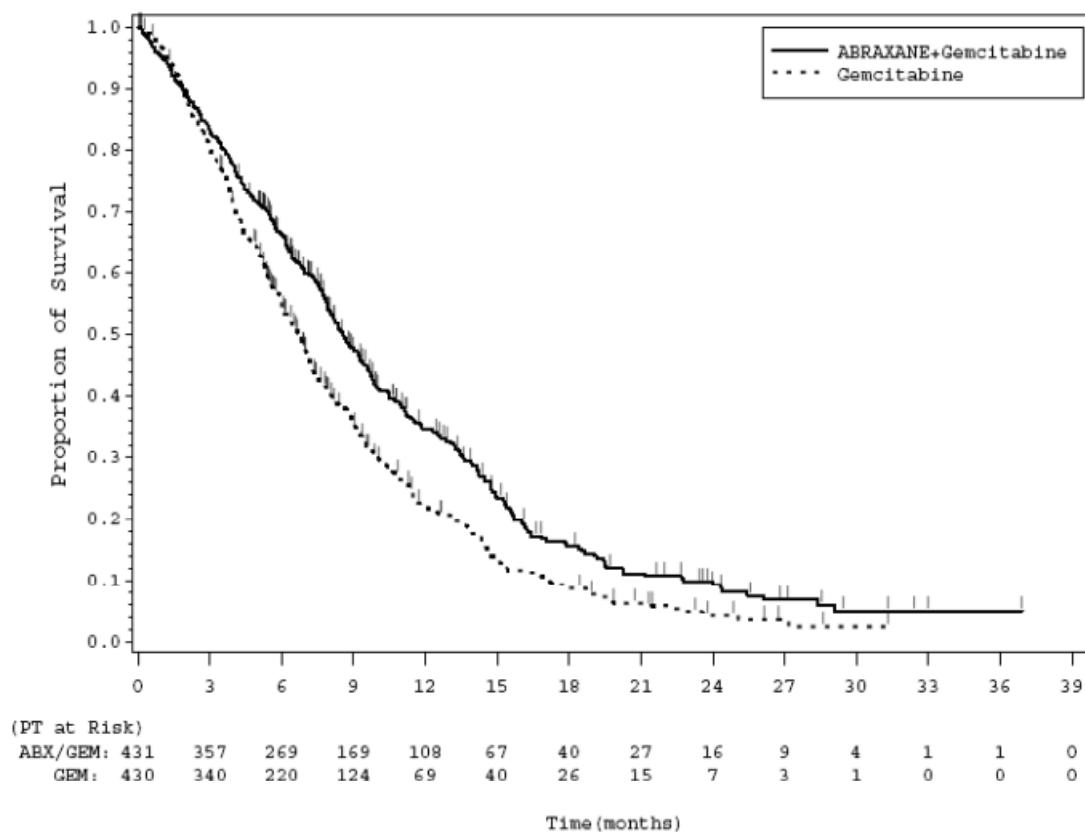
As discussed in the statistical review, the treatment effect on survival was robust as demonstrated in multiple sensitivity analyses and adjustments (or lack of adjustment) for stratification variables.

8. Safety

Size of the database

The safety database of 421 Abraxane-treated patients in CA-046 was considered adequate to characterize adverse reactions occurring in 1% of patients receiving this combination. The randomized, add-on trial design allowed identification of adverse reactions occurring above the "background" rate of the underlying disease and adverse reactions of gemcitabine. Clinically significant adverse reactions identified in this trial included peripheral neuropathy (previously reported in clinical trial and product labeling), sepsis (not previously identified), and drug-induced pneumonitis (not previously identified). These risks are described in product labeling and summarized below:

Peripheral Neuropathy
Grade 3 peripheral neuropathy occurred in 17% of patients who received ABRAXANE/gemcitabine compared to 1% of patients who received gemcitabine only; no patients developed grade 4 peripheral neuropathy. The median time to first occurrence of Grade 3 peripheral neuropathy in the ABRAXANE arm was 140 days. Upon suspension of ABRAXANE dosing, the median time to improvement from Grade 3 peripheral neuropathy to ≤ Grade 1 was 29 days. Of Abraxane-treated patients with Grade 3 peripheral neuropathy, 44% resumed Abraxane at a reduced dose.

Sepsis
Sepsis occurred in 5% of patients who received Abraxane/gemcitabine compared to 2% of patients who received gemcitabine alone. Sepsis occurred in patients with and without neutropenia. Risk factors for sepsis included biliary obstruction or presence of biliary stent.

Pneumonitis
Pneumonitis occurred in 4% of patients who received Abraxane/gemcitabine compared to 1% of patients who received gemcitabine alone. Two of 17 cases of pneumonitis in the Abraxane-containing arm were fatal.

The most common adverse reactions of Abraxane (those occurring at a higher incidence with the Abraxane/gemcitabine arm than in the gemcitabine alone arm), are provided in the two tables below which are abstracted from the product labeling.

Selected Adverse Reactions with a Higher Incidence (≥5% for All Grade Toxicity or ≥2% for Grade 3 or Higher) in the Abraxane-containing Arm

System Organ Class	Adverse Reaction	Abraxane plus gemcitabine (N=421)		Gemcitabine (N=402)	
		All Grades	Grade 3 or Higher	All Grades	Grade 3 or Higher
General disorders and administration site conditions	Fatigue	248 (59%)	77 (18%)	183 (46%)	37 (9%)
	Peripheral edema	194 (46%)	13 (3%)	122 (30%)	12 (3%)
	Pyrexia	171 (41%)	12 (3%)	114 (28%)	4 (1%)
	Asthenia	79 (19%)	29 (7%)	54 (13%)	17 (4%)
	Mucositis	42 (10%)	6 (1%)	16 (4%)	1 (<1%)
Gastrointestinal disorders	Nausea	228 (54%)	27 (6%)	192 (48%)	14 (3%)
	Diarrhea	184 (44%)	26 (6%)	95 (24%)	6 (1%)
	Vomiting	151 (36%)	25 (6%)	113 (28%)	15 (4%)
Skin and subcutaneous tissue disorders	Alopecia	212 (50%)	6 (1%)	21 (5%)	0
	Rash	128 (30%)	8 (2%)	45 (11%)	2 (<1%)
Nervous system disorders	Peripheral neuropathy[a]	227 (54%)	70 (17%)	51 (13%)	3 (1%)
	Dysgeusia	68 (16%)	0	33 (8%)	0
	Headache	60 (14%)	1 (<1%)	38 (9%)	1 (<1%)
Metabolism and nutrition disorders	Decreased appetite	152 (36%)	23 (5%)	104 (26%)	8 (2%)
	Dehydration	87 (21%)	31 (7%)	45 (11%)	10 (2%)
	Hypokalemia	52 (12%)	18 (4%)	28 (7%)	6 (1%)
Respiratory, thoracic and mediastinal disorders	Cough	72 (17%)	0	30 (7%)	0
	Epistaxis	64 (15%)	1 (<1%)	14 (3%)	1 (<1%)
Infections and infestations	Urinary tract infections [b]	47 (11%)	10 (2%)	20 (5%)	1 (<1%)
Musculoskeletal and connective tissue disorders	Pain in extremity	48 (11%)	3 (1%)	24 (6%)	3 (1%)
	Arthralgia	47 (11%)	3 (1%)	13 (3%)	1 (<1%)
	Myalgia	44 (10%)	4 (1%)	15 (4%)	0

[a] Peripheral neuropathy is defined by the MedDRA Version 15.0 Standard MedDRA Query neuropathy (broad scope).
[b] Urinary tract infections includes the preferred terms of: urinary tract infection, cystitis, urosepsis, urinary tract infection bacterial, and urinary tract infection enterococcccal.

Selected Hematologic Laboratory-Detected Abnormalities with a Higher Incidence (≥ 5% for Grades 1-4 or ≥ 2% for Grades 3-4) in the Abraxane-containing Arm

	Abraxane plus Gemcitabine[d]		Gemcitabine	
	Grades 1-4 (%)	Grade 3-4 (%)	Grades 1-4 (%)	Grade 3-4 (%)
Neutropenia[a,b]	73	38	58	27
Thrombocytopenia[b,c]	74	13	70	9

[a] 405 patients assessed in ABRAXANE/gemcitabine-treated group
[b] 388 patients assessed in gemcitabine-treated group
[c] 404 patients assessed in ABRAXANE/gemcitabine-treated group
[d] Neutrophil growth factors were administered to 26% of patients in the ABRAXANE/gemcitabine group.

Major safety concerns related to labeling
The trial identified significant adverse reactions of sepsis and pneumonitis in this patient population which were added to the Warnings and Precautions _____ (b) (4) section of the product labeling, as described above.

Postmarketing data
Spontaneous reports of postmarketing data; review of such data was limited to information collected in clinical trials.

Final labeling recommendations
Labeling was revised in accordance with FDA's Guidance for Industry: Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format (January 2006) to describe adverse reactions occurring above the "background rate" and to include information on adverse reactions resulting in dose modification or discontinuation.

REMS
The review team did not identify the need for a REMS to assure safe and effective use; I concur with this determination.

PMRs and PMCs
The review team did not identify the need for post-marketing studies; I concur with this determination.

9.   Advisory Committee Meeting

This efficacy supplement was not referred to the Oncologic Drugs Advisory Committee because this drug is not the first in its class, the safety profile is acceptable for products used for treatment of metastatic pancreatic cancer, the clinical study design is similar to that used for previously approved products for this indication, evaluation of the safety data did not raise significant safety issues in the intended population (metastatic pancreatic cancer), and there were no controversial issues that would benefit from advisory committee discussion.

10.   Pediatrics

Abraxane was granted orphan-drug designation for the treatment of pancreatic cancer in the United States on 03 September 3, 2009 for the treatment of pancreatic cancer. Therefore, this application is exempt from the requirements of the Pediatric Research Equity Act (PREA).

11.   Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12.   Labeling

- Proprietary name: Not applicable

- Physician labeling: All major issues were resolved and recommendations from labeling consultants were addressed through revisions of the proposed labeling. Substantive modifications to the applicant's proposed labeling included the following:

  - Indication: Requested removal   (b) (4)

  - Dosage and Administration: Added information on dosing for the new indication; removed information   (b) (4)

                                    Removed information   (b) (4)
                                                             (b) (4)

                                                                    Section 2.5 edited for brevity and consistency with the dose modifications in the clinical protocol.
  - Dosage Forms and Strengths: modified to include dosage form (for injectable suspension) and to include a description of the product as a lyophilized powder

- Warnings and Precautions: Edited for brevity (referenced section 2 for dose modifications _____ (b) (4) in this section of the label); included incidence information on severe hematologic toxicity (section 5.1); editorial changes to proposed new sections on sepsis and pneumonitis; deleted proposed (b) (4)
_____

- Adverse Reactions: Demographic and exposure information provided for the new indication and adverse reactions presented in tabular format were limited to those occurring at a higher incidence than in the control arm. The listing of adverse reactions occurring in <10% patients were revised to include only clinically important adverse reactions (e.g., _____ (b) (4) removed) which might alter a physician's decision to prescribe this drug. Subsections on sepsis, peripheral neuropathy, and pneumonitis edited to remove redundant information (i.e., information _____ (b) (4)) and to include incidence information from the comparative study.

- Drug Interactions: Deleted proposed _____ (b) (4)
_____

- Use in Specific Populations: Edited in accordance with 21 CFR 201.57 for Use in Geriatric Patients subsection. Added the following sentence to Hepatic Impairment subsection: "Abraxane has not been studied in combination with gemcitabine for the treatment of pancreatic cancer in patients with a bilirubin greater than the upper limit of normal."

- Description: added dosage form and included non-proprietary name in this section.

- Clinical Pharmacology: The following statement was added "*Pharmacokinetic Interactions between and ABRAXANE and Gemcitabine* Pharmacokinetic interactions between ABRAXANE and gemcitabine have not been studied in humans."

- Clinical Studies: The following information was removed from this subsection as (b) (4)
_____

The _____ (b) (4) was removed as not necessary (b) (4)
_____

- Carton and immediate container labels: No carton or immediate container labeling modifications were approved under this supplement.

- Patient labeling/Medication guide: The existing patient labeling was modified to reflect the new indication, to improve understanding at a 6th grade reading level, and for consistency with current FDA policies for patient labeling, as per the Patient Labeling consult.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Approval

- Risk Benefit Assessment
Metastatic pancreatic cancer is a serious disease, with a 2% 5-year survival rate; there are no effective screening tools for this cancer which commonly presents as advanced disease. Although there are FDA-approved drugs, the improvements in survival are modest. The benefits of the addition of Abraxane to a standard gemcitabine regimen include a statistically robust increase in overall survival [HR 0.72 (95% CI: 0.62,0.83); p-value < 0.0001] with an increase in the estimated median survival time of 1.8 months, based on the estimated median survival times of 8.5 months and 6.7 months in the Abraxane/gemcitabine and gemcitabine alone arms, respectively; a significant improvement in progression-free survival (PFS) based on independent review [HR 0.69 (95% CI=0.58, 0.82) p-value <0.0001] with median PFS times of 5.5 months and 3.7 months in the Abraxane/gemcitabine and gemcitabine alone arms, respectively; and a significantly higher objective response rate for the with the combination (23% vs. 7%, p-value <0.0001) as compared to gemcitabine alone. These benefits outweigh the incremental increase in toxicity with the addition of Abraxane, which includes increased incidence of the following Grade 3-4 adverse reactions: neutropenia (38% vs. 27%), thrombocytopenia (13% vs. 9%), fatigue (18% vs. 9%), peripheral neuropathy (17% vs. 1%). dehydration (7% vs. 2%), sepsis (5% vs. 2%), and drug-induced pneumonitis (4% vs. 1%). These toxicities, while clinically important, are considered reasonable risks for patients undergoing treatment for incurable, aggressive cancers and did not result in a reduction in survival.

In placing these results in context with alternative treatment, the magnitude of the effects on survival are slightly better than those observed with the addition of erlotinib to gemcitabine, although at the cost of greater toxicity with Abraxane. Similarly, the magnitude of the treatment effect on survival with FOLFIRINOX (which have not been reviewed by FDA) is larger than those observed with the addition of Abraxane to gemcitabine but the reported toxicity of FOLFIRINOX is also greater.

Based on the results demonstrated in an adequate and well-controlled trial, the benefits observed outweigh the risks of treatment for this patient population and provide results which are in line with currently accepted and/or FDA-approved treatment which forms the current standard of care.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
  I concur with the clinical reviewer and CDTL that a REMS is not required to assure safe use of Abraxane for this indication. The risks of Abraxane, given in combination with gemcitabine, are not unusual and are considered acceptable given the life-threatening nature (2% 5-year survival rates) of metastatic pancreatic cancer.

- Recommendation for other Postmarketing Requirements and Commitments
  No post-marketing requirements or commitments have been requested by the review team members.

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/s/

PATRICIA KEEGAN

09/06/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21660Orig1s037

OFFICER/EMPLOYEE LIST

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 29, 2013

From: Meredith Libeg, B.S., Regulatory Health Project Manager

Subject: *NDA 21660/S-037 – ABRAXANE (paclitaxel protein-bound particles for injectable suspension)*
Officer / Employee List

The following lists the officers / employees who participated in the decision to approve this application and consented to be identified on this list:

Officer / Employee
Fuller, Barbara
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<u>CROSS DISCIPLINE TEAM LEADER REVIEW</u>

Cross-Discipline Team Leader Review

Date	16 Aug 2013
From	Steven Lemery, M.D., M.H.S.
Subject	Cross-Discipline Team Leader Review
NDA #	021660/37
Applicant	Abraxis BioScience, LLC, a wholly-owned subsidiary of Celgene Corporation
Date of Submission	21 Mar 2013
PDUFA Goal Date	21 Sep 2013 *(Priority Review)*
Proprietary Name / Established Name	Abraxane / paclitaxel protein-bound particles for injectable suspension (ABI-007)
Dosing Regimen	125 mg/m^2 administered as an intravenous infusion over 30-40 minutes on days 1, 8, and 15 of each 28-day cycle in combination with 1,000 mg/m^2 gemcitabine as an intravenous infusion over 30-40 minutes immediately after the completion of each dose of Abraxane.
Proposed Indication(s)	First-line treatment of patients with $\quad$ (b) (4) $\quad$ metastatic adenocarcinoma of the pancreas in combination with gemcitabine
Recommended:	*Approval pending final agreement on labeling*

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1. Introduction

FDA received a supplemental NDA to Application 021660 on 21 Mar 2013 requesting marketing authorization (regular approval) for paclitaxel protein-bound particles for injectable suspension (ABI-007) marketed as Abraxane for the first-line treatment of patients with ^{(b) (4)} ^{(b) (4)} metastatic adenocarcinoma of the pancreas in combination with gemcitabine. Celgene requested this labeling expansion based on the results of one adequate and well controlled trial that enrolled patients with metastatic pancreatic adenocarcinoma (i.e., carcinoma of the exocrine pancreas). Celgene requested that the Agency grant priority review of this application stating that ABI-007 "provides a significant improvement compared with the marketed drug products in the treatment of pancreatic adenocarcinoma." Celgene stated in the cover letter that the Agency granted orphan-drug designation for the treatment of pancreatic cancer in the U.S. on 03 Sep 2009 and believes that Celgene is entitled to a 7 year period of orphan-drug marketing exclusivity under the provisions of 21 CFR 316.31.

Disclaimer: Any data or information described below that Celgene does not own (for example, summary data from other drugs used to treat patients with metastatic pancreatic cancer or other cancers) is included for descriptive purposes only. This information was not relied upon or necessary to make a decision regarding this application. Although ABI-007 was initially approved as a 505(b)(2) application that relied on FDA's prior findings of safety and effectiveness for the listed drug Taxol, this efficacy supplement was supported by data from an adequate and well controlled trial for an indication not included in the Taxol label.

The following section describes the primary scientific issues identified during the review of this application:

1.1 One versus two trials

FDA considered whether the results of a single adequate and well-controlled trial were sufficient to support approval of this sNDA. FDA Guidance (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078749.pdf) identified characteristics that can contribute to the conclusion that results from a single study can support an efficacy claim. The characteristics identified were (a) large multicenter study; (b) consistency across study subsets; (c) multiple studies in a single study; (d) multiple endpoints involving different events; and (e) statistically very persuasive findings. Results of the CA046 trial submitted in support of this sNDA satisfied all of these characteristics except (c).

CA046 was a large, randomized (1:1), multi-national trial that randomized 861 patients with metastatic pancreatic cancer (most of whom received no prior chemotherapy). Patients in CA046 received ABI-007 plus gemcitabine or gemcitabine alone. Table 1 (data obtained from the statistical review) summarizes the efficacy results from CA046. The results (demonstrating that ABI-007 in combination with gemcitabine prolonged overall survival in patients with first-line metastatic pancreatic cancer) were statistically robust and supported by consistent results in subgroup analyses.

Table 1 Summary of efficacy results

	ABI-007 + Gemcitabine N = 431	Gemcitabine N = 430
Overall survival		
# of events	333	359
Median (in mos.)	8.5	6.7
HR (95% CI)	0.72 (0.62, 0.84)	
p-value (two-sided)	< 0.0001	
Progression free survival		
# of events	277	265
Median (in mos.)	5.5	3.7
HR (95% CI)	0.69 (0.58, 0.82)	
Objective response rate		
Point estimate	23%	7%

The May 1998 FDA Guidance document (listed above) also states that reliance on a single trial will generally be limited to situations in which a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with a potentially serious outcome and confirmation of the results in a second trial would be practically or ethically impossible.

CA046 established that patients receiving ABI-007 in combination with gemcitabine experienced a modest improvement in overall survival compared to gemcitabine alone. Based on the CA046 study results, it is unlikely that physicians would agree to conduct an additional study of ABI-007 in the first-line setting that would randomize patients to receive gemcitabine alone (in the control arm).

1.2 Unplanned sample size adjustment

Amendment 4 to the CA046 protocol increased the planned sample size to 842 (from 630) and number of events to at least 608 (from 455) in order to increase the statistical power from 80% to 90%. This sample size adjustment appeared to be unplanned. The amendment stated that "higher enrollment may ensure that important subgroups are adequately represented" and that "increasing the power to 90% may decrease the risk that the study will not reach its primary objective to the level of risk that regulatory authorities place on concluding that an ineffective therapy is efficacious." *Comment: This reviewer found no correspondence in files related to the product IND where FDA communicated that such an approach would decrease regulatory risk.*

According to this reviewer's analysis, approximately 137 deaths occurred prior to the date of the amendment. This represented approximately 30% of the planned number of events based on the original statistical analysis plan.

This reviewer disagreed with the premise that the sample size adjustment decreased the risk related to a regulatory submission. This reviewer believes that the regulatory risk was increased because of the uncertainty regarding the study's true Type I error rate given the sample size adjustment. In general, this reviewer recommends against unplanned sample size

adjustments in studies intended to support approval of a drug or an indication. However, if a sample size adjustment (of a pivotal trial) is deemed necessary, this reviewer recommends that sponsors obtain advice from regulatory agencies (including FDA) in order to ensure that the sample size adjustment is conducted using scientifically sound methods (e.g., with adjustment of alpha, if necessary).

Despite the concerns expressed regarding the unplanned sample size adjustment, this reviewer is confident that the overall survival effect observed in Study CA046 is a true finding. The analysis performed by the statistical reviewer after 455 events provided the strongest evidence supporting the claimed treatment effect. In other words, the trial would have been a positive study even if the trial was analyzed based on the original sample size estimation. In fact, the overall survival (OS) results after 455 events were almost identical to the results based on the final analysis. Additionally, the OS results of the final analysis (after 692 events) were almost identical to the results based on 608 events (planned number of events after the fourth protocol amendment). Table 2 shows the hazard ratios (and 95% CIs) for each analysis.

Table 2 FDA analyses of OS based on the final analysis and based on pre-specified number of events (from original protocol and following amendment four)

Analysis	Event total	OS HR (95% CI)*	Difference* in median OS (months)
Primary (final)	692	0.72 (0.62, 0.83)	1.87
Planned, following amendment 4	608	0.73 (0.62, 0.86)	1.77
Planned, original protocol	455	0.69 (0.58, 0.84)	1.94

*between arms with longer OS in the ABI-007 arm

Ultimately, the adjustment to the planned sample size resulted in an overpowered study that took longer to complete than originally planned.

1.3 Claimed indication

In the sNDA, Celgene requested the following indication: first-line treatment of patients with (b) (4) metastatic adenocarcinoma of the pancreas in combination with gemcitabine. DOP2 recommended that Abraxis limit the indication to patients with metastatic adenocarcinoma. (b) (4)

1.4 Control arm

The primary study supporting this sNDA administered single-agent gemcitabine to patients in the control arm. Although, erlotinib was approved for the treatment of patients with metastatic pancreatic cancer, the improvement in overall survival conferred by erlotinib was less than half a month. Thus, this reviewer agrees that it was reasonable not to require patients to receive erlotinib in the CA046 trial (based on the modest survival effect and additional toxicity).

The paper describing the results of the FOLFIRINOX regimen (Conroy et al., NEJM 2011; 364: 1817-1825) was not published until May of 2011, after the initiation of Study CA046.

Although, ABI-007 plus gemcitabine was not compared to FOLFIRINOX in a randomized trial, Study CA046 demonstrated evidence of safety and effectiveness isolating a beneficial effect of ABI-007 (compared to gemcitabine alone). A comparative standard for effectiveness is not required for (regular) FDA drug approval, justifying the recommendation for approval of nab-paclitaxel for the treatment of patients with metastatic pancreatic cancer. Nevertheless, this reviewer recommends careful consideration of the control arm in any yet-to-be initiated study that enrolls previously untreated patients with metastatic pancreatic cancer who have good performance status. Although there is not a comparative standard of effectiveness, patients with good performance status (especially who are randomized to a control arm) likely should receive combination therapy based on evidence from randomized controlled trials (in order to provide the best care for such patients).

Finally, any comparisons between ABI-007/gemcitabine and FOLFIRONX are tenuous at best. Determination of the optimal therapy could only be done by conducting an additional trial. Although the point estimate for OS was of longer duration in the FOLFIRINOX trial, the FOLFIRINOX trial enrolled a different population (e.g., single country). Likewise, without a comparative trial, this reviewer would not necessarily agree that the ABI-007-regimen is a safer regimen than FOLFIRINOX.

2. Background

2.1 Disease and therapy related issues

Because pancreatic cancer is incurable in the metastatic setting, the goals of therapy are to prolong life and/or improve quality of life. Table 3 shows drugs approved by the Agency for the treatment of patients with pancreatic cancer. Data regarding mitomycin C and fluorouracil were limited as FDA approved these drugs prior to 1984. Although the Agency approved erlotinib based on an effect on overall survival (OS), the effect was modest (the difference in median overall survival was less than one month in duration).

FDA approved gemcitabine based on the results of a trial with "clinical benefit response" as the primary endpoint. FDA made this decision prior to the promulgation of the PRO Guidance and prior to the development of modern standards regarding patient reported outcomes. Nevertheless, this approval was supported by an effect on overall survival, the "gold standard" for clinical benefit.

Table 3 Drugs approved by FDA for the treatment of exocrine pancreatic cancer (adenocarcinoma)

Drug	Date Indication Approved	Pancreatic Cancer Indication	Primary Basis for Approval
Erlotinib	02 Nov 2005	First-line, locally advanced, unresectable or metastatic disease in combination with gemcitabine	OS: HR 0.81; $p = 0.028$
Gemcitabine	15 May 1996	First-line, locally advanced (non-resectable stage II or III) or metastatic disease. Second-line after 5-FU	Primary Endpoint: Clinical benefit response* versus active control (5-FU); supported by improvement in OS and time to disease progression (also supported by data from a single-arm trial)
Fluorouracil	--	Palliative management	--
Mitomycin C	--	Disseminated adenocarcinoma of the pancreas	--

*$\geq$ 50% reduction in pain or a 20 point improvement in Karnofsky performance status for at least 4 weeks; or stable pain, performance status, and analgesic consumption with at least $\geq$ 7% weight gain for greater than or equal to four weeks

National Comprehensive Cancer Network (NCCN) Guidelines, Version 2.2012 (http://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf, accessed 26 Mar 2013), described one additional Category 1 non-gemcitabine based regimen (FOLFIRINOX) for the treatment of patients with metastatic adenocarcinoma of the pancreas. The recommendation regarding the FOLFIRINOX regimen was based on a published report (Conroy et al., 2011) comparing FOLFIRNOX (oxaliplatin 85 mg/m^2; irinotecan 180 mg/m^2; leucovorin 400 mg/m^2 and fluorouracil 400 mg/m^2 administered as a bolus followed by 2,400 mg/m^2 administered as a 46-hour continuous infusion, every other week) to gemcitabine. The trial required that patients have an ECOG performance status of 0 or 1 and a bilirubin level $\leq$ 1.5 times the upper limit of normal. Less than 40% of patients had a tumor localized to the head of the pancreas. The published report stated that median overall survival was 11.1 months in the FOLFIRINOX arm compared to 6.8 months among patients randomized to receive gemcitabine (HR 0.57, $p < 0.001$).

2.2 U.S. regulatory history

The following summarizes the pertinent regulatory history and meetings held in relation to this sNDA. Meetings held to discuss clinical trials pertinent to other indications are not summarized in this review.

09 Sep 2008 (Type A meeting with Abraxis BioScience):
FDA agreed that the endpoint of overall survival (OS) was acceptable to assess the efficacy of ABI-007 as a first-line treatment for patients with pancreatic adenocarcinoma (i.e., in Study CA046). FDA stated that the acceptability of a study that proposed to use gemcitabine without erlotinib as the control would be a review issue given that erlotinib was approved in combination with gemcitabine for the treatment of patients with pancreatic adenocarcinoma.

FDA agreed with the proposed gemcitabine dose that would be administered according to the package insert and requested justification if gemcitabine would be dosed weekly for the first three out of every four weeks in all cycles.

FDA requested that Abraxis pre-specify the priority of testing for secondary endpoints in the protocol and in the statistical analysis plan in order to control the overall family-wise type I error rate at a one-sided 0.025 level.

(b) (4)

03 Sep 2009 (Orphan designation):
FDA granted orphan-drug designation for ABI-007 (the active moiety of the drug and not the formulation of the drug) for the treatment of pancreatic cancer pursuant to Section 526 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 360bb).

05 Oct 2010 (Information Amendment to IND 55974)
Abraxis BioScience sent an amendment to IND 55974 that responded to a request from FDA concerning sepsis events in Study CA046. At the time of the amendment, Abraxis BioScience stated that 350 patients (of a planned 630 patients) enrolled in the protocol and there were 7 sepsis events in the ABI-007 arm compared to 1 in the gemcitabine-alone arm. Four of the events were fatal. Based on this safety analysis, Abraxis BioScience sent a letter to investigators dated 17 Sep 2010 with the following recommendations:

- Permitted G-CSF for Grade 4 neutropenia in the absence of a fever. If Grade 4 neutropenia occurred for more than 14 days despite G-CSF, the patient was to be discontinued from the study.
- Recommended dose reduction for gemcitabine for Grade 4 neutropenia (first instance).
- Required dose reduction for both gemcitabine and ABI-007 for a second instance of Grade 4 neutropenia.
- Instituted provisions for the self-initiation of ciprofloxacin or amoxicillin/clavulanate for fever of ≥ 38.5 degrees Celsius (even in absence of neutropenia). Patients were also supposed to immediately contact their physician to be evaluated for sepsis/need for hospitalization and an assessment of blood counts.
- Required interruption of chemotherapy in febrile patients regardless of neutrophil count pending a full sepsis work-up. If the febrile neutropenia resolved within the protocol specified time-period, the doses of both drugs were to be reduced.
- Allowed, at the discretion of the physician, long-term prophylactic treatment with ciprofloxacin or alternate antibiotic following a first febrile episode.
- Allowed administration of prophylactic antibiotics to patients with biliary stents.

04 Aug 2011 (Type C meeting with Celgene)
FDA did not agree with Celgene's proposal   (b) (4)

                                        FDA stated that overall survival should remain the
primary endpoint and Celgene stated that the study will continue as planned.

Additional discussion occurred regarding assessments for drug-drug interactions and sparse
pharmacokinetic monitoring. Regarding the potential for drug-drug interactions, FDA agreed
with Celgene's approach that included conducting an assessment in rats and providing
information contained in the gemcitabine label stating that gemcitabine has little or no effect
on the pharmacokinetics of paclitaxel and paclitaxel has little or no effect on the
pharmacokinetics of gemcitabine.

FDA also accepted Celgene's justification to not conduct sparse PK sampling for exposure-
response relationships. First, Celgene estimated that there would be an insufficient sample
size for the ER analysis in the ongoing CA046 study based on enrollment numbers presented
during the Type C meeting. Celgene also provided summary ER results from retrospective
analyses over a range of ABI-007 doses in patients with solid tumors.

07 Oct 2011 (Information Amendment to IND 55974)
Celgene notified FDA of 10 reports of interstitial pneumonitis, including 3 fatal cases
(compared to one case in the control arm) among 622 patients enrolled into Study CA046. As
a result of these findings, Celgene sent letters to investigators summarizing the cases and
updated the consent form and protocol to describe this information. The revised protocol also
contained recommendations to exclude patients with a history of slowly progressive dyspnea
and unproductive cough, to assess episodes of dyspnea with unproductive cough or fever, and
to interrupt therapy in patients diagnosed with interstitial pneumonitis.

16 Oct 2012 (Advice/information request from FDA to Celgene)
FDA provided written responses to Celgene's questions regarding a proposed plan to
summarize and present data in a supplemental New Drug Application for a new indication,
pancreatic cancer, for ABI-007.

FDA agreed with Celgene's proposal to summarize the efficacy data from the randomized trial
(CA046) and the single-arm trial (CA040) separately. FDA also agreed with Celgene's
proposal to not include original CT or MRI scans in the sNDA.

Regarding safety data, FDA agreed to a proposal to integrate safety data of patients receiving
ABI-007 125 mg/m^2 followed by gemcitabine 1,000 mg/m^2; however, FDA also requested that
Celgene provide safety data, in a side-by-side format, from patients who received other doses
of ABI-007 in combination with gemcitabine. FDA agreed to the proposal for Celgene to
submit data from Study CA046 in CDISC STDM and ADaM formats and to submit data from
CA040 in legacy non-CDISC format.

8 Nov 2012 (Informal telephone conference between Celgene and FDA)
Celgene provided top-line results from Study CA046 and stated that the study met the primary endpoint of a statistically significant effect on overall survival. FDA agreed to look at the meeting calendar to determine if there were available dates to hold a pre-sNDA meeting earlier than what was already scheduled on 5 Feb 2013. To facilitate the submission of the Application, the Agency offered to address any specific issues in writing prior to the pre-sNDA meeting.

03 Jan 2013 (Advice/information request letter from FDA to Celgene)
FDA stated that Celgene's proposal to present side-by-side comparisons of safety data from different doses of ABI-007 was acceptable provided that Celgene confirm the integrated summary would include all data obtained from patients who received ABI-007 plus gemcitabine (i.e., include patients with any cancer who received the combination of ABI-007 plus gemcitabine).

FDA provided feedback regarding a Celgene proposal to submit safety narratives from Study CA046 from all patients in the ABI-007 arm who experienced a treatment-emergent adverse event (TEAE) resulting in death on study or within 30 days of treatment discontinuation, a TEAE resulting in discontinuation of ABI-007 or gemcitabine, or a TEAE that was a serious adverse event. FDA requested that Celgene also provide narratives in the sNDA from patients in the ABI-007 arm who discontinued study drugs for reasons categorized as other, lost to follow-up, physician decision, or subject decision.

Finally, FDA agreed that Celgene could submit data from Study CA046 using SDTM version 3.1.2; however, FDA requested the inclusion of the following additional variables to facilitate timely review of the data: actual treatment arm (i.e., actual treatment received), death flag, date of death, date of informed consent, and date of first exposure to study drug.

11 Jan 2013 (FDA preliminary responses to Type B pre-sNDA meeting questions)
FDA stated that the top-line efficacy and safety data provided in the briefing package, including a reported improvement in OS among patients randomized to ABI-007 in combination with gemcitabine were adequate to support the sNDA. However, FDA stated that the Agency would make determinations regarding approvability and labeling following the submission and review of the application. FDA requested that Celgene provide summary results of any exploratory analyses of efficacy according to SPARC expression from Study CA046.

14 Jan 2013 (Email from Celgene to FDA)
Celgene acknowledged receipt of FDA's responses to the Type B meeting planned on 15 Jan 2013. Based on FDA's responses, Celgene elected to cancel the meeting. In a separate communication, Celgene stated that they were working on a robust, standardized assay for SPARC expression and will be assessing SPARC expression from a cohort of approximately 400 patients who consented to the optional submission of archival tumor tissue. Celgene did not plan to include this information in the sNDA targeted for April 2013. Celgene anticipated submitting the information from this exploratory analysis to the ABI-007 IND approximately

August 2013. FDA agreed in a separate 14 Jan 2014 email that the proposal to submit the exploratory analyses to the IND was acceptable.

2.3 Application history

The following table summarizes the purpose(s) of amendments submitted to this NDA.

Table 4 Amendments to sNDA 21660 (as of the date of the completion of this review)

Date of Submission	Purpose of Submission
21 Mar 2013	Original submission
21 May 2013	Provided information requested by the Agency on 10 May 2013 regarding the derivation of progression free survival and codes in a submitted dataset.
03 Jun 2013	Clarification regarding manufacturing sections of the NDA.
06 Jun 2013	Response to FDA requests regarding labeling issues that were included in a filing communication letter dated 20 May 2013.
10 Jun 2013	Clarification regarding a Finished Product Specification document.
17 Jun 2013	Submission of four month safety update.
19 Jun 2013	Provided statistical and clinical information based on a request by the Agency dated 03 June 2013.
28 Jun 2013	Provided response to labeling edits proposed by the Agency that were sent to Abraxis on 19 Jun 2013. The revised label also included a description of neutropenic sepsis that was approved by the Agency in a Prior Approval Labeling Supplement on 07 Jun 2013 (S-036).
12 Jul 2013	Provided revised labeling with visible tracked-changes based on a request sent by the Agency on 02 Jul 2013.
09 Aug 2013	Response to FDA information request dated 20 May 2013
13 Aug 2013	Provided revised labeling in response to FDA edits communicated to Abraxis on 06 Aug 2013.

3. CMC

As described in product labeling, ABI-007 is an albumin-bound form of paclitaxel. Single-use vials contain 100 mg paclitaxel bound to approximately 900 mg of human albumin (containing sodium caprylate and sodium acetyltryptophanate). ABI-007 is supplied as a white to yellow, sterile, lyophilized powder and is to be reconstituted with 20 mL of 0.9% Sodium Chloride Injection.

The active ingredient in ABI-007 is paclitaxel and paclitaxel acts through inhibition of microtubules, thus promoting the assembly of microtubules from tubulin dimers and stabilization of microtubules through the prevention of depolymerization.

This sNDA did not contain new CMC information.

3.1 Drug substance review

Not applicable for this sNDA.

3.2 Drug product review

Not applicable for this sNDA.

4. Nonclinical Pharmacology/Toxicology

5. Clinical Pharmacology

Celgene did not submit new pharmacokinetic data in this application. Refer to the 04 Aug 2011 meeting summary above regarding the justification not to submit drug-drug interaction data or sparse pharmacokinetic (PK) data. A clinical pharmacology memorandum was completed to address proposed changes to Section 7 of product labeling (see clinical pharmacology review for details).

6. Clinical Microbiology

This section is not applicable to this review.

7. Clinical/Statistical-Efficacy

The clinical reviewer (Dr. Abhilasha Nair) recommended approval of this application based on the improvement in overall survival demonstrated in the CA046 clinical trial that was conducted in patients with metastatic pancreatic cancer. The statistical reviewer (Dr. Yuan Li Shen) concluded that based on the data and analyses from CA046, ABI-007 plus gemcitabine demonstrated a statistically significant improvement in OS, progression free survival, and objective response rate.

7.1 Background of clinical program

The initial protocol for the pivotal trial (CA046) was dated 12 Nov 2008 and contained the following title: A randomized phase III study of weekly ABI-007 plus gemcitabine versus gemcitabine alone in patients with metastatic adenocarcinoma of the pancreas.

CA046 was the only adequate and well controlled trial conducted in the indicated patient population submitted in support of this sNDA. Abraxis also submitted data and a clinical study report from Study CA040, a single-arm, uncontrolled, supportive dose finding study. Section 7.2.5 below, describes the major revisions to pivotal trial CA046 described in protocol amendments. A total of 10 patients (~1% of 861) were enrolled under the original version of the protocol.

7.2 Design of CA046 (original protocol)

7.2.1 Primary endpoint

The primary endpoint of CA046 was overall survival (OS), defined as the time from randomization to the date of death due to any cause. *Comment: As stated in the May 2007 FDA Guidance Document regarding endpoints for cancer drugs (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf; accessed on 12 Jul 2012), survival is considered the most reliable cancer endpoint, and when studies can be conducted to adequately assess survival, it is usually the preferred endpoint. An effect on OS is considered regulatory evidence of clinical benefit used by the Agency to substantiate regular approval of a drug.*

7.2.2 Secondary endpoints

The secondary endpoints defined by the protocol included progression free survival (PFS), objective tumor response rate (ORR), safety and tolerability, functional tumor response according to EORTC using PET scans, changes in CA 19-9 levels, and assessments of outcomes related to secreted protein acidic and rich in cysteine (SPARC) levels.

The protocol contained a provision to control the alpha at 0.05 (two-sided) for progression free survival and ORR; thus, this reviewer considered the other secondary endpoints as exploratory (the endpoints should be considered as supportive and not as substantial evidence of a treatment effect).

The analysis of PFS was based on a blinded central radiology assessment. PFS was defined as the duration from the day of randomization to the start of disease progression or death (any cause). ORR was assessed per RECIST guidelines and compared between treatment arms using the chi-squared test.

7.2.3 Eligibility criteria

The *original* protocol specified the following inclusion criteria: histologically or cytologically confirmed and measurable/evaluable metastatic adenocarcinoma of the pancreas excluding patients with islet cell neoplasms; age $\geq$ 18 years; no previous therapy except 5FU or gemcitabine administered as a radiation sensitizer or adjuvant treatment with gemcitabine (at least six months must have elapsed); neutrophil count $\geq$ 1,500/mcL; platelets $\geq$ 100,000/mcL; hemoglobin $\geq$ 9 g/dL; total bilirubin $\leq$ upper limit of normal; creatinine clearance $\geq$ 60 mL/min/1.73 m^2; Karnofsky performance status (KPS) $\geq$ 70%; and asymptomatic for pain, jaundice, and ascities prior to day 1.

The *original* protocol excluded patients with the following: known brain metastases unless previously treated and well-controlled for at least three months; on therapeutic warfarin; active infection; known HIV, hepatitis B or hepatitis C; major surgery within 4 weeks; and any serious medical risk factors involving any major organ system.

7.2.4 General study design/treatment plan

- The trial was an open-label, randomized (1:1), multi-center, international trial. The protocol included a provision for imaging to be sent to a blinded central imaging reader within 2 weeks of exam completion.

- CA046 randomized patients to either ABI-007 125 mg/m^2 as a 30-minute infusion followed by gemcitabine 1,000 mg/m^2 as a 30-minute infusion weekly for three weeks followed by one week of rest *or* gemcitabine 1,000 mg/m^2 weekly for seven weeks as a 30 minute infusion followed by a week of rest, followed by weekly infusions for the first three weeks of every four week cycle.

  Comment: The more intense gemcitabine dosing regimen in the control arm was acceptable (the gemcitabine product label describes this schedule).

- The protocol contained provisions for dose modifications based on toxicities depending on whether they occurred on day 1 or within a treatment cycle. Treatment with ABI-007 plus

gemcitabine was to be delayed for at least one week for the following occurring on day 1 of a cycle: neutrophil count < 1,500/mcL; platelets < 100,000/mcL; Grade 3 non-hematological toxicity. Patients were to be removed from therapy for Grade 4 non-hematologic adverse events occurring on day 1 of a cycle and the gemcitabine dose was to be reduced for Grade 3 non-hematologic adverse events (following recovery to Grade 2 or less).

Within a treatment cycle, gemcitabine was to be held for neutrophil counts less than 500/mcL, platelets less than 50,000/mcL, or Grade 4 non-hematological toxicities. ABI-007 was to be held for Grade 4 non-hematological toxicities. Gemcitabine and ABI-007 were to be held or dose-reduced for Grade 3 non-hematological toxicites. Gemcitabine was also dose-reduced for febrile neutropenia and for neutrophil counts between 500 and 999/mcL *in combination with* platelets between 50,000 and 74,000/mcL. The protocol required a dose reduction of ABI-007 for recurrent febrile neutropenia; $\geq$ Grade 3 peripheral neuropathy; Grade 2 or 3 cutaneous toxicity; and Grade 3 mucositis or diarrhea.

- Patients continued treatment until progressive disease, unacceptable toxicity, withdrawal of consent; initiation of other anti-cancer therapy; or if deemed in the best interest of the patient according to the investigator's judgment.

- Patients underwent assessments for tumor progression every 8 weeks with CT or MRI.

- The protocol required weekly evaluations of vital signs, performance status, adverse events and hematology labs. Chemistry labs and a peripheral neuropathy evaluation were assessed on day 1 of each cycle.

- Patients were followed for survival status monthly for six months and then every three months thereafter for 18 additional months in the post-study follow-up period.

7.2.5 Statistical design and analysis issues

Randomization/Stratification Factors
No stratification factors were specified in the original protocol.

Determination of Sample Size
The original protocol stated that 315 patients were to be randomized to each treatment arm (n=630). The protocol required 455 events (deaths) to perform the statistical test to reject the null hypothesis (HR 1.0) with the following assumptions: 80% power; two-sided Type I error rate of 0.05; and an assumed effect size of HR 0.769.

Analyses
The protocol stated that the primary efficacy analysis would be tested using a stratified log-rank test after a total of at least 455 events. The protocol specified that the primary analysis would be conducted using the intent-to-treat population consisting of all patients randomized. The secondary efficacy endpoints of objective tumor response and PFS were only to be tested if the primary endpoint was statistically significant. The protocol described the use of the Hochberg procedure to control the Type I error rate for the analyses of the secondary endpoints.

Protocol Amendments
Amendment 1 (dated 20 Mar 2009)
A total of 118 patients were enrolled under Amendment 1 to the protocol such that 15% of the (final) total study population (n=861) were enrolled prior to Amendment 2 (10 patients were enrolled under the original protocol for a cumulative enrollment of 128 prior to the second amendment).

The following list describes major changes described in Amendment 1:

- Modified eligibility guidelines to allow patients with pain at baseline as long as the pain symptoms remained stable.

- Permitted an unscheduled CT scan to confirm objective response.

- Clarified that imaging studies (e.g., CT and PET) were to be performed every 8 weeks regardless of regimen.

- Updated the statistical analysis plan (SAP) to allow for a planned interim efficacy analysis once at least 200 randomized patients were followed for at least six months. The protocol stated that this was an analysis for futility and adjusted the overall type I error (two-sided) for the final analysis to be 0.049 with an alpha of 0.001 allocated for the interim analysis.

- Modified the SAP regarding the ORR endpoint to clarify that confirmation of a response must be made at least four weeks after the initial response.

- Added a section regarding the Data Monitoring Committee to facilitate safety analyses and to conduct the planed futility analysis.

Comment: These revisions were scientifically acceptable and occurred early in the conduct of the study after 10 patients were enrolled. Allowance of patients with pain at baseline was acceptable (and probably necessary) because most patients with pancreatic cancer experience pain. The new futility analysis at this early stage was unlikely to affect the integrity of the trial.

Amendment 2 (dated 17 Nov 2009)
A total of 147 patients were enrolled under Amendment 2 to the protocol such that 32% of the total study population (n=861) were enrolled prior to Amendment 3.

The following list describes major changes described in Amendment 2:

- Added the following stratification factors: Geographic region; Karnofsky performance score (70-80 vs. 90-100); and presence of liver metastasis (yes or no). *(Comment: Dr. Shen received clarification from the applicant that although the original protocol did not describe stratified randomization, the original randomization authorization form included these three strata, thus this protocol change clarifying the randomization procedure was deemed acceptable).*

- Changed the plan to control for Type I error for the two secondary endpoints of PFS and ORR from the Hochberg procedure to a hierarchical/sequential plan (test for PFS first followed by ORR if PFS was significant).

- Revised eligibility criteria such that patients were not eligible if they received cytotoxic doses of gemcitabine in the adjuvant setting (only radiosensitizing doses of gemcitabine were permitted in the adjuvant setting).

- Clarified that patients with symptomatic ascities could be enrolled in the trial as long as the patient underwent drainage of the ascities.

- Excluded patients with the following: Any use of warfarin; history of connective tissue disorders; history of chronic leukemia; patients at high cardiovascular risk; history of peripheral artery disease; or serious psychiatric disorders.

- Revised the exploratory endpoint based on PET scans from an evaluation of "functional tumor response" to PET response according to EORTC criteria.

- Revised the protocol to only require PET imaging for the first 200 patients enrolled in the study (the applicant stated the change was made in order to enroll and complete the study in the planned time frame).

- Revised the dose modification guidelines: for Grade 3 non-hematological toxicites within a cycle, the investigator was to hold one or both drugs until the toxicity resolved, followed by a dose reduction; the amendment also required permanent discontinuation from the study if $\geq$ Grade 3 peripheral neuropathy lasted $\geq$ 21 days.

- Clarified that PET scans or CA19-9 levels would not be used as criteria for progression to withdraw a patient from the study.

Amendment 3 (dated 19 Apr 2010)
A total of 181 patients were enrolled under Amendment 3 to the protocol such that 53% of the total study population (n=861) were enrolled prior to Amendment 4.

The following list describes major changes described in Amendment 3:

- Changed eligibility criteria to require two observers to assess Karnofsky performance status with the lower value to be used to determine eligibility. Also stipulated that metastatic disease must have been initially diagnosed within $\leq$ 6 weeks.

- Excluded patients with the following characteristics: $\geq$ 10% decrease in KPS between baseline and 72 hours prior to randomization; $\geq$ 20% decrease in serum albumin levels between baseline and 72 hours prior to randomization; and history of interstitial lung disease.

- Required randomization within 14 days of baseline assessment (rather than 28 days) and required treatment within 3 days of randomization (rather than 7).

- Changed the plan for the exploratory PET analysis to target the first 200 patients with 2 PET scans who completed a minimum of 16 weeks of treatment.

- Revised dose modification guidelines to require a dose reduction of gemcitabine for a neutrophil count between 500 and 1,000/mcL *or* a platelet count between 50,000 and 74,999/mcL.

- Revised dose modification guidelines to allow continued treatment for asymptomatic or mild pulmonary embolism (with concomitant anti-coagulation with a low-molecular weight heparin).

Amendment 4 (dated 30 Sep 2010)
A total of 59 patients were enrolled under Amendment 4 to the protocol such that 60% of the total study population (n=861) were enrolled prior to Amendment 5.

The following list describes major changes described in Amendment 4:

- Increased the sample size to 842 and number of events to 608 in order to increase the statistical power from 80% to 90% to reject the null hypothesis. The sponsor stated that the decision to increase the sample size was not due to a sponsor review of data, and that "higher enrollment may ensure that important subgroups are adequately represented", and that "increasing the power to 90% may decrease the risk that the study will not reach its primary objective to the level of risk that regulatory authorities place on concluding that an ineffective therapy is efficacious."

  This reviewer's analysis of the database demonstrated that approximately 137 deaths occurred prior to the date of 30 Sep 2010. This represented approximately 30% of the planned number of events based on the original statistical analysis plan. Refer to Section 1 above that delineates this reviewer's concerns regarding the unplanned sample size adjustment .

  The planned interim analysis occurred on 11 April 2011, after Amendment 4 was released, when "at least 200 randomized patients were followed for at least 6 months from the date of randomization."

- Further modified plans regarding PET scan analyses. This amendment stipulated that PET scans would only be obtained at baseline for patients enrolled until the date of this amendment; that PET scans would be obtained for patients who obtained a baseline PET scan and were still receiving treatment; and that no further PET scans would be obtained subsequent to week 16.

- Instructed investigators to thoroughly evaluate patients older than 80 years to ensure fitness to receive chemotherapy including using clinical judgment to assess a patient's susceptibility to infection (based on fatal cases of sepsis).

- Revised dose modification guidelines to require dose reduction of ABI-007 (without interruption) and a second dose reduction of gemcitabine for recurrent Grade 4 neutropenia within a treatment cycle (neutrophils less than 500/mcL). Required dose interruption followed by dose reduction of both drugs for febrile neutropenia. G-CSF was permitted according to institutional guidelines for the prevention of febrile neutropenia in patients with Grade 4 neutropenia.

- Included provisions described above (in this review) in the 05 Oct 2010 information amendment to the IND regarding antibiotics and management of patients with neutropenic sepsis. Oral antibiotics were to be distributed to patients with instructions to initiate treatment if febrile; prophylactic antibiotics were permitted following a febrile episode or in patients with uncomplicated biliary stents.

- Required discontinuation of therapy if Grade 4 neutropenia did not resolve within 14 days despite uninterrupted G-CSF.

Amendment 5 (dated 12 Jan 2011)

A total of 291 patients were enrolled under Amendment 5 to the protocol such that 94% of the total study population (n=861) were enrolled prior to Amendment 6.

The following list describes major changes described in Amendment 5:

- Clarified that cross-over from gemcitabine to gemcitabine plus ABI-007 was not permitted and recommended patients be treated with other available therapies following progression.
- Stipulated dose reduction for both gemcitabine and ABI-007 for Grade 3 non-hematological toxicities occurring in the previous cycle (however, Grade 3 peripheral neuropathy only required dose reduction of ABI-007).
- Provided new dose modification criteria based on day 8 and day 15 blood counts (Table 5).
- Required permanent discontinuation of study therapy for neutropenia lasting 21 days despite uninterrupted G-CSF (rather than 14 days).

Table 5 Revised dose modification criteria

Day 8 Counts	Day 8 ABI-007	Day 8 Gem	Day 15 Counts	Day 15 ABI-007	Day 15 Gem
N > 1000 and P ≥ 75000	100%	100%	N > 1000 and P ≥ 75,000	100%	100%
			N 500-1000 or P 50000-75000	100% add G-CSF	100% add G-CSF
			N < 500 or P < 50000	Hold; add G-CSF	Hold; add G-CSF
N 500–1000 or P 50000-75000	Decrease dose	Decrease dose	N > 1000 and P ≥ 75000	Return to full dose; add G-CSF	Return to full dose; add G-CSF
			N 500-1000 or P 50000-74,999	Same dose as Day 8; add G-CSF	Same dose as Day 8; add G-CSF
			N < 500 or P < 50000	Hold; add G-CSF	Hold; add G-CSF

N < 500 or P < 50000	Hold	Hold	N > 1000 and P $\geq$ 75000	Decrease day 8 dose; add G-CSF	Decrease day 8 dose; add G-CSF
			N 500-1000 or P 50000-75000	Decrease day 8 dose; add G-CSF	Decrease day 8 dose; add G-CSF
			N < 500 or P < 50000	Hold; add G-CSF	Hold; add G-CSF

N = neutrophils (counts/mcL); P = platelets (counts/mcL); G-CSF = granulocyte-colony stimulating factor (addition of G-CSF was optional if only platelets were affected).

In addition to the criteria described above, both drugs were to be held following febrile neutropenia. Upon resumption, the protocol instructed investigators to decrease the doses of both drugs.

Amendment 6 (dated 12 Dec 2011)
The final 55 patients were enrolled under Amendment 6 to the protocol.

The following list describes major changes described in Amendment 6:

- Instituted the changes described above (in this review) in the 07 Oct 2011 information amendment to IND 55974. Celgene instituted these changes primarily in response to ongoing safety monitoring of CA046 with respect to interstitial pneumonitis. Nine events occurred in the ABI-007 arm (3 fatal) versus 1 event (fatal) in the gemcitabine alone arm.

- Required reduction of ABI-007 and gemcitabine for Grade 2 cutaneous toxicity.

- Instructed investigators to follow all patients for survival status until death.

7.3 Design of CA040

Because this application primarily was submitted based on the results of Study CA046, only a brief summary of Study CA040 is described in this review.

The primary objective of Study CA040 was to determine a maximally tolerated dose of ABI-007 in combination with gemcitabine. The investigators planned to obtain additional information regarding tolerability and anti-tumor activity of the combination in a dose expansion cohort.

In general, the eligibility criteria were similar to the eligibility criteria described in the original protocol for Study CA046 in that the study enrolled patients with metastatic adenocarcinoma of the pancreas who received no prior treatment for metastatic disease. The protocol required a Karnofsky performance status of $\geq$ 70 or ECOG performance status of 0 to 1.

The protocol was designed as a standard 3 plus 3 dose-escalation trial where all patients received gemcitabine 1,000 mg/m^2 on days 1, 8, and 15 of a 28 day cycle. The protocol described the following planned dose level cohorts for ABI-007 administered on days 1, 8, and 15 of a 28 day cycle: 100 mg/m^2, 125 mg/m^2, and 150 mg/m^2.

The original protocol defined DLT as any Grade 3 or 4 treatment-related non-hematological toxicity, any Grade 4 treatment-related hematologic toxicity or neutropenic fever, or any Grade 3 treatment-related hematologic toxicity requiring treatment delay beyond 3 weeks (or unable to receive 3 consecutive doses).

An amendment (Amendment 3) modified the DLT definition to include ≥ Grade 3 non-hematological toxicities attributable to study drug (except alopecia and fatigue); Grade 3 thrombocytopenia with hemorrhage; Grade 4 neutropenia with fever; Grade 4 neutropenia > 3 days in the absence of growth factor support; or any other Grade 4 hematologic toxicity.

To assess for anti-tumor activity, patients underwent more frequent imaging with CT scans (compared to CA046) obtained on Day 1 of each cycle. Patients underwent safety assessments including assessments of blood counts weekly during treatment.

Although originally designed as a 3 plus 3 trial, the protocol was amended to study up to 12 additional patients at the first dose level. Although two of six patients required dose interruption on day 8 [one due to asymptomatic neutropenia (850/mcL) and one due to asymptomatic thrombocytopenia (60,000/mcL)], the sponsor observed objective responses in three patients and noted potential risk factors for myelosuppression in the two patients (older age and possible ethanol abuse).

Amendment 3 modified the protocol to allow enrollment of up to 42 patients at the MTD in order have 95% power of observing an SAE with an incidence rate of ≥ 7%.

7.4 Summary results of CA046

As described in Dr. Shen's review, the first patient was randomized on 08 May 2009 and the last patient was randomized on 17 Apr 2012. The data cutoff date was 17 Sep 2012.

7.4.1 Demographics

Baseline demographics in both arms appeared balanced (refer to tables in the respective clinical and statistical reviews). Median age of patients randomized to both arms was 63 years and 42% of patients were 65 years of age or older. A higher proportion of patients in both arms (58%) were men and the majority of patients were White (93%). A total of 60% of patients enrolled were KPS (Karnofsky performance status) 90-100 and 40% were KPS 70-80. Two patients enrolled into the ABI-007 arm had a KPS score less than 70. Over half (63%) of patients were enrolled in North America; 15% in Eastern Europe; 15% in Australia; and 9% in Western Europe.

Characteristics of the underlying pancreatic cancer were similar between treatment arms (refer to tables in the clinical and statistical reviews). Across both arms, the primary tumor location was described as the pancreatic head for 43% of patients, body for 31% of patients, and tail for 25% of patients. The majority of patients in both arms (80%) were diagnosed with metastatic disease and 7% of patients underwent a prior Whipple procedure. A total of 17% of patients in both arms had a biliary stent at screening with a slightly higher frequency in the experimental ABI-007 arm (19% versus 16%).

As expected in a trial enrolling patients with metastatic pancreatic cancer, the majority of patients across both arms had hepatic metastases (84%). A total of 90% of patients across both arms had abdominal/peritoneal metastases (3% with peritoneal carcinomatosis). The next most common organ-specific site of metastasis was in the lung [(39% across both arms with a higher proportion in the gemcitabine-alone arm (43% versus 35%)]. Although more patients in the gemcitabine arm had pulmonary/thoracic metastases, the distribution of number of lesions was balanced between arms. Few patients across both arms received prior chemotherapy (as expected based on the amended protocol design and the low number of patients who underwent prior Whipple procedure).

7.4.2 Disposition

The investigators followed almost all patients for survival with two patients in the ABI-007/gemcitabine arm and five patients in gemcitabine-alone arm being lost to follow-up. It is unlikely that these patients would have resulted in a large effect on the final OS results. A total of 27 patients in the gemcitabine-alone arm were not treated in the protocol (24 based on the patient's own decision). This compared to 11 patients in the ABI-007/gemcitabine arm. Additionally, one patient in the gemcitabine-alone arm received ABI-007 plus gemcitabine. This patient was analyzed in the gemcitabine-alone arm in the ITT analyses for efficacy and in the ABI-007/gemcitabine group for safety analyses.

Table 6 shows the percentage of patients in the ITT population who were classified by Abraxis in the major disposition categories. The list is incomplete (e.g., does not include patients who were not treated) and the denominator is the ITT population so the columns do not add to 100%. The proportion of patients progressing also differed from the proportion of patients described in the PFS analyses below because progression continued to be followed in many of the patients following drug discontinuation. Nevertheless, more patients discontinued gemcitabine-alone due to progression and more patients discontinued treatment in the ABI-007 arm due to adverse events.

Table 6 Reasons for treatment discontinuation, CA046

	ABI-007 gemcitabine N=431 (%)	Gemcitabine N=430 (%)
Progression	45	57
Adverse events	30	17
Physician Decision	6	4
Protocol violation	2	1
Withdrawal by patient	6	9
Other	2	1
Therapy ongoing	6	3

Narrative summaries and line listings were reviewed for patients in the ABI-007/gemcitabine arm regarding disposition/discontinuation events not deemed as progression or adverse events. Reasons for withdrawal by the patient varied and in some cases were due to family or logistical reasons (e.g., the patient moved). Some patients appeared to withdraw from the study due to adverse events; however, in many cases (for example, fatigue), it was difficult to

determine whether the adverse event was related to treatment, to the disease (e.g., fatigue occurs in pancreatic cancer), or both. A few patients decided to discontinue treatment shortly after chemotherapy initiation and entered hospice. A few patients discontinued after six or more cycles after experiencing tumor shrinkage including one patient who attempted resection of residual disease.

Reasons for withdrawal due to physician decision also varied; some patients were withdrawn for what clearly appeared to be disease-related reasons including non-CT radiographic progression (e.g., new lesions on ultrasound or MRI) or other clinical evidence of progression. Some investigators withdrew patients because the investigator believed that the patient's general health was deteriorating.

7.4.3 OS analyses

Table 7, data copied from the statistical review, shows the OS results determined at the time of the primary data cut-off date for Study CA046. The results of Study CA046 showed that patients who received ABI-007 in combination with gemcitabine lived (modestly) longer than patients treated with gemcitabine alone (median duration 8.5 months in the ABI-007 arm versus 6.7 months in the control arm). This effect was statistically robust as demonstrated by a p value of less than 0.0001.

In this reviewer's opinion, the sample size re-estimation that occurred in Amendment 4 resulted in an over-powered study as represented by the low p value. As stated above in this review, the sample size re-estimation was not described in the original version of the protocol (i.e., the re-estimation was un-planned) and occurred after approximately 30% of patients died (according to the original statistical analysis plan).

This reviewer requested that the statistical reviewer conduct an analysis of OS based on the first 455 events (i.e., the planned number of events/deaths according to the original protocol). As shown in the statistical review, the HR for this analysis was 0.69 and the 95% CI was 0.58 to 0.84. Additionally, the median survival durations were similar in this analysis (8.6 months in the ABI-007 arm versus 6.6 months in the control arm) as compared to the final analysis. On 9 Aug 2013, Celgene submitted their analysis of OS after 455 events.   The applicant's analysis was similar to the FDA analysis [stratified HR was 0.70 (95% CI: 0.58, 0.84) with a p value of 0.0002, unstratified HR was 0.72 (95% CI: 0.60, 0.87) with a p value of 0.0005].

Despite the concern regarding the true Type I error rate, this reviewer is confident that the OS effect was a real finding based on (1) the (statistically) robust finding in the final analysis and (2) the fact that the original planned analysis would have been statistically significant.

Table 7 OS analyses, Study CA046 (17 Sep 2012 data cut-off)

	ABI-007 / Gemcitabine	Gemcitabine
N	431	430
Number of deaths, n (%)	333 (77%)	359 (83%)
Median Overall Survival (months)	8.5	6.7
95% CI	(7.9, 9.5)	(6.0, 7.2)
HR (95% CI) [b]	0.72 (0.62, 0.84)	
Stratified Log-Rank Test P-value [a,b]	< 0.0001	

a Stratified by planned stratification factors: geographic region; Karnofsky PS; liver metastases
b Estimated using the stratified Cox proportional hazards model

Figure 1, copied from the statistical review, shows the separation in the KM curves that occurred in Study CA046.

Figure 1 K-M curves for OS, CA046 (17 Sep 2012 data cut-off)
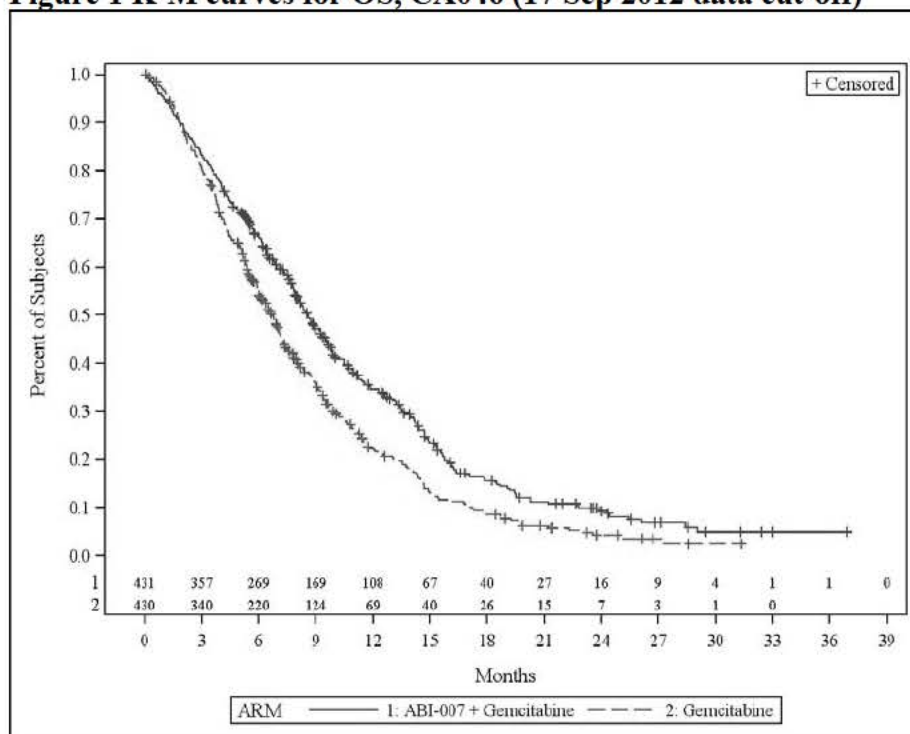
Table 8 (data copied from the statistical review) shows that for almost all subgroups tested, that the HR (point estimate) was less than one (additional analyses are presented in the statistical review). These results provided additional evidence for the consistency of effects on OS and the overall robustness of the results. The 95% CIs crossed one for many of the analyses; however, the sample size in these subgroups was smaller (than the overall patient population) and thus these subgroups were not powered to demonstrate a nominally "significant" effect on OS.

The only OS point estimates that were greater than one were for the subgroups of patients ≥ 75 years of age [HR 1.08 (0.65, 1.80)] and for patients with a normal CA 19-9 level [HR 1.07 (0.69, 1.66)]. These results (as should the other subgroup analyses) should be considered

exploratory and interpreted with caution. The numbers of patients in these two groups were small and there is no biologically plausible reason that patients with a normal CA19-9 would be expected to fare worse following ABI-007 treatment. This reviewer acknowledges there could be some concern regarding whether older patients could tolerate additional therapy; however, because of imbalances in baseline prognostic characteristics in this non-randomized subgroup, no definitive conclusions can be made. As described in the applicant's clinical study report, patients ≥75 years of age and randomized to the ABI-007 arm were more likely to have KPS 70-80 (54% versus 43% with gemcitabine alone) and have ≥ 4 metastatic sites (15% versus 8% with gemcitabine alone). Additionally, there was differential withdrawal of patients in the two arms prior to treatment [10% for gemcitabine alone (all due to patient decision) versus 2% for ABI (one patient with a protocol violation)]. Finally, the median OS of 8.0 months in the gemcitabine arm among patients ≥ 75 years of age was greater than that in the overall population.

Table 8 Subgroup analyses for OS, CA046

Subgroup	Number	HR (95% CI)
Race		
White	804	0.73 (0.63, 0.86)
Non-White	57	0.67 (0.44. 1.01)
Gender		
Men	502	0.72 (0.59, 0.88)
Women	359	0.72 (0.56, 0.93)
Age in years		
<65	496	0.64 (0.53, 0.79)
≥ 65	365	0.81 (0.63, 1.03)
≥ 75	90	1.08 (0.65, 1.80)
Region		
Australia	120	0.67 (0.44, 1.01)
Eastern Europe	126	0.84 (0.58, 1.23)
Western Europe	76	0.72 (0.35, 1.47)
North America	539	0.68 (0.56, 0.82)
KPS		
70-80	319	0.67 (0.52, 0.85)
90-100	542	0.75 (0.62, 0.91)
Primary site		
Pancreatic Head	371	0.58 (0.46, 0.74)
Other	487	0.80 (0.65, 0.98)
Prior biliary stent		
Yes	148	0.57 (0.39, 0.84)
No	713	0.74 (0.63, 0.88)
Prior Whipple		
Yes	62	0.52 (0.28, 0.98)
No	799	0.73 (0.62, 0.85)

An additional exploratory subgroup analysis of patients with pain at baseline was conducted as patients with pain were allowed to be enrolled following Amendment 1. The statistical reviewer found that the results in two separate populations (those receiving narcotics, and those who received narcotics or reported pain) were consistent with the primary OS analyses. The HR was 0.62 (95% CI: 0.51, 0.76) among 509 patients in the former analysis (patients on narcotics) and 0.67 (95% CI: 0.57, 0.78) among 734 patients in the later analysis (patients reporting pain or on narcotics).

Reviewer comment: For multiple reasons (e.g., lack of randomization of subgroups and lack of alpha allocation for subgroups), substantial evidence of effectiveness does not exist for any subgroup analyses not included in product labeling. These analyses should be considered only as exploratory and supportive (i.e., of the robustness of the primary analysis).

Finally, the FDA review team requested that Celgene conduct exploratory analyses of overall survival based on subgroups of patients enrolled into each amendment. Because the amendments instituted various dose modification changes, FDA wanted to consider whether these changes affected the OS outcome. OS did not appear to be influenced by amendment based on the applicant's analyses (both by amendment and cumulative analyses). The K-M curves did not appear to separate among patients enrolled in the first and fourth amendments; however only 10 patients and 59 patients enrolled into these amendments, respectively. Based on these analyses, it is unlikely that the specific dosing regimen described in product labeling would have a major effect on outcome compared to the regimens described in any of the various protocol amendments.

7.4.4 Secondary endpoints

Table 9 (data copied from the statistical review) shows the PFS results demonstrating a modest PFS improvement when ABI-007 was administered with gemcitabine. The PFS effects were statistically robust (based on the measured p value/CIs and based on sensitivity analyses) and although the statistical reviewer noted the potential for differential censoring between arms (in the independent analysis), any potential bias appeared to be against the ABI-007 arm.

Table 9 PFS analyses (ITT), CA046 (17 Sep 2012, cut-off date)

	ABI-007 N=431	Gemcitabine N=430
No. of Events (%)	277 (64%)	265 (62%)
No. of Deaths, (%)	115 (27%)	109 (25%)
Median PFS (months), 95%CI	5.5 (4.5, 6.0)	3.7 (3.6, 4.0)
Stratified HR (95% CI) [P value]	0.69 (0.58, 0.82) [<0.0001]	

Figure 2 shows the K-M curves for the modest PFS effect observed during the CA046 clinical trial. The "stair-step" pattern likely occurred based on the timing of radiographic imaging during the clinical trial.   (b) (4)

Figure 2 K-M curves for PFS, CA046
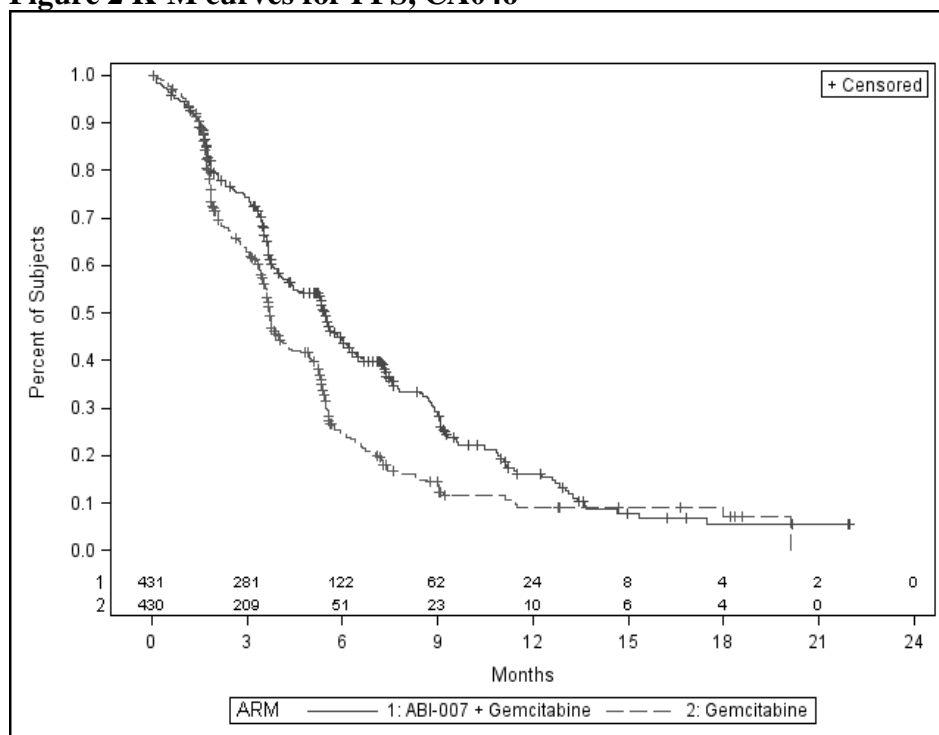
Table 10 shows that more patients experienced a reduction in tumor size who were treated in the ABI-007 arm compared to those patients who received gemcitabine alone. As shown in the statistical review, the duration of response was similar in the two arms: 7.4 months (95% CI 5.6, 8.5) in the ABI-007 arms and 7.1 months (95% CI 7.1, NA) in the gemcitabine-alone arm. As described in the statistical review, these numbers differed from those of the applicant.

The ORR was lower in the controlled clinical trial (CA046) compared to the objective response rate described in the clinical study report for Study CA040. Abraxis stated that 17 of 44 patients (39%) who received ABI-007 at 125 mg/m^2 in combination with 1,000 mg/m^2 responded. The point estimate for ORR In the CA046 trial was lower than the lower bounds of the 95% CI in the CA040 trial (95% CI: 24.2, 53.0). *Comment: based on the size of the study, this reviewer is more confident in the ORR effect size in Study CA046 compared to that in CA040.*

Table 10 Response rate (ITT), CA046

	ABI-007 N=431	Gemcitabine N=430
Overall response, n (%)	99 (23%)	31 (7%)
Complete response, n (%)	1 (< 1%)	0 (0%)
Partial response, n (%)	98 (23%)	31 (7%)

8. Safety

8.1 Adequacy of database

The clinical reviewer (Dr. Abhilasha Nair) primarily focused on data from CA046 as this was the large controlled trial intended to support approval of ABI-007 for the indicated patient population. The add-on design allowed for the isolation of the contribution of adverse events caused by ABI-007 when added to gemcitabine. The safety population of CA046 included 402 patients with metastatic pancreatic cancer who received ABI-007 plus gemcitabine and 420 who received gemcitabine alone. One patient received ABI-007 plus gemcitabine who was randomized to the gemcitabine-alone arm. The applicant and FDA analyzed the data from this patient in the gemcitabine-alone arm for efficacy (i.e., ITT analysis) and in the ABI-007 plus gemcitabine group for safety (safety population). A total of 11 patients in the ABI-007 group and 27 patients in the gemcitabine did not receive any study therapy. The most common reason [especially in the control group (24/27)] was withdrawal due to the patient's decision.

This reviewer found the safety database to be adequate to take an action on this supplemental application following the demonstration of an improvement in OS in a patient population with terminal cancer. Abraxis submitted the data in standardized format (i.e., SDTM).

In CA046, patients received ABI-007 plus gemcitabine for a median of 3 cycles (mean of 4.4) compared to 2 cycles (mean of 3.3) for gemcitabine alone. The median number of ABI-007 and gemcitabine (in the experimental arm) doses administered was 12 compared to 9 in the gemcitabine-alone arm. A total of 41% of patients required at least one ABI-007 dose reduction. A total of 47% of patients in the experimental group required at least one dose reduction of gemcitabine compared to 33% of patients in the gemcitabine-alone group.

8.2 Deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests

8.2.1 Deaths

The applicant followed all patients for survival based on the primary endpoint of Study CA046. The clinical reviewer found that the majority of deaths occurred due to progressive pancreatic cancer. Additionally, the clinical reviewer found that a total of 126 patients died within 30 days of a last dose of study therapy. The majority of these deaths occurred due to progressive disease (90). A total of 36 deaths were considered by Abraxis to be a treatment-emergent adverse event with an outcome of death (a total of 18 in each arm or 4% of the total safety population in each group).

The largest between-group difference by SOC (for deaths) was in the Infections/infestations SOC with 7 patients in the ABI-007 group (2%) experiencing a death due to infection (deemed treatment-emergent) compared to 3 (1%) in the gemcitabine-alone group. Sepsis-related events contributed to five of the seven deaths in the ABI-007 group versus two of three deaths in the gemcitabine-alone group.

Other than a slightly higher rate of fatal sepsis in the ABI-007 group and a higher rate of deaths due to disease progression in the gemcitabine-alone group, the incidence and causes of "treatment-emergent" deaths were similar between the two groups. Although appropriately classified as adverse events, attribution of some of the deaths was difficult because the deaths could also have occurred in the absence of chemotherapy (e.g., pulmonary embolism). Refer to the clinical review that presents the specific causes of deaths that occurred in Study CA46.

Overall, the analysis of overall survival performed in CA046 provided assurance of the relative safety of ABI-007.

8.2.2 SAEs

In general, the clinical reviewer found the incidence rate of most nonfatal serious adverse events occurring in CA046 to be similar between the two groups. Only the SAEs (at the preferred term level) pyrexia (6% versus 2%), dehydration (5% versus 3%), febrile neutropenia (3% versus 1%), and anemia (2% versus <1%) occurred with a between group difference of more than 1% (after rounding) with a greater incidence rate in the ABI-007 group. Nevertheless, more infectious SAEs clearly occurred in patients in the ABI-007 group (16% versus 9%); these numbers did not include cholangitis which is described in the hepatobiliary SOC (2% versus 1%).

8.2.3 Drop-outs and discontinuations due to adverse events

The applicant's clinical study report stated that 35% of patients in the ABI-007 group experienced at least one adverse event leading to treatment discontinuation (of ABI-007) compared to 24% in the gemcitabine-alone group. The most common adverse events leading to treatment discontinuation among patients treated with ABI-007 were peripheral neuropathy (8%, grouped under the SMQ), fatigue (4%), and thrombocytopenia (2%). Most other events at the preferred term level leading to discontinuation occurred at an incidence rate of less than 2%. Infections as a group resulted in the discontinuation of ABI-007 in 4% of patients versus 3% in the gemcitabine-alone group.

Treatment-emergent adverse events leading to dose reduction occurred more frequently in patients receiving ABI-007 (38% for ABI-007 and 44% for gemcitabine) compared to patients receiving gemcitabine alone (31%). The most common adverse events leading to dose reductions of ABI-007 were neutropenia (10%), peripheral neuropathy (6%, preferred term), thrombocytopenia (4%), and fatigue (4%).

8.2.4 Common adverse events

Table 11, with data copied from the clinical review, shows the most common adverse events that occurred during CA046. In general, the adverse event profile (for common adverse events) appeared as expected based on prior experience with ABI-007 and gemcitabine.

Gastrointestinal toxicity occurred more frequently in the pancreatic cancer trial compared to prior experience, likely as a result of concomitant treatment with gemcitabine and underlying pancreatic dysfunction. Peripheral edema also occurred more frequently in the CA046 trial.

For some adverse events, the data presented in the Table below do not match the table in product labeling. In these instances, different levels of the MedDRA hierarchy were determined by either the sponsor or FDA as better representing the incidence rate of the particular event. For example, Abraxis proposed including the MedDRA SMQ (standardized MedDRA query) incidence of peripheral neuropathy rather than the preferred term. Because the SMQ better approximated the incidence rate of this event, FDA agreed with this decision.

The table shows that that the most common severe adverse events ($\geq$ Grade 3) at the preferred term level included fatigue, neutropenia, thrombocytopenia, and anemia.

Table 11 Per-patient incidence rate of reported adverse events ($\geq$ 10% in ABI-007 group, MedDRA preferred term level), Study CA046

Preferred Term	ABI-007 + Gemcitabine (N=421)		Gemcitabine (N=402)	
	All Grades	Severe[a]	All Grades	Severe[a]
	%	%	%	%
Fatigue	59	18	46	9
Nausea	54	6	48	3
Alopecia	50	1	5	0
Edema peripheral	46	3	31	3
Diarrhea	44	6	24	1
Anemia	42	12	33	8
Neutropenia	42	33	30	21
Pyrexia	41	3	29	1
Decreased appetite	36	5	26	2
Vomiting	36	6	28	4
Thrombocytopenia	30	13	29	8
Constipation	30	3	28	2
Rash	28	2	10	0
Neuropathy peripheral	28	8	3	0
Peripheral sensory neuropathy	25	8	4	0
Abdominal pain	23	6	23	8
Dehydration	21	8	11	2
Asthenia	19	7	13	4
Dyspnea	17	3	15	3
Cough	17	0	7	0
Dysgeusia	16	0	8	0
Insomnia	15	0	11	1
Epistaxis	15	0	3	0
Headache	14	0	9	0
Leukopenia	14	9	10	4

Preferred Term	ABI-007 + Gemcitabine (N=421)		Gemcitabine (N=402)	
	All Grades	Severe[a]	All Grades	Severe[a]
	%	%	%	%
Weight decreased	14	0	12	0
Hypokalemia	12	4	7	1
Depression	12	0	6	0
Chills	12	0	9	0
Pain in extremity	11	1	6	1
Dizziness	11	1	8	0
Arthralgia	11	1	3	0
Alanine aminotransferase increased	11	3	9	4
Myalgia	10	1	4	0
Abdominal pain upper	10	2	7	1
Mucosal inflammation	10	1	4	0
Hemoglobin decreased	10	3	7	2
Back pain	10	1	10	1
Urinary tract infection	10	2	4	0

[a] ≥ Grade 3

8.2.5 Laboratory tests

Grade 3 or greater neutropenia and thrombocytopenia occurred in a higher proportion of patients who received ABI-007 plus gemcitabine compared to gemcitabine alone (38% versus 27% for neutropenia, and 13% versus 9% for thrombocytopenia). A total of 11% of patients in the ABI-007 group experienced Grade 4 neutropenia and 2% experienced Grade 4 thrombocytopenia. The incidence rate of severe neutropenia (≥ Grade 3) was close to 20% per cycle irrespective of cycle (through cycle 6). The per-patient incidence rate of severe anemia was similar between groups (13% versus 12%, ABI-007 versus gemcitabine-alone).

8.3 Special safety concerns

8.3.1 Drug-demographic interactions

The clinical reviewer for safety conducted analyses of adverse events by age range (≥ 65 years versus less than 65 years), gender, and ethic background. Too few subjects ≥ 75 years old (n < 50) received ABI-007 to make conclusions regarding this subgroup. Additionally, meaningful conclusions of differences in adverse events were difficult to make because these were non-randomized subgroups, and in some cases, the numbers of patients in certain groups was small. Diarrhea, decreased appetite, dehydration, and epistaxis occurred more frequently in patients ≥ 65 years of age compared with patients younger than 65 years of age.

8.3.2 Additional in-depth analyses of specific events

The clinical review describes specific adverse events in greater detail. This review discusses sepsis and pneumonitis below because these events constituted two new warnings in product labeling.

Sepsis: Sepsis occurred at a higher incidence rate among patients who received ABI-007 (compared to gemcitabine alone). In order to assess sepsis, Abraxis performed a broad search strategy consisting of 87 preferred terms that included sepsis-related terms and terms related to specific organisms. The clinical reviewer found the approach as comprehensive. A sensitivity analysis of Grade 4 (life-threatening) infectious events appeared to select fewer events than the applicant's strategy (likely related to the applicant's approach that included events based on specific organisms and events of lower severity). Using this strategy, a total of 22 patients (5%) experienced 25 sepsis events in the ABI-007 group compared to 10 (2%) in the Abraxane group [five versus two events were fatal as described above (two additional fatal pneumonia events also occurred in ABI-007-treated patients)].

In Study CA046, sepsis was not limited to those patients with severe neutropenia. Of the 25 events in the ABI-007 group, 8 occurred in the setting of ≥ Grade 3 neutropenia. According to Abraxis, median time to the onset of sepsis was longer among ABI-007-treated patients: 76 days compared to 34 days for gemcitabine).

Abraxis found that about half of the reported cases of sepsis occurred in the setting of a patient with a biliary stent/biliary obstruction (with the origin of 44% of the sepsis events related to an abdominal infection due to cholangitis). Given that less than 20% of patients had a stent at screening, this appeared to be a risk factor for severe sepsis and this reviewer agreed with inclusion of this information in the label.   Age did not appear to be an important risk factor for the development of sepsis (median age of patients with sepsis was 61 years compared to 63 years in the total study population); however, among the five patients who died of sepsis, three were over 70, suggesting a possible influence of age on severity of sepsis.

Abraxis could only provide indirect estimates of prophylactic antibiotic use during the CA046 clinical trial because it was difficult to determine prophylactic use versus treatment use. Following amendment 4, Abraxis estimated that 25% of patients received prophylactic antibiotics in the Abraxane arm compared to 20% prior to the amendment. This compared to 13% and 19% of patients in the gemcitabine-alone arm before and after the amendment. Abraxis was not able to provide, based on the CRFs/datasets an estimated duration of time from the self administration of antibiotics in the setting of fever until first medical evaluation (in order to determine whether patients were helped or harmed by this intervention).

Pneumonitis: Abraxis used a broad-scope SMQ to investigate potential pneumonitis and found that 4% of patients in the ABI-007 group experienced pneumonitis compared to 1% in the gemcitabine group. The incidence of ≥ Grade 3 cases was 2% versus 1% in the ABI-007 and gemcitabine-alone groups, respectively. Two patients in the ABI-007 group died following the development of pneumonitis. Abraxis found no predictable risk factors for the development of pneumonitis including baseline pulmonary metastases. Although the etiology of these events may have been unclear (i.e., without biopsy in most cases), the difference among groups regarding this event was such that a warning should be included in product labeling (as proposed by Abraxis).

Discussion of Other Events: Cystoid macular edema (CME) resulted in drug discontinuation for one patient who received ABI-007 and gemcitabine. The Abraxane label lists CME in the

post-marketing section. Based on the rarity of this already described adverse reaction, and because the event occurred in a clinical trial, this reviewer agrees that this Adverse Reaction can be listed in Section 6.3 of the product label.

Two reported hemolytic uremic events occurred among ABI-007/gemcitabine-treated patients versus one among gemcitabine-alone-treated patients. Because microangiopathic hemolytic anemia can occur following the administration of gemcitabine, there was insufficient evidence to conclude that there was a causal relationship between the occurrence of the adverse event and the use of ABI-007.

9. Advisory Committee Meeting

The review team determined that an ODAC meeting was not necessary for review of this supplemental NDA. The effect on OS was statistically robust, and trained oncologists are familiar with the types of toxicities caused by ABI-007 (a taxane).

10. Pediatrics

In the NDA, Celgene referred to the orphan-designation granted by the Agency on 03 Sep 2009 (Request #09 2910). As such, this application is exempt from the requirement to contain a pediatric assessment or conduct additional studies under PREA.

11. Other Relevant Regulatory Issues

11.1 Application Integrity Policy (AIP)

The Application contained a statement signed by Dr. Jay Backstrom that certified that Celgene did not and will not use, in any capacity, the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

11.2 Financial disclosures

The majority of investigators and sub-investigators reported that they did not enter into any financial arrangements whereby the value of compensation to the investigator would be expected to affect the outcome of the study as defined in 21 CFR 54.2(a). The applicant also certified that the listed investigators referenced on Form 3454 did not disclose financial interests as defined in 21 CFR 54.2(b) or significant payments as described in 21 CFR 54.2(f).

Celgene submitted FDA Form 3455 concerning three sub-investigators, all from the United States, and all at different sites who reported conflicts of interest. One sub-investigator from a site (b)(6) reported receiving a grant from Celgene with a monetary value of more than $25,000. This sub-investigator (b)(6) enrolled a total of (b)(6) patients ((b)(6)% of those treated). (b)(6)

The other two sites with sub-investigators who reported conflicts of interests enrolled fewer patients ((b) (6) % each). One site (b) (6) enrolled (b) (6) patients where the sub-investigator reported (b) (6) (b) (6) One site (b) (6) enrolled (b) (6) patients where the sub-investigator reported a significant equity interest of 8,000 shares of Celgene stock (b) (6) (b) (6)

Overall, based on the statistical robustness of study results, large size of the study enrolling patients at multiple sites, and primary endpoint of overall survival, it is unlikely that bias due to these three conflicts resulted in qualitative effects on the overall study results, at least with respect to the primary endpoint.

11.3 GCP issues

Celgene provided a list of all IRBs and IECs and chairpersons that authorized the conduct of the clinical trial at each study site. Additionally, Celgene indicated that each patient was required to sign an informed consent form to participate in the study. Celgene provided quality assurance audit certificates from 22 sites. Celgene identified one U.S. site that enrolled a total of three patients that required closure despite corrective actions due to protocol violations and drug discrepancies.

Comment: Celgene identified this site and closed the site when only three patients were enrolled; thus, it is unlikely that findings related to this site resulted in a bias in favor of the ABI-007 arm (OS data from this site actually favored the placebo arm).

The numbers of protocol violations related to eligibility criteria were similar in the two arms (7%). Violations related to both chemistry labs (e.g., liver transaminases) and criteria related to KPS appeared to be the most common violations. Dosing violations (e.g., failure to reduce the dose) were more frequent in the ABI-007 arm (8% versus 3%). *Comment: The protocol was amended multiple times in order to revise the dose modification rules in the ABI-007/gemcitabine arm. This may have contributed to the discrepancy between arms.*

Comment: In summary, although protocol violations occurred, the violations did not appear such that they would have influenced the study results in favor of a treatment effect in the ABI-007 arm.

11.4 OSI audits

DOP2 did not recommend an OSI audit for this efficacy supplement. The application was supported by a robust effect on overall survival and this was the third disease setting under review for ABI-007. Removal of data from one or a few sites would not appear to change the overall study results.

During the review of the application, DOP2 notified OSI by email of the site that required closure described in Section 11.3 of this review. DOP2 believed that inspection of this site identified by the Sponsor was not necessary to ensure that the ABI-007 effects on OS were accurate (see Section 11.3 above); however, OSI was notified to determine whether this site required inspection for other reasons (e.g., enrollment of patients in other studies).

11.5 Other discipline consults

11.5.1 Patient labeling (Division of Medical Policy Programs)

Nathan Caulk from DMPP completed a review of Patient Labeling on 2 Jul 2013. Some edits recommended by DMPP were communicated to Abraxis on 6 Aug 2013. DMPP recommendations communicated to Abraxis included splitting out the indications under the "What is Abraxane?" section; adding a statement "you should not become pregnant while receiving Abraxane"; revising neuropathy language to be consistent with the PI; modifying the applicant's proposed language regarding serious adverse effects including sepsis and pneumonitis; and modifying the language regarding hypersensitivity.

DOP2 did not incorporate the recommendation to separate common side effects by indication. This reviewer believes this could mislead patients receiving ABI-007. This was communicated to DMPP by phone on 6 Aug 2013 who understood DOP2's rationale. In addition, DOP2 did not incorporate the following DMPP recommendations based on specific input from DOP1 who holds primary responsibility for ABI-007 based on the approval of ABI-007 in breast cancer: removal of neuropathy symptoms from common side effects of ABI-007 (as this is listed in the serious side effects section); removal of "bound to human albumin" from the ingredients section; and deletion of "in case of severe allergic reaction, ABI-007 should not be used again" (from a specific section).

11.5.2 OPDP

Marybeth Toscano completed her labeling review on 2 Jul 2013. The Division incorporated her recommendation to remove a specific line from Section 6.3 of the label in provisional labeling sent to Abraxis on 5 Aug 2013.

12. Labeling

FDA sent draft labeling recommendations to Abraxis prior to the date stipulated by the 21st Century Review Process on 19 Jun 2013. Labeling recommendations described below should not be considered final because labeling negotiations are ongoing. Abraxis responded to FDA edits to the label on 28 Jun 2013 and 12 Jul 2013. FDA subsequently communicated additional edits to Abraxis on 05 Aug 2013.

In general, DOP2 only revised sections of the label pertaining to this supplement. Command language was preferred as directed by the PLR. The remainder of this section of the review will solely focus on high-level issues regarding the label submitted by Abraxis. Numbering below is consistent with the applicable sections in product labeling. This review will not comment on all sections (for example, if only minor edits were made to a section). This CDTL agreed with the recommendations made by the review teams that are described below.

　　1. **Indication and Usage:** This reviewer agreed that substantial evidence did not exist to support a claim _____ (b) (4)

　　2. **Dosage and Administration:** Consideration of this section was a major challenge during the review of this application. The sponsor revised the dose modification section of CA046 multiple times and the complicated dose modification criteria likely resulted in

increased protocol violations in the ABI-007 arm. This reviewer would expect such complicated rules to result in a high rate of medication errors when administered in the community. DOP2 initially recommended changing the dose modification rules to bulleted lists (rather than multiple lengthy tables) to make the label parallel with the other indications. Abraxis counter-proposed a simplified table that DOP2 believes will better allow for standardized administration of the regimen in the community. Recommendations (b) (4) were removed (b) (4)

DOP2 also recommended removal   (b) (4) from Section (b) (4) of the label. Section 14 (clinical studies) contains this information.

6. Adverse Reactions: DOP2 recommended moving exposure information to this section. DOP2 recommended removal of adverse *events* that were not adverse *reactions* (for example,   (b) (4)). Some information was removed from Section 6.0 in order to minimize redundant information (for example, with the Warning section).

8.5. Geriatric use: DOP2 deleted (b) (4)

14. Clinical Studies: DOP2 added   (b) (4) to this section (b) (4)

Additional information regarding study design was added to this section (for example strata). DOP2 recommended removal (b) (4)

DOP2 also recommended against (b) (4)

DOP2 recommended deletion (b) (4) However, as previously stated in this review, DOP2 agrees that there is substantial evidence to support presentation of these (specific) curves.

13. Recommendations/Risk Benefit Assessment

13.1 Recommended regulatory action

This reviewer recommends regular approval of sNDA 21660/37 based on substantial evidence from one adequate and well controlled trial demonstrating a modest but statistically robust effect on OS (clinical benefit) observed in CA046. This approval recommendation is contingent upon reaching agreement on final labeling.

13.2 Risk-benefit assessment

The recommendation for approval of this application is based on a modest effect on OS observed in CA046. According to the May 2007 FDA Guidance Document regarding endpoints for cancer drugs (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf; accessed on 12 Jul 2012), survival is considered the most reliable cancer endpoint, and when studies can be conducted to adequately assess survival, it is usually the preferred endpoint. An effect on OS is considered regulatory evidence of clinical benefit used by the Agency to substantiate regular approval of a drug.

Because metastatic pancreatic cancer is an incurable disease, the goal of treatment is to prolong life and/or improve quality of life. The CA046 trial established that patients who received ABI-007 in combination with gemcitabine lived a median 1.8 months longer than patients who received gemcitabine alone [HR 0.72 (95% CI: 0.62, 0.84)].

The effect on OS was supported by a statistically significant effect on progression free survival and consistent results across subsets. The modest effects on PFS should be considered supportive of the robustness of the OS results rather than as direct evidence of direct benefit.

Adverse events observed in the CA046 trial were generally considered in-line with toxicities expected following treatment with cytotoxic chemotherapy (i.e., with gemcitabine and a taxane). Although ABI-007 causes multiple, including serious, toxicities, the overall toxicity profile was considered acceptable because ABI-007 (when combined with gemcitabine) improves overall survival in patients with terminal metastatic pancreatic cancer. The most frequently observed adverse reactions (occurring in $\geq 20\%$ of patients) that occurred in patients treated with ABI-007 plus gemcitabine were neutropenia, thrombocytopenia, fatigue, peripheral neuropathy, nausea, alopecia, peripheral edema, diarrhea, pyrexia, vomiting, decreased appetite, rash, and dehydration. Peripheral edema and gastrointestinal toxicities occurred more frequently in Study CA046 compared to prior trials with ABI-007.

The most serious adverse reactions caused by ABI-007 (plus gemcitabine) in Study CA046 included pyrexia (6%), dehydration (5%), pneumonia (4%) and vomiting (4%). Sepsis also occurred more frequently among patients treated with ABI-007 plus gemcitabine (5%) compared to gemcitabine alone. Five reports of sepsis were fatal. Sepsis occurred irrespective of severe neutropenia. Identified risk factors for sepsis included biliary obstruction or presence of biliary stent. This information was included in a new warning for sepsis in product labeling. The incidence of pneumonitis also occurred more frequently among ABI-007-treated patients (4%) supporting a new warning for this adverse reaction that can facilitate monitoring and management.

In summary, CA046 (an adequate and well controlled trial) demonstrated substantial evidence of safety and effectiveness (modest improvement in OS) of ABI-007 combined with gemcitabine compared to gemcitabine alone. Oncologists will need to communicate the overall risk/benefit profile with their patients in order for patients to make the determination of whether they should receive ABI-007 plus gemcitabine versus other available regimens supported by data from randomized controlled trials.

13.3 Recommendation for postmarketing Risk Evaluation and Management Strategies

The review teams did not identify any REMS as necessary prior to this marketing expansion for ABI-007. ABI-007 will be prescribed by oncologists who are trained how to monitor, diagnose, and manage serious toxicities caused by anti-neoplastic drugs including taxanes. Standard practice in oncology dictates informed consent prior to prescribing or administering anti-neoplastic drugs.

13.4 Recommendation for other postmarketing requirements and commitments

FDA review staff did not identify any postmarketing requirements or commitments as necessary prior to the approval of this efficacy supplement.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21660Orig1s037

<u>CLINICAL REVIEW(S)</u>

CLINICAL REVIEW

Application Type	sNDA
Application Number(s)	21660/Supplement-37
Priority or Standard	Priority
Submit Date(s)	March 21, 2013
Received Date(s)	March 21, 2013
PDUFA Goal Date	September 21, 2013
Division / Office	DOP2/OHOP
Reviewer Name(s)	Abhilasha Nair,MD
	Steven Lemery,MD,MHS(TL)
Review Completion Date	8/15/2013
Established Name	Paclitaxel protein-bound particles for injectable suspension) (albumin-bound)
(Proposed) Trade Name	Abraxane
Therapeutic Class	Microtubule inhibitor
Applicant	Abraxis Bioscience, LLC (wholly owned subsidiary of Celgene Corporation)
Formulation(s)	100 mg of paclitaxel in a single-use vial
Dosing Regimen	125 mg/m2 intravenously over 30-40 minutes on Days 1, 8 and 15 of each 28-day cycle
Indication(s)	(b) (4)

(b) (4) metastatic adenocarcinoma of the pancreas as first-line treatment, in combination with gemcitabine.

Intended Population(s)   Adults>18 years of age

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1   Recommendations/Risk Benefit Assessment

1.1   Recommendation on Regulatory Action

This clinical reviewer recommends regular approval of new drug application NDA 21660, Supplement- 37, for Abraxane in combination with gemcitabine for the first-line treatment of patients with metastatic pancreatic cancer.

This NDA is primarily supported by a single multicenter open-label randomized controlled trial in patients with metastatic pancreatic cancer, study CA046. Study CA046 enrolled a total of 861 patients with metastatic pancreatic cancer, in multiple centers, across eleven countries, between April 2002 and May 2009, randomized 1:1 to the combination of Abraxane with gemcitabine or gemcitabine alone.

The assessment of benefit in this application is based on the primary endpoint of overall survival. This reviewer's recommendation for approval is based on the review of the clinical data, which supports the conclusion that Abraxane given in combination with gemcitabine prolongs overall survival for patients with metastatic pancreatic cancer compared to gemcitabine given as a single agent in this setting. A statistically significant, clinically meaningful prolongation in overall survival was observed in patients randomized to receive the combination of Abraxane and gemcitabine: median overall survival was 8.5 months (95% CI=7.89, 9.53) on the combination arm and 6.7 months (95% CI=6.01, 7.23) on the gemcitabine arm with a hazard ratio of 0.72 (95% CI: 0.62, 0.84; $p < 0.0001$).

Study CA046's secondary efficacy parameter of progression-free-survival (PFS) was prolonged according to both the independent assessment and the investigator assessment. The independent-assessed PFS results showed a 1.8 month longer median PFS in the patients treated with the combination of Abraxane and gemcitabine compared to those treated with single-agent gemcitabine. The estimated hazard ratio for PFS was 0.69 (95% CI: 0.58, 0.82) in favor of the combination arm.

Study CA046 also demonstrated an improvement in objective response rate which was statistically significant based on independent assessment (23% vs. 7%, on the combination arm and gemcitabine arm respectively, p-value < 0.0001). The median duration of response was 7.4 (95% CI=5.6, 8.5) and 7.1 (95% CI=3.8, NA) months for Abraxane /gemcitabine and gemcitabine alone, respectively.

There are inherent limitations of relying on the results of a single, randomized, well-controlled study; however, this reviewer concludes that this submission provides sufficient scientific and regulatory bases for approval, as set forth in the Guidance for Industry, entitled "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products." The guidance states that *"reliance on only a single study will generally be limited to situations in which a trial has demonstrated a clinically*

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meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible." In this regard, Study CA046 is a large, multicenter trial that demonstrated a clinically meaningful improvement in overall survival that was consistent across many different subgroups, in a population of advanced pancreatic cancer patients who in the present day, still have limited treatment options, such that the confirmation of this result in a second trial would be practically and ethically impossible.

1.2   Risk Benefit Assessment

Since the original FDA approval for Abraxane in metastatic breast cancer in 2005, the cumulative patient exposure to Abraxane during clinical trials and commercial experience is 182,439 patients. (*Source: Summary of clinical safety, sNDA 21660/37*). Safety data from the pivotal trial CA046 was consistent with prior trials of Abraxane conducted in non-small cell lung cancer (NSCLC) and metastatic breast cancer (MBC) and data from post marketing experience with the drug since 2005. The most common adverse events (>20%) experienced by the 421 patients who received the combination of Abraxane and gemcitabine included neutropenia, thrombocytopenia, fatigue, peripheral neuropathy, nausea, alopecia, peripheral edema. diarrhea, pyrexia, vomiting, rash, and dehydration.

As evidenced by the improvement in overall survival, more treatment emergent deaths [deaths during or within 30 days of receiving the study drug (including deaths due to progression] occurred on the gemcitabine-alone arm (18%) as opposed to the Abraxane/gemcitabine arm (13%). The percentage of patients who experienced a treatment emergent adverse event (TEAE) with an outcome of death was similar between the two treatment arms (4%). The incidence of serious adverse events (SAE's) was higher on the Abraxane combination arm (50% for the Abraxane/gemcitabine arm and 43% for the gemcitabine alone arm). The most frequently reported SAE on the Abraxane arm was Pyrexia (6.4%). The SAEs that had the greatest difference in incidence between the two arms were pyrexia, febrile neutropenia, dehydration, anemia, diarrhea, pneumonia, and vomiting.

Among the 421 Abraxane-treated patients, the incidence of Grade 3 or greater neutropenia as analyzed by the HLT of "neutropenias" (including the preferred terms of neutropenia, febrile neutropenia and agranulocytosis) was 35% (vs.22% on the gemcitabine alone arm). Less than 1% of patients on both arms had drug permanently discontinued due to neutropenia. Ten percent of patients on the combination arm had dose reductions due to neutropenia.

Peripheral neuropathy (as analyzed by the SMQ) was the most common adverse event leading to study drug discontinuation (8% of patients). The incidence of all grades of peripheral neuropathy was 54% in the Abraxane arm and 13% in the gemcitabine arm.

The incidence of Grade 3 peripheral neuropathy was 17% in the Abraxane arm vs. 1% in the gemcitabine arm. There were no reports of Grade 4 peripheral neuropathy.

New safety signals of sepsis and pneumonitis were identified during the conduct of Study CA046 that led to protocol amendments intended to reduce the incidence/severity of the events. Analyses of the safety data submitted revealed that the incidence of interstitial lung disease was 4% on the Abraxane arm and 1% on the gemcitabine arm-alone. The incidence of Grade 3 or higher pneumonitis on the Abraxane arm was 2% versus 1% on the gemcitabine arm. Two patients died on the Abraxane arm due to pneumonitis. There were 5 deaths on the Abraxane arm due to sepsis and an analysis of sepsis risk factors by the applicant revealed the presence of a biliary stent as a risk factor.

In summary, after careful review of the safety and efficacy data submitted in NDA 21660 this reviewer concludes that Abraxane in combination with gemcitabine has an acceptable-risk benefit profile in patients with metastatic pancreatic cancer, a life threatening disease with few existing treatment options. The 1.8 month improvement in overall survival demonstrated by Study CA046 is a reflection of safety as well as efficacy. In addition, the safety database demonstrates that the adverse events observed with Abraxane used in combination with gemcitabine are relatively predictable given the numerous years of experience with the drug and manageable with prudent patient selection, surveillance, dose delays, and reductions.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No additional clinical post-marketing risk management activities are required at this time. The proposed USPI contains patient counseling information for prescribing physicians (oncologists) as well as a Patient Package Insert.

1.4 Recommendations for Postmarket Requirements and Commitments

No post-marketing requirements or commitments are required based on this submission.

2 Introduction and Regulatory Background

The applicant seeks approval for Abraxane for the following indication: - "ABRAXANE is indicated for the first-line treatment of patients with _____ (b) (4) metastatic adenocarcinoma of the pancreas, in combination with gemcitabine." The application was submitted on March 21, 2013 and the PDUFA goal date is September 21, 2013.

This review will describe the efficacy and safety data supporting approval and the recommendations of the clinical reviewer.

2.1 Product Information

Please refer to previous product reviews and summary reviews. No new product information was submitted in this efficacy supplement.

2.2 Tables of Currently Available Treatments for Proposed Indications

Metastatic pancreatic cancer still remains incurable despite recent advances in oncology and carries a dismal prognosis with a 5-year survival of 2% (*Cancer Facts and Figures, 2012*). Hence, the approved agents for this disease have demonstrated only improvement in the patient's symptoms and a modest improvement in overall survival or a combination of both.

In the past 20 years, FDA has only approved two drugs for the treatment of patients with metastatic pancreatic cancer. Erlotinib, the most recent approval for this disease stage, was approved in 2005 for the treatment of locally advanced, unresectable or metastatic pancreatic cancer in combination with gemcitabine based on a modest improvement (< 1 months) in overall survival.

FDA approved gemcitabine in 1996 in the first-line (locally advanced and metastatic) and second-line settings (after treatment with 5FU) based on a study with a "clinical benefit response" as the primary endpoint ($\geq$ 50% reduction in pain or a 20 point improvement in Karnofsky performance status for at least 4 weeks OR stable pain, performance status, analgesic consumption with at least $\geq$ 7% weight gain for greater than or equal to four weeks). This endpoint was supported however, by a beneficial effect on overall survival.

Table 1: Currently available treatments for metastatic pancreatic cancer *(shaded agents are FDA approved)*

Study	FDA approval	N	Overall Survival			
			Exp	Gem	HR	P value
Gemcitabine vs 5FU (Burris,1997)	15 May 1996	126	4.4	5.7	NR	<0.0025
Gemcitabine ± erlotinib (Moore,2007)	02 Nov 2005	569	6.2	5.9	0.82	0.038
FOLFIRINOX vs gem (Conroy,2011)	NA	342	11.1	6.8	0.57	<0.001

Guidelines for the treatment of pancreatic cancer including the NCCN guidelines also list the regimen of FOLFIRINOX as a category 1 recommendation. This is based on the published results of a French study (*Conroy et al,2011*) comparing FOLFIRINOX (oxaliplatin 85 mg/m^2; irinotecan 180 mg/m^2; leucovorin 400 mg/m^2 and fluorouracil 400 mg/m^2 administered as a bolus followed by 2,400 mg/m^2 administered as a 46-hour continuous infusion, every other week) to gemcitabine. The trial demonstrated that median overall survival was 11.1 months in the FOLFIRINOX arm compared to 6.8 months among patients randomized to receive gemcitabine (HR 0.57, p < 0.001). The regimen resulted in significant toxicity with 45% of patients experiencing Grade 3 or 4 neutropenia and a febrile neutropenia rate of 5.4% despite growth factor support in more than 40% of the patients. FOLFIRINOX was also associated with a higher incidence of thrombocytopenia, diarrhea, and sensory neuropathy, as well as grade 2 alopecia.

2.3   Availability of Proposed Active Ingredient in the United States

The proposed active ingredient is available as Abraxane® (albumin-bound paclitaxel) and as paclitaxel (brand name Taxol®, and under multiple ANDAs).

2.4   Important Safety Issues with Consideration to Related Drugs

Abraxane or paclitaxel protein-bound particles for injectable suspension (albumin-bound) contains paclitaxel, a taxane, as the active ingredient.

Paclitaxel carries a boxed warning that describes anaphylaxis and severe hypersensitivity reactions. Such reactions may occur ⁽ᵇ⁾⁽⁴⁾ The boxed warning also states that paclitaxel should not be administered to patients with baseline neutrophil counts less than 1,500/mcL and patients with AIDS-related Kaposi's sarcoma if the baseline neutrophil count is less than 1000 cells/mm^3 due to risks related to drug-induced myelotoxicity. Paclitaxel carries an additional warning describing severe conduction abnormalities. Other class specific toxicities of taxanes include peripheral neuropathy (predominantly sensory), injection site reactions, arthralgia and myalgia, mucositis and alopecia.

2.5   Summary of Presubmission Regulatory Activity Related to Submission

FDA and Abraxis met on September 9, 2008 to discuss two proposed trials to be conducted in patients with pancreatic cancer. Abraxis was proposing to submit an sNDA ⁽ᵇ⁾⁽⁴⁾ Trial CA046 (first line trial for metastatic pancreatic cancer) was discussed and FDA agreed with the primary endpoint of overall survival and agreed to the use of gemcitabine as the control arm considering that erlotinib may not be available in some international sites. Agreement was also reached on using the dosing schedule of gemcitabine specified in the package insert. ⁽ᵇ⁾⁽⁴⁾

FDA granted orphan designation for the pancreatic cancer indication on September 3, 2009. Hence the Pediatric Research Equity Act (PREA) is not applicable and a waiver for pediatric studies was not required.

FDA and Celgene held a Type C meeting on August 4, 2011 regarding the interim analysis results of study CA046. FDA did not agree with a proposal to submit an NDA based on an interim analysis of PFS from the ongoing CA046 study. During the meeting, Abraxis Bioscience agreed that Study CA046 would continue as originally planned, based on the Agency's advice that overall survival should remain the primary endpoint of the study. FDA accepted Celgene's justification as to why additional PK sampling would not be conducted from the ongoing trial (based on an insufficient sample size given that the study was already enrolling patients).

IND 115027 was submitted as an administrative split from IND 055974 for Abraxane in the treatment of pancreatic cancer in April 2012.

On October 16, 2012, FDA sent written responses addressing questions from Celgene regarding a proposed sNDA for Abraxane in pancreatic cancer. FDA provided advice regarding the integrated datasets and the specific format for the datasets, the provision of patient safety narratives and case report forms in the sNDA.

On November 8, 2012, Celgene provided top-line results from Study CA046 and stated that the study demonstrated a statistically significant effect on overall survival. FDA agreed to look for alternative dates to schedule an upcoming pre-sBLA meeting and agreed to provide responses in writing to earlier questions to facilitate the review of Abraxane for the intended indication.

On January 3, 2012, FDA provided additional feedback regarding an upcoming sNDA submission and regarding the presentation of safety data in the application. FDA subsequently provided additional advice to Celgene on January 11, 2013 regarding the application and requested confirmation that all safety data will be submitted in the sNDA for patients receiving the combination of gemcitabine plus Abraxane in Abraxis-sponsored trials regardless of indication for treatment. This prompted Celgene to cancel the pre-sNDA meeting.

2.6   Other Relevant Background Information

Not applicable to this sNDA.

3   Ethics and Good Clinical Practices

3.1   Submission Quality and Integrity

This NDA submission was of adequate quality to allow for the review to be conducted. Datasets were submitted in standard (CDISC) format, and there were no items identified as impediments to the conduct of a timely review.

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3.2 Compliance with Good Clinical Practices

All study reports submitted to the sNDA contained a statement that the study was conducted in accordance with Good Clinical Practice (GCP), as denoted in the International Conference on Harmonization (ICH) E6 requirements for GCP and in accordance with the ethical principles outlined in the Declaration of Helsinki.

During the conduct of Study CA046, site 771 that had enrolled 3 patients was cited by the sponsor during (sponsor) inspections for multiple protocol violations and drug discrepancies. The sponsor placed the site on hold on Mar 5, 2010 and subsequently closed the site to enrollment on Jun 24, 2010. The sponsor also notified FDA of these findings.

The applicant submitted the required electronic case report forms (eCRF's) as discussed prior to the submission of the sNDA. Forty random eCRF's were audited during the clinical review to determine if demographic and adverse event information contained in the datasets were an accurate reflection of the records documented in the eCRF's. In general, audited data contained within the CRFs matched the data in the datasets.

3.2.1 DSI inspections

There were no DSI inspections conducted in this application for the following reasons:

- Robust effect on overall survival; removal of data from one or a few sites would not change the overall direction of the study results.
- Third disease setting under review for Abraxane. Removal of data from one or a few sites is unlikely to affect the overall study results.

3.2.2 Protocol Violations Study

A review of Study CA046 conducted by Celgene revealed 126 (15%) patients with protocol violations. One category of protocol violations differed in incidence between treatment arms: - dose modifications (dose not being reduced in the setting of Grade 3-4 toxicity with a subsequent Grade 3-4 toxicity (8% on the combination of Gemcitabine/ABI-007 and 3% on the gemcitabine arm) (shaded in Table 2).

__Reviewers Comment:-__Differences between treatment arms for this violation were probably due to the multiple changes that were made to the dose modification guidelines in various amendments of the protocol. These changes to the dose modification guidelines may have led to confusion in the investigator's interpretation of the dose modification rules. The higher number of such deviations on the combination arm may have reflected the lack of clear, consistent guidelines in the original protocol for management of toxicities on the combination arm.

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Table 2: Protocol Violations in Study CA046

VARIABLE	ABI-007 + Gemcitabine (%) N=431	Gemcitabine (%) N=430	All patients (%) N=831
Patients with protocol violation	75 (17)	51 (12)	126 (15)
Reason for protocol violation			
Dose Escalation Between Cycles	13 (3)	9 (2)	22
Dose Not Reduced In The Setting Of Grade 3-4 AE/Toxicity, With A Subsequent Grade 3-4 AE/Toxicity	35 (8)	14 (3)	49 (6)
Dosing Continued Following Disease Progression	5 (1)	2 (<1)	7 (1)
Inclusion/Exclusion Criteria Not Met	32 (7)	30 (7)	62 (7)

There were 7% of patients in each of the arms that did not meet the inclusion/exclusion criteria which was the most common protocol violation. Common reasons in this category included violations regarding chemistry labs and violations regarding Karnofsky performance status.

Reviewers Comment: - _Inclusion and exclusion criteria were also modified several times throughout the protocol which may have led to these violations. However the incidence of this protocol violation was balanced between the two arms. Therefore, this reviewer concludes that it is unlikely that these protocol violations affected the overall study results._

3.3   Financial Disclosures

Celgene submitted Form 3454 for both study CA046 and study CA040. The form certified that Celgene had no financial arrangements with the listed clinical investigators on the form for these studies. Celgene provided a list of investigators who certified that they had no financial conflicts of interest as defined in 21 CFR 54.2(a) (b) and (f). Celgene submitted Form 3455 for three of the investigators on study CA046 disclosing potential conflict of interests. Celgene submitted a justification that bias was minimized based on the fact that these investigators did not have an influence on the primary endpoint of overall survival and that they all were sub-investigators at sites that enrolled less than 10% of the total enrolled patients such that it would be unlikely to bias the overall study results.

Reviewers Comment: - _This reviewer agrees that based on the numbers of patients enrolled at the three sites, along with the overall robustness of the overall survival_

results, these financial conflicts of interest were unlikely to have had a significant effect on the overall study results.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

No new CMC data were submitted in the application.

4.2 Clinical Microbiology

This section was not applicable to this sNDA.

4.3 Preclinical Pharmacology/Toxicology

This section was not applicable to this sNDA.

4.4 Clinical Pharmacology

This section was not applicable to this sNDA.

4.4.1 Mechanism of Action

This section was not applicable to this sNDA.

4.4.2 Pharmacodynamics

This section was not applicable to this sNDA.

4.4.3 Pharmacokinetics

This section was not applicable to this sNDA. PK measurements were not obtained from Study CA046.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 3 lists the clinical studies submitted in support of the sNDA application. Data from study CA046 serves as the primary basis for efficacy evaluation. The supportive evidence was provided from study CA040.

Table 3: **Listing of Clinical Trials Submitted to the sNDA**

Study Description	Study CA046	Study (CA040)
Treatment Regimen	Abraxane 125 mg/m^2 IV followed by gemcitabine 1000 mg/m^2 IV were administered on Days 1, 8, 15 and 29, 36, 43 of a 56-day cycle in Cycle 1 only (i.e., weekly for 3 weeks with a 1-week rest x 2) and subsequently administered on Days 1, 8, and 15 of a 28-day cycle in Cycle 2 and onwards. OR Gemcitabine 1000 mg/m^2 was administered on Days 1, 8, 15, 22, 29, 36, 43 of a 56-day cycle in Cycle 1 (i.e., weekly for 7 weeks and a 1-week rest period) and subsequently administered on Days 1, 8, and 15 of a 28 day cycle in Cycle 2 and onwards	Abraxane 100, 125, or 150 mg/m^2 IV followed by gemcitabine 1000 mg/m^2 IV on Days 1, 8, and 15 of a 28-day cycle
Duration of Treatment	Until PD or unacceptable toxicity	Until PD or unacceptable toxicity
Primary objective	Evaluate effects on OS of the combination of Abraxane /gemcitabine versus gemcitabine in patients with metastatic adenocarcinoma of the pancreas	To determine the MTD and DLTs of gemcitabine plus Abraxane in patients with metastatic pancreatic cancer.
Primary endpoint	Overall Survival	MTD and DLTs of gemcitabine plus Abraxane

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Study Description	Study CA046	Study (CA040)
Secondary endpoints	Progression Free Survival (RECIST guidelines) Objective Response Rate (RECIST) guidelines Time to response and duration of response Disease control rate (i.e., objective tumor response or stable disease for ≥ 16 weeks)	Disease Control Rate Duration of Response Progression Free Survival and Overall Survival.
Exploratory endpoints	Evaluation of antitumor activity by PET/CT Changes in CA19-9 levels SPARC expression	Evaluation of antitumor activity by PET/CT Changes in CA19-9 levels SPARC expression

5.2   Review Strategy

Safety and efficacy data, including clinical study reports, CRFs, and datasets, were reviewed for study ABI-007-CA046, the only completed randomized clinical trial that was submitted to the NDA. Data from the supportive, single arm study CA040 was reviewed primarily for safety to identify any important safety signals that did not emerge from the analysis of Study CA046. Section 5.3 contains a detailed discussion of the design of study CA046, and a review of the design of study CA040.

5.3   Discussion of Individual Studies/Clinical Trials

5.3.1 ABI-007-CA046

This sNDA submission is primarily supported by results of Study ABI-007 CA046 ("Study CA046") titled "A Randomized Phase III Study of Weekly ABI-007 plus Gemcitabine versus Gemcitabine Alone in Patients with Metastatic Adenocarcinoma of the Pancreas."

Study CA046 was an industry sponsored, multicenter, international, randomized controlled open label study conducted in 151 sites in 11 countries. The data cutoff point was 17 Sep 2012. The following describes the study protocol and the amendments that were submitted subsequent to the original protocol.

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5.3.1.1 Objectives

The primary objective of the study was to evaluate the efficacy of the combination of ABI-007(Abraxane) and gemcitabine versus gemcitabine alone in improving overall survival in patients with metastatic adenocarcinoma of the pancreas.

__Reviewers comment__: The choice of gemcitabine as an active comparator in this trial of metastatic pancreatic cancer patients is acceptable. Although a clinical trial of FOLFIRINOX showed that this regimen improved the survival of patients with metastatic pancreatic cancer, most patients were enrolled in CA046 prior to the publication of the report. Additionally, although erlotinib is approved for patients with metastatic pancreatic cancer based on an effect on overall survival, the effect was of such magnitude (less than 0.5 months) that it was reasonable not to require the use of the drug in the comparator arm.

The secondary objectives were:

- Evaluation of progression-free survival according to Response Evaluation Criteria in Solid Tumors (RECIST) guidelines.
- Evaluation of the objective tumor response according to RECIST guidelines.
- Evaluation of the safety and tolerability of this combination in this patient population.

Exploratory objectives included evaluation of tumor response by Positron-emission tomography (PET) analysis, evaluation of changes in serum carbohydrate antigen (CA19-9) and possible correlation with clinical outcomes, evaluation of plasma secreted protein acidic and rich in cysteine (SPARC/osteonectin) and any correlation with clinical outcomes, evaluation of tumor markers and any correlation with clinical outcomes.

5.3.1.2 Inclusion and exclusion criteria *(modified from the protocol for brevity)*
__Inclusion criteria__*:*
- Patients with histologically or cytologically confirmed and measurable/evaluable metastatic adenocarcinoma of the pancreas.
- Initial diagnosis of metastatic disease must have occurred ≤ 6 weeks prior to randomization.
- Men and non-pregnant and non-lactating women ≥ 18 years of age who agreed to use adequate contraception.
- No previous radiotherapy, surgery, chemotherapy or investigational therapy for the treatment of metastatic disease.
- Prior treatment with 5-fluorouracil (FU) or gemcitabine administered as a radiation sensitizer in the adjuvant setting was allowed, provided at least 6 months elapsed since completion of the last dose and no lingering toxicities are present. Patients having received cytotoxic doses of gemcitabine or any other chemotherapy in the adjuvant setting were not eligible.

> ***Reviewers comment:*** *This study entry criterion was modified in both Amendment 1 and 2. The original version of the protocol allowed for patients who had received gemcitabine in the adjuvant setting (provided tumor recurrence occurred at least 6 months after completing the last dose of gemcitabine) or as a radiation sensitizer.*

- Karnofsky performance status (KPS) ≥ 70.
- One or more metastatic tumors measurable by CT or MRI.
- Asymptomatic for jaundice prior to Day 1. Significant or symptomatic amounts of ascites should have been drained prior to Day 1. Pain symptoms should have been stable and should not require modifications in analgesic management prior to Day 1.
- Adequate organ function as evidenced by:
    - AST (SGOT), ALT (SGPT) ≤ 2.5 × upper limit of normal range (ULN), unless liver metastases are clearly present, then ≤ 5 × ULN was allowed
    - Total bilirubin ≤ ULN
    - Serum creatinine within normal limits or calculated clearance ≥ 60 mL/min/1.73 m^2
    - Absolute neutrophil count (ANC) ≥ 1.5 × 10^9/L
    - Platelet count ≥ 100,000/mm3 (100 × 10^9/L)
    - Hemoglobin (Hgb) ≥ 9 g/dL
    - PT, PTT, UA within normal limits

Major exclusion criteria*:*
- Patients with known brain metastases, unless previously treated and well-controlled for at least 3 months.
- Patients with only locally advanced disease.
  Reviewers Comment: *This criterion was added as part of Amendment 1. Since the trial excluded patients with locally advanced disease, any conclusions regarding Abraxane's efficacy in the locally advanced setting cannot be assessed accurately.*
- Patients using Coumadin.
- Patients with a history of allergy or hypersensitivity to any of the study drugs or any of their excipients.
- Patients with active, uncontrolled bacterial, viral, or fungal infection(s) requiring systemic therapy.
- Patients with known infection with HIV, hepatitis B, or hepatitis C.
- Patient with a ≥10% decrease in KPS or ≥ 20% decrease in serum albumin level between baseline visit and within 72 hours prior to randomization.
  Reviewers Comment*: This exclusion criterion was added as part of Amendment 3. This decreased the risk that patients would be enrolled that had a rapid pace of disease progression.*
- Patients with a history of connective tissue disorders (e.g., lupus, scleroderma, arteritis nodosa).

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- Patients with a history of interstitial lung disease, history of slowly progressive dyspnea and unproductive cough, sarcoidosis, silicosis, idiopathic pulmonary fibrosis, pulmonary hypersensitivity pneumonitis or multiple allergies.
- Patients with a history of chronic leukemia (e.g., chronic lymphocytic leukemia), peripheral arterial disease.
- Patient with high cardiovascular risk, including, but not limited to, recent coronary stenting or myocardial infarction in the past year.
  Reviewers Comment: *This reviewer acknowledges that there were a significant number of exclusion criteria for comorbid conditions that may reduce the generalizability of this study to patients with such conditions (e.g., the safety and efficacy of this combination was only investigated in patients with good performance status and without significant co-morbid medical conditions).*
- History of malignancy in the last 5 years.
- Patients unwilling or unable to comply with study procedures, or planning to take vacation for 7 or more consecutive days during the course of the study.

5.3.1.3 Study Design and Plan

Study design

- Study CA046 was an open-label, randomized, multi-center trial that compared ABI-007 in combination with gemcitabine administered weekly to standard treatment gemcitabine monotherapy. Overall, following Amendment 4 (see below) 842 patients were planned to be randomized in a 1:1 ratio, with 421 patients in the ABI-007/gemcitabine arm and 421 patients in the gemcitabine arm.
- Baseline assessments would be performed ≤14 days prior to randomization. All patients must have begun their treatment within 3 days after randomization.
- Patients were evaluated for complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD) based on blinded, central review of CT scans performed every 8 weeks using RECIST guidelines.
- PET scans were performed every 8 weeks up to week16.
  Reviewers Comment: *The number of patients that would need PET scans performed was changed by the sponsor in numerous amendments. Also, the frequency of follow up PET scans to be performed was also changed. These changes may affect the interpretability of the data regarding PET scan responses. Since the primary endpoint of the study was overall survival this did not significantly affect the study results.*
- Responders and patients with stable disease were allowed to continue on study unless they developed an unacceptable toxicity.
- Progressive disease or unacceptable toxicity were criteria for treatment failure and discontinuation from study treatment.
- Laboratory and clinical evaluations to assess AEs and other study measures were performed when patients were removed from study treatment.

- Any AE that started after initial study drug administration and up to 30 days after the last dose of study drug or end of study whichever was later were collected. ***Reviewers Comment***: *This design for the collection of adverse events may have resulted in an underestimation of the incidence of certain adverse events. For example, if a patient developed late onset neuropathy that occurred more than 30 days after the final dose of ABI-007, the adverse event might not be reported.*
- For patients randomized to ABI-007+gemcitabine, if ABI-007 was discontinued but gemcitabine continued, this would be considered as continuation of the study regimen and imaging would continue.
- Following the discontinuation of study treatment, overall survival status would be monitored on a monthly basis for 6 months and then every 3 months thereafter until death, the study closed or 3 years elapsed since subject discontinuation from treatment. This evaluation may have been conducted by record review and/or telephone contact with the patient's treating physician

Study chemotherapy administration

Figure 1: Drug Dosing Schedule

Treatment Arm	Cycle 1(Day)								Cycle 2 Onward(Day)			
	1	8	15	22	29	36	43	50	1	8	15	22
Abraxane /Gemcitabine	X	X	X	--	X	X	X	--	X	X	X	--
Gemcitabine	X	X	X	X	X	X	X	--	X	X	X	--

- Patients received ABI-007 plus gemcitabine or gemcitabine alone on an outpatient basis.
- The protocol recommended initial antiemetic prophylaxis prior to chemotherapy.
- Patients receiving ABI-007 plus gemcitabine received 125 mg/m^2 ABI-007 as a 30- to 40-minute infusion (maximum infusion time not to exceed 40 minutes) followed by gemcitabine 1000 mg/m^2 as a 30- to 40-minute infusion (maximum 40 minutes) for 3 weeks followed by a week of rest.
- Patients receiving gemcitabine alone received 1000 mg/m^2 gemcitabine as a 30- to 40-minute infusion (maximum 40 minutes) administered weekly for 7 weeks followed by a week of rest (8-week cycle; Cycle 1 only), followed by cycles of weekly administration for 3 weeks (on Days1, 8, and 15) followed by one week of rest (4-week cycle).
- Crossover of patients from the gemcitabine-only treatment arm into the ABI-007/gemcitabine treatment arm after disease progression on, or treatment discontinuation from the gemcitabine-only treatment arm was not permitted.
- Supportive care per the institution's normal standard of care including concomitant medications was allowed at the Investigator's discretion.

- If a dose could not be administered on Day 1 of a cycle, that cycle was not considered to have begun until the day that the dose was actually administered.
- If a Day 8 dose was missed, the cycle would continue per protocol, with one dose not given. The same would apply to any intra-cycle dose of single-agent gemcitabine.
- If a Day 15 dose was missed, that week would become the week of rest.
- The maximum delay between a missed scheduled dose and the next one (whichever dose was missed) would not be longer than 21 days (except for peripheral neuropathy).

  Reviewers comment: *This particular interval was modified several times by the sponsor in protocol amendments. This may have affected drug exposure and influenced the incidence of adverse events in different protocol versions making the overall interpretation of the safety data difficult and affecting the exposure to both the drugs. Hence at the request of FDA Abraxis performed an analysis of exposure to the drug per amendment the results if which are described in the analysis of safety (section 7.2.2) below.*

5.3.1.4 Dose Modification guidelines

Table 4: Dose modifications

Dose Level	Abraxane Dose(mg/m2)	Gemcitabine(mg/m2)
Study dose	125	1000
-1	100	800
-2	75	600

- A maximum of 2 dose level reductions was allowed.
- Dose reductions may or may not have been concomitant.
- If a toxicity requiring dose modification occurred following the second dose reduction of either study drug, further treatment was discontinued.
- When a dose reduction was required, no dose re-escalation was permitted for the duration of study treatment [with one exception on Day 15: re-escalation with granulocyte-colony stimulating factor (G-CSF) support was permitted, after a previous dose reduction on Day 8 of the same cycle].

  Reviewers Comment: *This change was made in the protocol after the review of sepsis events by the Data Monitoring Committee analysis (Amendment 6). This reviewer notes that this change was following the enrollment of the majority of patients in the clinical trial.*

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Abhilasha Nair,MD
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Dose Modifications for Day 1 of each cycle

Dose modifications for both Abraxane and gemcitabine due to hematologic or non-hematologic adverse events on day 1 of each cycle were made according to Table 5 and Table 6 below.

Table 5: Dose modifications for Day 1 of each cycle (Hematologic Toxicity)

Treatment Day Counts and Toxicity			
ANC		**Platelets**	**Timing**
$\geq 1.5 \times 10^9$	And	$\geq 100 \times 10^9$	Treat on Time
$<1.5 \times 10^9$	Or	$<100 \times 10^9$	Delay by one week until recovery

Table 6: Dose Modifications for Day 1 of Each Cycle (Non-Hematologic Toxicity)

Non Hematologic Toxicity and/or Dose Hold with Previous Cycle	
Toxicity/dose held	**Gemcitabine/Gemcitabine+ABI-007 dose this cycle**
Grade 0, 1 or 2 toxicity	Same as Day 1 of previous cycle (except for Grade 2 cutaneous toxicity where doses of gemcitabine and ABI-007 should both be reduced to next lower dose level)
Grade 3 toxicity[a]	Decrease gemcitabine and ABI-007 to next lower dose level[a]
Grade 4 toxicity[a,b]	Off protocol treatment[b]
Dose held in 2 previous consecutive cycles	Decrease gemcitabine to next lower dose level and continue throughout the rest of treatment

[a]If the toxicity was limited to neuropathy, then only ABI-007 was reduced.
[b]Pulmonary embolism (a Grade 4 toxicity in the CTCAE version) if mild or a symptomatic, would be exempt from this requirement

Reviewers Comment: *The above tables were modified by the sponsor numerous times in protocol amendments making it challenging to interpret patient exposures as the criteria for dose reductions varied at different points in the study.*

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Dose adjustments within each treatment cycle
Dose modifications due to hematologic within a treatment cycle would be adjusted as outlined in Table 7 below.

Table 7: Dose Modifications for Hematologic Toxicity within a Cycle *(copied from protocol)*

Day 8 Blood Counts	Day 8 ABI-007	Day 8[a] Gemcitabine	Day 15 Blood Counts	Day 15 ABI-007	Day 15[a] Gemcitabine	Any Day ABI-007	Any Day Gemcitabine
ANC >1000 and Platelets ≥75,000	100%	100%	ANC >1000 and Platelets ≥75,000	100%	100%		
			ANC 500-1000 or Platelets 50,000-74,999	Full Dose (treat on time) + G-CSF[b]	Full Dose (treat on time) + G-CSF[b]		
			ANC <500 or Platelets <50,000	Hold + G-CSF[b]	Hold + G-CSF[b]		
ANC 500-1000[a, c] or Platelets 50,000-74,999	Decrease dose by 1 level (treat on time)	Decrease dose by 1 level (treat on time)	ANC >1000 and Platelets ≥75,000	Return to Previous Dose level (treat on time) + G-CSF[b]	Return to Previous Dose Level (treat on time) + G-CSF[b]		
			ANC 500-1000 or Platelets 50,000-74,999	Same Dose (as Day 8, treat on time) + G-CSF[b]	Same Dose (as Day 8, treat on time) + G-CSF[b]		
			ANC <500 or Platelets <50,000	Hold + G-CSF[b]	Hold + G-CSF[b]		
ANC <500[b] or Platelets <50,000	Hold	Hold	ANC >1000 and Platelets ≥75,000	Decrease Day 8 dose by 1 level (treat on time) + G-CSF[b]	Decrease Day 8 dose by 1 level (treat on time) + G-CSF[b]		
			ANC 500-1000 or Platelets 50,000-74,999	Decrease Day 8 dose by 1 level (treat on time) + G-CSF[b]	Decrease Day 8 dose by 1 level (treat on time) + G-CSF[b]		

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Day 8 Blood Counts	Day 8 ABI-007	Day 8 Gemcitabine	Day 15 Blood Counts	Day 15 ABI-007	Day 15[a] Gemcitabine	Any Day ABI-007	Any Day Gemcitabine
			ANC <500 or Platelets <50,000	Hold + G-CSF[b]	Hold + G-CSF[b]		
Febrile Neutropenia (Grade 3 or 4)[d]						Hold. Upon resuming dosing, decrease to next lower level and do not re-escalate throughout the rest of treatment.	Hold. Upon resuming dosing, decrease to next lower dose level and do not re-escalate throughout the rest of treatment.
Recurrent Febrile Neutropenia (Grade 3 or 4)[c]						Decrease to next lower dose level and do not re-escalate throughout the rest of treatment.	Decrease 2 dose levels (to 600 mg/m^2) and do not re-escalate throughout the rest of treatment.

Abbreviations: ANC = Absolute neutrophil count; G-CSF = Granulocyte colony stimulating factor.
a The dose-modification rules indicated for Day 8 and Day 15 of a doublet cycle also apply to the gemcitabine monotherapy arm, post Cycle 1.
b G-CSF is optional if descent only affects platelets.
c If patients do not experience resolution of neutropenia within 21 days, despite uninterrupted G-CSF treatment, study treatment will be discontinued.
d Febrile patients (regardless of neutrophil count) should have their chemotherapy treatment interrupted. A full sepsis diagnostic work-up should be performed while continuing broad spectrum antibiotics. If cultures are positive, the antibiotic may or may not be changed, depending on the sensitivity profile of the isolated organism. Patients with persisting fever after 3 weeks, despite uninterrupted antibiotic treatment, will discontinue study treatment. Febrile neutropenic patients can also receive G-CSF, in addition to antibiotic treatment, to hasten the resolution of their febrile neutropenia (following current institutional guidelines). In all cases, blood counts must have returned to baseline levels before resuming chemotherapy treatment.

For Gemcitabine Cycle 1 (of 8 weeks duration), intra-cycle dose modifications were managed by either holding the dose, or reducing the dose, at the physician's discretion and based on the nature and severity of the hematologic toxicity.
If patients required a treatment delay within a treatment cycle due to toxicities, those doses held during the cycle would not be made up.

Reviewers Comment: *The sponsor made several changes to the dose modification criteria for hematologic toxicity. Specifically changes were made to the dose reductions and doses in subsequent cycles for both drugs. This affected the review and interpretation of exposure data and safety/adverse event interpretation. Based on this an information request was sent to the sponsor on 5/20/13 asking for submission of exposure analyses, including raw data, specifying when patients were enrolled (noting each protocol amendment they were enrolled under) to determine whether the multiple revisions to the dose modification criteria in protocol amendments had any effects on exposure of Abraxane or gemcitabine. Please refer to the discussion of these analyses in the safety section of this review.*

Dose modifications within a cycle for non-hematologic toxicity
For Grade 1-2 (and grade 3 nausea/vomiting and alopecia) adverse events, the dose would remain the same as that administered on Day1. For Grade 3 non-hematologic toxicities (except nausea/vomiting and alopecia) the dose of either one or both drugs (except cutaneous toxicity) would be held until resolution to ≤ Grade1. The protocol

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instructed investigators to interrupt treatment for Grade 4 non-hematologic adverse events. The decision as to which drug should be modified would depend upon the type of non-hematologic toxicity seen and which course is medically most sound in the judgment of the physician/investigator.

ABI-007 treatment was to be withheld in patients who experienced ≥Grade 3 peripheral neuropathy. Gemcitabine administration could continue during this period. The protocol allowed resumption of ABI-007 treatment at the next lower dose level in subsequent cycles after the peripheral neuropathy improved to ≤ Grade 1. Peripheral neuropathy that required a delay in scheduled ABI-007 dosing for ≥ 21 days would require discontinuation of study treatment.

Development of Grade 2 or 3 cutaneous toxicity would require dose reduction to the next lower dose level for both drugs. If the patient continued to experience these reactions, despite dose reduction, treatment would be discontinued. Patients who developed Grade 4 cutaneous toxicity discontinued treatment. If Grade 3 mucositis or diarrhea occurred, the study drug was withheld until resolution to ≤ Grade 1, then reinstituted at the next lower dose level (both drugs). Patients who developed Grade 4 mucositis or diarrhea would discontinue treatment.
The protocol permitted treatment for asymptomatic or clinically mild pulmonary embolism with low-molecular-weight heparin without interruption of therapy. Moderate to severe pulmonary embolism required permanent discontinuation of treatment.
Study drugs were permanently discontinued for interstitial pneumonitis.

5.3.1.5 Concomitant medication use
- Colony stimulating factors were allowed to be administered according to institutional guidelines for the treatment of neutropenic fever or infections associated with neutropenia and for the prevention of febrile neutropenia in patients with an ANC < 500 cells/µL.
- Patients not experiencing resolution of neutropenia within 21 days, despite uninterrupted G-CSF treatment, would discontinue study treatment.
- Due to the incidence of non-neutropenic sepsis during the trial, antibiotics (ciprofloxacin or amoxicillin/clavulanate) were provided to patients for self-administration at the first occurrence of fever ≥ 38.5 °C (regardless of neutrophil count). The protocol also instructed patients to immediately seek medical attention for such fevers.
  **Reviewers comment**: This change was made in Amendment 4 subsequent to reported deaths and cases of non-neutropenic sepsis per the advice of the Data Monitoring Committee.
- Radiation was not allowed during the study.
- Erythropoietin was administered at the discretion of the Investigator, consistent with institutional guidelines.
- Administration of prophylactic antibiotics to otherwise uncomplicated patients with biliary stents was permitted and administered at the discretion of the treating

physicians. Biliary stents were to be monitored closely to determine the need for replacement.

5.3.1.6 Discontinuation from the Study

Patients were to discontinue study treatment if any of the following occurred:
- Progressive disease per CT or MRI (not PET or CA19-9).
- Development of toxicity that was unacceptable in the opinion of the Investigator.
- Moderate to severe pulmonary embolism.
- Patient declined to continue therapy (i.e., withdrew consent).
- Recurrence of the following after a second dose reduction: Grade 4 neutropenia, or any other Grade 3 or 4 hematologic toxicity or non-myelosuppressive AE, unless per the Investigator there was evidence of continuing benefit to the patient that outweighed the risk of recurrent toxicity, and after consultation with the Sponsor.
- Patient did not experience resolution of Grade 4 neutropenia within 21 days, despite uninterrupted G-CSF treatment.
- Initiation of other anticancer therapy.
- In the investigator's judgment, it was in the patient's best interest to discontinue the study treatment.

5.3.1.7 Schedule of Assessments for Study CA046 *(adapted from the protocol)*

Figure 2:-Schedule of assessments for Study CA046

Assessment[a]	Baseline[b]	72 hrs prior to randomi-zation	Cycle 1(Day)								Every 8 Weeks (Starting from Cycle 1 Day 1)
			1[c]	8	15	22	29	36	43	50	
Informed Consent	X	-	-	-	-	-	-	-	-	-	-
Medical History	X	-	-	-	-	-	-	-	-	-	-
Physical Examination	X	-	X	-	-	-	-	-	-	-	-
Height and Weight	X	-	X[d]	-	-	-	-	-	-	-	-
BSA Calculations[e]	-	-	X	-	-	-	-	-	-	-	-
Urinalysis (a urine dipstick may be used)	X	-	X	-	-	-	-	-	-	-	-

Assessment[a]	Baseline[b]	72 hrs prior to randomi-zation	Cycle 1(Day)								Every 8 Weeks (Starting from Cycle 1 Day 1)
			1[c]	8	15	22	29	36	43	50	
Prior/Concomitant Medication Evaluation	X	-	X	X	X	X	X	X	X	X	-
Concurrent Procedures	-	-	X	-	-	-	-	-	-	-	-
Peripheral Neuropathy Evaluation	X	-	X	-	-	-	-	-	-	-	-
Vital Signs	X	-	X	X	X	X	X	X	X	X	-
KPS	X[f]	X[f]	X	X	X	X	X	X	X	X	-
Serum β-HCG[g]	X	-	-	-	-	-	-	-	-	-	-
ECG (12 lead)	X	-	-	-	-	-	-	-	-	-	-
Clinical Chemistry Panel	XF	X[f, h]	X	-	-	-	X	-	-	-	-
CBC, Differential, Platelet Count	X	-	X	X	X	X	X	X	X	X	-
PT, PTT[i]	X	-	-	-	-	-	-	-	-	-	-
Consent to use diagnostic tumor biopsy for molecular marker analysis (optional)	X	-	-	-	-	-	-	-	-	-	-
CT scan[j]	X	-	-	-	-	-	-	-	-	-	X
PET scan for SUV[k]	X	-	-	-	-	-	-	-	-	-	X
Serum CA19-9[l]	-	-	X	-	-	-	-	-	-	-	-
Plasma SPARC[k]	-	-	X	-	-	-	-	-	-	-	-
Treatment: Gemcitabine-only arm[m]	-	-	X	X	X	X	X	X	X	-	-

Assessment[a]	Baseline[b]	72 hrs prior to randomi- zation	Cycle 1(Day)								Every 8 Weeks (Starting from Cycle 1 Day 1)
			1[c]	8	15	22	29	36	43	50	
Treatment: ABI 007/Gemcitabine arm[l]	-	-	X	X	X	-	X	X	X	-	-
Adverse Events	-	-	X	X	X	X	X	X	X	X	-
Phone Follow-up[n]	-	-	-	-	-	-	-	-	-	-	-

Assessment[a]	Cycle 2 onward				Every 8 Weeks (Starting from Cycle 1 Day 1)	EOS	AE Resolution	Post- study Follow- up
	1[c]	8	15	22				
Informed Consent	-	-	-	-	-	-	-	-
Medical History	-	-	-	-	-	-	-	-
Physical Examination	X	-	-	-	-	X	X	-
Height and Weight	X[d]	-	-	-	-	X[d]	X[d]	-
BSA Calculations[e]	-	-	-	-	-	-	-	-
Urinalysis (a urine dipstick may be used)	X	-	-	-	-	-	-	-
Prior/Concomitant Medication Evaluation	X	X	X	X	-	X	X	-
Concurrent Procedures	X	-	-	-	-	X	X	-
Peripheral Neuropathy Evaluation	X	-	-	-	-	X	X	-
Vital Signs	X	X	X	X	-	X	X	-
KPS	X	X	X	X	-	X	X	-
Serum β-HCG[g]	-	-	-	-	-	-	-	-

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Assessment[a]	Cycle 2 onward				Every 8 Weeks (Starting from Cycle 1 Day 1)	EOS	AE Resolution	Post-study Follow-up
	1[c]	8	15	22				
ECG (12 lead)	-	-	-	-	-	-	-	-
Clinical Chemistry Panel[h]	X	-	-	-	-	X	X	-
CBC, Differential, Platelet Count	X	X	X	X	-	X	X	-
PT, PTT[i]	-	-	-	-	-	-	-	-
CT scan[j]	-	-	-	-	X	X	-	X
PET scan for SUV[k]	-	-	-	-	X	X	-	X
Serum CA19-9[l]	X	-	-	-	-	-	-	-
Plasma SPARC[l]	X	-	-	-	-	-	-	-
Treatment: Gemcitabine-only arm[l]	X	X	X	-	-	-	-	-
Treatment: ABI-007/Gemcitabine arm[l]	X	X	X	-	-	-	-	-
Adverse Events	X	X	X	X	-	X	X	-
Phone Follow-up[m]	-	-	-	-	-	-	-	X

Foot notes

[a] Unless otherwise specified, visits where response assessments are not performed must occur within ± 2 days of the planned visit date.

[b] Baseline evaluations to be obtained ≤14 days prior to randomization.

[c] Day 1 evaluations can be omitted if Baseline evaluations are performed within 72 hours of Day 1 of Cycle 1.

[d] Weight only.

[e] Body Surface Area (BSA) calculations to be performed Day 1 of Cycle 1, and recalculated per the site's standard of care, or if body weight changes by more than 10%.

[f] The patient will be excluded from participation if a 10% or greater decrease in Karnofsky Performance Status (KPS) occurs between Baseline and within 72 hours prior to randomization, or if a ≥20% decrease in serum albumin level occurs between Baseline visit and within 72 hours prior to randomization.

[g] For women of childbearing-potential only. This will be conducted 72-hours (or fewer) prior to first study drug administration (negative results required for study drug administration).

[h] Only serum albumin measurement at this time point.

[i] Local laboratory results for Prothrombin (PT)/Partial Thromboplastin Time (PTT) analysis are allowed to confirm patient eligibility.

[j] Magnetic Resonance Imaging (MRI) is acceptable if patient is allergic to contrast agent. Computed Tomography (CT) scan of the thorax/liver/abdomen/pelvis and any other
studies required for tumor imaging will be performed at Baseline (within 14 days prior to Cycle 1 Day 1), every 8 weeks (at any time during that week) regardless of regimen,
and EOS (only if required per the defined study imaging schedule). In order to confirm objective response, an unscheduled CT scan will be allowed 4 weeks (a minimum of 28
days) from the initial documented complete or partial response. For such patients, all subsequent CT scans should return to the original schedule performed every 8 weeks
starting from the date of first dose of study therapy. An unscheduled CT scan for suspected progression may be performed at any time. Whichever method of assessment is chosen at Baseline to follow tumors should remain consistent throughout study duration.

[k] Positron-Emission Tomography (PET) scans will be performed every 8 weeks up to Week 16. These scans will also be reviewed by a blinded central imaging reviewer using the European Organization for Research and Treatment of Cancer (EORTC) criteria. The original target total (200 patients with 2 PET evaluations who have completed a minimum of 16 weeks of treatment) has been modified as follows: PET scans will be obtained at baseline for patients enrolled up until the initiation of Protocol Amendment 5 only. Follow-up PET scans will be obtained for patients that have obtained a baseline PET scan and are still actively receiving treatment.
Follow-up PET scans for active patients will be obtained in Week 16, but no further PET scans will be obtained after Week 16.

[l] Blood samples for the evaluation of the Carbohydrate Antigen (CA)19-9 and Secreted Protein Acidic and Rich in Cysteine (SPARC/osteonectin) molecular biomarkers will be
collected on Cycle 1 Day 1 for both treatment arms. Then, blood will be drawn every 8 weeks (on Day 1 of Cycle 2, Cycle 4, Cycle 6, etc.) for CA19-9 and SPARC assessment.
Plasma SPARC samples only required for those sites with adequate freezer facilities.

[m] In order to keep cycle numbers similar between the 2 arms, Cycle 1 in the gemcitabine-only arm will include weekly dosing for 7 weeks followed by a rest week, and Cycle 1 in the ABI-007/gemcitabine arm will be comprised of two 4-week cycles (total of 8 weeks). After Cycle 1, both arms receive 3 weeks of weekly drug administration followed by 1 week of rest.

[n] Patients will be followed by monthly telephone calls or review of records for 6 months and then every 3 months thereafter until death, the study closes or 3 years have elapsed since subject discontinuation for treatment, which ever happens first.

5.3.1.8 Adverse Event Reporting

The severity of adverse events occurring during the study were assessed according to the NCI CTCAE. Adverse events were coded to a MedDRA term by the applicant. The protocol required collection of any AE or SAE that occurred between the first administration of study drug to 30 days after the last dose of study drug or EOS (whichever is later). The protocol required that non-serious adverse events, other than neuropathy, be followed for 30 days after the patient's last dose of study drug. The protocol required that investigators follow patients with neuropathy until improvement to Grade 1, or at least 3 months elapsed without improvement or worsening, or the patient initiated any other anticancer therapy. AE follow-up continued in patients who discontinue ABI-007 but continue gemcitabine. All serious adverse events (regardless of relationship to study drug) were to be followed until resolution. All SAEs required completion of an SAE Report Form in addition to being recorded on the AE page/screen of the CRF.

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5.3.1.9 Statistical Design/Sample Size

- Study CA046 was an open-label, multi-center, randomized (1:1) trial designed to evaluate the efficacy of the combination of ABI-007 and gemcitabine vs. gemcitabine alone in improving overall survival in patients with metastatic adenocarcinoma of the pancreas.
- Following amendment four, four hundred twenty-one patients were planned to be randomized into to each treatment arm (842 patients in total).
- This sample size provided 90% power with two-sided Type I error of 0.049 to reject the primary efficacy null hypothesis that the ABI-007 plus gemcitabine/gemcitabine hazard ratio for overall survival was equal to 1.0.
  This sample size calculation assumed an alternative hypothesis of a 30% improvement in overall survival for patients randomized to the ABI-007 plus gemcitabine compared to gemcitabine alone (HR=0.769) and patient follow up would continue until at least 608 deaths occurred.
- The randomization would be stratified by the following strata: Geographic Region (Australia, Eastern Europe, North American, or Western Europe); Karnofsky performance score (70 -80 vs. 90-100); and presence of liver metastasis (yes or no).
- A planned interim efficacy analysis would be performed once at least 200 randomized patients were followed for at least 6 months from the date of randomization. The purpose of this interim analysis was to evaluate futility.
- The interim analysis would be performed on the observed death rate at 6 months follow-up from the date of randomization.
- The criterion for stopping the study for futility was a conditional power of less than 10%.
- The alpha spending function would allocate alpha of 0.001 and 0.049 at the interim and final analyses, respectively to preserve the overall study-wise Type 1 error at 0.050.
- All efficacy analyses would be based on the ITT population, which included all randomized patients regardless of whether the patient received any study drug or had any efficacy assessments collected. The Treated population included all randomized patients who received at least 1 dose of study drug, and would be the analysis population for all safety analyses.
- The primary efficacy endpoint was overall survival which would be analyzed using Kaplan-Meier methods. Survival was defined as the time from the date of randomization to the date of death (any cause). Patients who are alive were censored at the last known time that the patient was alive.
- Patient survival would be summarized by median survival time (including 95% CI) for each treatment arm along with the hazard ratio (including 95.1% CI). The Kaplan-Meier curve for survival would be presented for each treatment arm and differences in the curves would be tested using the stratified log-rank test.
- Tumor response and PFS would be assessed by RECIST guidelines on images obtained with CT scans. The secondary endpoint of PFS based on a blinded

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radiology assessment of response using RECIST response guidelines was to be analyzed using Kaplan-Meier methods. PFS was defined as the time from the day of randomization to the start of disease progression or death (any cause), whichever occurred first.

- The secondary efficacy endpoints (PFS and objective tumor response) would be evaluated only if the primary efficacy endpoint demonstrates superiority for ABI-007+gemcitabine over gemcitabine alone.
- To control the overall family-wise Type I error rate at two-sided α = 0.050 for the 2 secondary efficacy endpoints, PFS would be tested first at α = 0.050; objective tumor response would be tested at α = 0.050 only if PFS shows significant improvement.

5.3.1.10 Amendments of the protocol

The original protocol was submitted on Nov 12th, 2008. Six amendments to this protocol were submitted between Mar 20th, 2009 and Dec 12th, 2011. The following paragraphs summarize the important aspects of each of the six amendments.

Table 8: Dates of the original Protocol and Protocol Amendments for Study CA046

Protocol or Amendment	Submission Date
Original Protocol	Nov 12th,2008
Amendment 1	Mar 20th,2009
Amendment 2	Nov 17th,2009
Amendment 3	April 19th,2010
Amendment 4	Sep 30th,2010
Amendment 5	Jan 12th,2011
Amendment 6	Dec 12th,2011

Amendment 1 (20th Mar 2009)

- The **secondary objectives** were updated to reflect that changes in both serum CA-19-9 and plasma SPARC levels were part of the study.

- The **inclusion criteria** were modified to state that "Prior treatment with 5-FU or gemcitabine administered as a radiation sensitizer was allowed (if there is lingering

toxicity then the sponsor should be consulted). If a patient received gemcitabine in the adjuvant setting, tumor recurrence must have occurred at least 6 months after completing the last dose of gemcitabine."

- The inclusion criterion for pain symptoms was modified as follows: "Pain symptoms should be stable and should not require modifications in analgesic management prior to Day 1.*"*

- Addition of an **exclusion criterion** for patients with locally advanced disease.

- Clarification that **patients with malignancies** that were cured with surgery alone and patients who had been continuously disease free for at least 5 years were eligible.

- Modified **follow up for overall survival** as "post-study, overall survival status will be monitored on a monthly basis for 6 months and then every 3 months thereafter for 12 months. Patients will be followed for a total of 18 months."

- Language added for **dose modification:** *"Two dose modifications are permitted according to the criteria below. If a toxicity requiring dose modification occurs following the second dose reduction, further treatment should be discontinued "* Addition of a table outlining dose levels -1 and -2.

- The **tables for dose modifications** on Day 1 of each cycle for hematologic and non-hematologic toxicities were updated. If a patient had an ANC of 500-999/mcL and platelet count between 50,000 and 74,000/mcL, the dose of gemcitabine was to be decreased to 800 mg and continued throughout the rest of the treatment.

- Clarification that following a second dose reduction if there is a recurrence of any Grade 3 or 4 hematologic or non-hematologic toxicity, patients would be discontinued from the study unless per the investigator there is evidence of continuing benefit that outweighs the risk of recurrent toxicity.

- The statistical plan was modified and updated to add **a planned interim analysis** by a Data Monitoring Committee(DMC) once 200 patients were randomized and followed for at least 6 months for the date of randomization to evaluate for futility(without stopping for outstanding early efficacy). An alpha spending function was utilized to preserve the overall study-wise Type 1 error at 0.050.

- Language was added to outline the **procedures of the DMC**. Clarification that the DMC was separate from the Steering Committee.

Amendment 2 (17 Nov 2009)

- The **secondary objectives** were modified to add that the RECIST criteria would be used for PFS and response rate assessments: PFS was moved up as the primary secondary endpoint and would be tested first (a hierarchical approach rather than the Hochberg procedure specified in the original version of the protocol). Objective response rate would be tested only if the PFS analysis is statistically significant.
- **Study entry criteria** were modified with the exclusion of patients who received any cytotoxic dose of gemcitabine or any other chemotherapy in the adjuvant setting." Prior treatment with 5-FU or gemcitabine administered as a radiation sensitizer in the adjuvant setting is allowed provided at least 6 months after completing have elapsed since completion of the last dose and no lingering toxicities are present. Patients having received cytotoxic doses of gemcitabine or any other chemotherapy in the adjuvant setting are not eligible for this study."
- **Exclusion criteria** further modified to allow patients who were disease free for 5 or more continuous years after a combination of curative surgery and radiotherapy for other cancers to enter the study.
- **Exclusion criteria** were modified to exclude patients with history of connective tissue disorders, chronic leukemia, high cardiovascular risk, peripheral arterial disease. "Additional exclusion criteria added in order to avoid potential impact of certain medical conditions on patient safety and data integrity."
- Language added to clarify that "Patients experiencing study **drug-related toxicities that require a delay** in scheduled ABI-007 or and gemcitabine dosing for **≥ 14 days** will be discontinued from further participation in this study (except for Peripheral Neuropathy, see Section 4.2.3.4.1). When a dose reduction is required for Day 1 of any cycle, no dose re-escalation will be permitted for the duration of study treatment."
- **Dose modification criteria for Day 1** of each cycle was further clarified: A).Grade 2 skin toxicity on day 1 would require dose reduction to the next lower level for both drugs and B) for grade 3 non-hematologic toxicity and for doses held in 2 previous consecutive cycles due to non-hematologic toxicity, gemcitabine dose would be decreased to next lower dose level and continued through the rest of the treatment.

- **Dose modifications for hematologic toxicity within a cycle was updated** as: A) Any combination of Grade 3 ANC AND a Grade 2 thrombocytopenia, the dose of gemcitabine would be deceased to the next lower dose and continued throughout the rest of treatment, B) for Grades 3 and 4 febrile neutropenia, the dose of gemcitabine would be decreased to the next lower dose and continued throughout the rest of the treatment, and C) for recurrent Grades 3 and 4 febrile neutropenia, the dose of Abraxane would be decreased to the next lower level and continued through the rest of the treatment, and the dose of gemcitabine would be decreased 2 dose levels and continued through the rest of the treatment.

- **Dose modifications for non-hematologic toxicities were changed as follows**: For Grade 3 toxicity (except nausea/vomiting) the dose of either or both the drugs would be held until resolution to ≤ Grade1. The dose would then be resumed at the next lower dose level.

- **Dose modification for neuropathy was changed as follows:** Gemcitabine can continue during this period. Abraxane treatment may be resumed at the next lower dose level in subsequent cycles after the peripheral neuropathy improves to ≤ Grade 1. Patients experiencing peripheral neuropathy that required a delay in scheduled Abraxane dosing for ≥ 21 days will be discontinued from further participation in this study.

- **Addition of the stratification factors:** Geographic region, Karnofsky performance score (70-80 vs. 90-100), presence of liver metastasis yes or no.

- **Clarification regarding the use of Coumadin and G-CSF:"**GCSF may be given according to institutional guidelines for the treatment of neutropenic fever or infections associated with neutropenia."

- Addition of language to state that PET scans or CA-19-9 would not be used as a criterion for patient withdrawal from the study.

- Addition of peripheral neuropathy assessment as an End of Study Evaluation.

- PET scans will only be required for the first 200 patients enrolled on the study.

- Clarification that progressive disease should not be considered an AE or SAE.

- Language added that efficacy claims with respect to response rate and PFS will be based on the blinded radiology assessment of response.

Amendment 3 (19 April 2010)

- Inclusion criteria updated to include that: 1) An initial diagnosis of metastatic disease must have occurred ≤ 6 weeks prior to randomization in the study, and 2) criteria changed to state that patient should have definitive histologically or

cytologically confirmed metastatic disease which will be made by integrating the histopathological data within the context of the clinical and radiographic data.

- Clarification that baseline laboratory data may be obtained ≤ 14 days prior to randomization.

- Revised the exclusion criteria to exclude the following patients: patients who experience: ≥10% decrease in KPS between the baseline visit and within 72 hours prior to randomization, patients with a ≥ 20% decrease in serum albumin level between baseline visit and within 72 hours prior to randomization, patients with a history of interstitial lung disease, patients unwilling or unable to comply with study procedures, or planning to take vacation for 7 or more consecutive days during the course of the study.

- Following language added: "The maximum delay between a missed scheduled dose and the next one (whichever dose was missed) should not be longer than 14 days (except for peripheral neuropathy; see Section 4.2.3.4.1)."

- The statement "Pulmonary embolism (a Grade 4 toxicity in the CTCAE tables) if mild or asymptomatic, will be exempt from this requirement (please see Section 4.2.3.4.4)" was added as a foot note for the dose modification tables for non0-hmatologic toxicity for Day 1 of each cycle and within a cycle.

- Dose modification for hematologic toxicity within a cycle was modified so that an ANC between 500-1000/mcL OR a platelet count between 50 and 74,999/mcL can result in a decrease of gemcitabine dose to the next lower dose level and continue throughout the rest of treatment.

- Section on pulmonary embolism was updated to state: "Asymptomatic or clinically mild pulmonary embolism can be treated with low-molecular-weight heparin without interruption of therapy. Moderate to severe pulmonary embolism will require permanent discontinuation of treatment." Moderate to severe pulmonary embolism was added as study discontinuation criteria.

Amendment 4 (30 Sep 2010) Sepsis Update

- Patient **sample size** and related **statistical considerations modified** to allow for an increase in statistical power from 80% to 90%. According to Abraxis, the increase in power was instituted to decrease the risk that the study will not reach its primary objective to the level of risk that regulatory authorities place on concluding that an ineffective therapy is efficacious. This resulted in increasing the required number of deaths to from 455 to 608 and total enrollment to 842 patients (from 630 as planned previously). **Reviewers Comment**: *This unplanned increase in sample size (in relation to the original protocol) this late in the study raises concerns regarding the interpretability of the results.*

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- Text added to describe **the cases of sepsis and septic deaths** and the analysis of the sponsor's pharmacovigilance monitoring. A Directive Letter, dated 17 September 2010, was distributed to investigators. The Directive Letter details measures to be implemented to prevent or minimize the occurrence of septic events (See Appendix 4). These measures were incorporated into the current protocol amendment.

- Modification of the **acceptable window of infusion** time of both gemcitabine and ABI-007 to between 30-40min.

- The **definition of AE modified** to state that AE's would be defined as "any event that begins or worsens in grade after the start of study drug through 30 days after the last dose of study drug or EOS, whichever is later."

- The **frequency of the PET scans** modified to state that PET scans will be obtained at baseline for patients enrolled until the date of this amendment. Follow-up PET scans for active patients would be obtained to Week 16, but no further PET scans will be obtained after Week 16.

- Language added that for patients randomized to Abraxane plus gemcitabine, if Abraxane is discontinued but gemcitabine is continued, this should be considered as continuation of the study regimen and imaging should continue.

- **Dose modifications for hematologic toxicity within a cycle** changed as follows:

  - If a patient has an ANC < 500/mcL or platelet count < 50,000 mcL, the dose of gemcitabine would be decreased to the next lower dose level and continued through the rest of treatment.

  - If the ANC < 500/mcL recurrently then the dose of Abraxane and gemcitabine would be decreased to the next lower level and continued through the rest of the treatment.

  - For cases of febrile neutropenia, the dose of both drugs would be held and upon resuming dosing decrease to the next lower level and continue through the rest of the treatment.

  - **Additional footnotes a and b were added:** a) for Grade 4 neutropenia within a treatment cycle (ANC <500/mcL) in the absence of fever, Abraxane dosing is not to be interrupted and Granulocyte-colony stimulating factor (G-CSF) may be initiated as per institutional guidelines. Patient's not experiencing resolution of

neutropenia within 14 days, despite uninterrupted G-CSF, will be discontinued from the study; b) "Febrile patients (regardless of neutrophil count) should have their chemotherapy treatment interrupted. A full sepsis diagnostic work-up should be performed while continuing broad spectrum antibiotics. If cultures are positive, the antibiotic may or may not be changed, depending on the sensitivity profile of the isolated organism. Patients with persisting fever after 2 weeks, despite uninterrupted antibiotic treatment, will be discontinued from the study. Febrile neutropenic patients can also receive G-CSF, in addition to antibiotic treatment, to hasten the resolution of their febrile neutropenia (following current institutional guidelines). In all cases, blood counts must have returned to baseline levels before resuming chemotherapy treatment."

- Clarification regarding the **G-CSF administration**: "Colony stimulating factors may be given according to institutional guidelines for the treatment of neutropenic fever or infections associated with neutropenia and for the prevention of febrile neutropenia in patients with an ANC <500 cells/μL. Patients not experiencing resolution of neutropenia within 14 days, despite uninterrupted G-CSF treatment, will be discontinued from the study."

- Section and text added for **prophylaxis of sepsis**: "Due to the incidence of non-neutropenic sepsis, at the first occurrence of fever ≥38.5 °C (regardless of neutrophil count), institution of ciprofloxacin (500 mg orally, twice daily)—or amoxicillin/clavulanate (500 mg orally, 2-3 times daily) in patients with allergy to fluoroquinolones would be initiated." "They should also immediately contact their physician for guidance on where to go for blood counts to be evaluated for sepsis as soon as possible. Hospitalization or evaluation in the emergency room may be required depending on the clinical presentation. "

- The following text added regarding **antibiotic prophylaxis**. "Ciprofloxacin (or the alternative antibiotic) should be distributed to patients with instructions to begin treatment if they experience a febrile episode. Administration of long-term prophylactic ciprofloxacin (or the alternative antibiotic) to prevent recurrences in patients already having experienced a first febrile episode will be at the discretion of the treating physician. Administration of prophylactic antibiotics to otherwise uncomplicated patients with biliary stents will be at the discretion of the treating physicians. Biliary stents should be monitored closely to determine need for replacement.

- The following criterion was added as a **study discontinuation criterion:** "If a patient does not experience resolution of Grade 4 neutropenia by 14 days despite uninterrupted G-CSF treatment."

Amendment 5 (12 Jan 2011)

- Sponsor's **name changed** from "Abraxis Bioscience, LLC" to "Abraxis BioScience, LLC, a wholly owned subsidiary of Celgene Corporation "to reflect the acquisition of Abraxis BioScience by Celgene Corporation.

- Updated analysis of the cases of sepsis and addition of language that the presence of diabetes mellitus or ascites can increase the risk of infection.

- Text added to **clarify that cross-over** of patients from the gemcitabine arm to the combination arm is prohibited.

- The **maximum delay for a patient to be able to stay on study** between a missed scheduled dose and the next one **was changed from 14 days back to 21 days (except for peripheral neuropathy)**. According to the sponsor "Maximum allowed delay has been modified to accommodate the dose modification schedule recommended and approved by the Data Monitoring Committee."

- Clarification added to **dose modification table for non-hematologic toxicity for Day 1** of each cycle that if the Grade 3 toxicity affects only neuropathy then only ABI-007 dose should be reduced.

- Clarification added to **dose modification table for non-hematologic toxicity for Day 1** of each cycle that pulmonary embolism Grade 4 if mild or asymptomatic, will be exempt from this requirement.

- **Dose modification table for hematologic toxicity within a cycle was changed** to reflect guidelines for each day of each drug dosing within a cycle according to recommendations resulting from the Data Monitoring Committee meeting of 15 NOV 2010.

- **The duration for which a Grade 4 neutropenia event can last despite uninterrupted G-CSF administration was changed to 21 days** prior to requiring discontinuation from study treatment.

- Similarly **patients who continue to experience fever** after 3 weeks (previously 2 weeks) despite antibiotic treatment will discontinue study treatment.

Details added regarding the relevant geographic regions for stratification (Australia, Eastern Europe, North America, or Western Europe) were added to the protocol.

Amendment 6 (12 Dec 2011)

- Introduction of the **pneumonitis directive measures** were added to the protocol based on recommendations of the Independent Data Monitoring Committee. Instructions were added to the protocol and a diagnostic/ treatment algorithm was provided as an appendix to the body of the protocol. A pneumonitis directive letter dated 5 Oct 2011 was also provided in an appendix in this amendment.

- To expand on the previously existing criterion of interstitial lung disease; other conditions were added as part of the exclusion criterion.

- Clarified that more than one tumor marker may be evaluated (in exploratory analyses) and clarified that the correlation will be evaluated for clinical rather than efficacy outcomes.

- Specification of a blinded review for PET scans using EORTC criteria.

- **Duration of post-treatment follow (for overall survival) up changed** to "until death, the study closes or 3 years have elapsed since subject discontinuation from treatment".

- Clarification that two dose level modifications were permitted but that any further dose modification requires prior sponsor approval.

- An **exception was added to the dose re-escalation rule** that on Day 15, re-escalation with granulocyte-colony stimulating factor (G-CSF) support is permitted, after a previous dose reduction on Day 8 of the same cycle.

- Clarification that the dose-modification rules indicated for hematologic toxicities within a treatment cycle on Day 8 and Day 15 of a doublet cycle also apply to the gemcitabine monotherapy arm, post Cycle 1. Further language added to modify the intracycle dose modification guidelines for gemcitabine.

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5.3.2 Supportive study -Study CA040

Study CA-040 was entitled "A Phase 1 Trial of gemcitabine plus ABI-007 in patients with advanced metastatic pancreatic cancer." This was an industry sponsored study conducted at four U.S. centers under IND 55974. The original protocol was submitted on Mar 1 2006 and there were 3 amendments between the original submission and October of 2007. The primary objective of this Phase I study was to determine the MTD and DLT of ABI-007 in combination with gemcitabine on Days 1, 8, and 15 of an every 28-day cycle. The secondary objectives of this study were to obtain additional data on the tolerance and efficacy of ABI-007 and gemcitabine, evaluate the safety and tolerability of this combination in this patient population, report any objective antitumor responses and disease stabilizations lasting at least 4 cycles.

The primary safety endpoint was to determine the MTD and DLT of gemcitabine plus ABI-007 in patients with advanced metastatic pancreatic cancer. Other secondary safety/tolerability endpoints included the incidence of treatment-emergent adverse events (AEs) and serious adverse events (SAEs), laboratory abnormalities and nadir of myelosuppression during study drug dosing and percentage of patients experiencing dose modifications, dose interruptions, and/or premature discontinuation for each study drug. Efficacy endpoints included: 1) number (%) of patients who achieved a confirmed complete or partial response (i.e., objective response) based on RECIST response criteria; 2) number (%) of patients with stable disease for ≥ 16 weeks, or confirmed complete or partial overall response (i.e., total response) based on RECIST response criteria; 3) duration of response; 4) estimation of progression-free survival; and 5) estimation of overall survival.

The study was originally designed as a standard 3 plus 3 dose-escalations Phase I study. To establish the MTD, a maximum of 24 evaluable patients were to be treated. Patients were eligible if they were 18 years of age or older and had histologically or cytologically confirmed metastatic adenocarcinoma of the pancreas, adequate organ function and performance status. Prior treatment with 5-FU or gemcitabine administered as a radiation sensitizer during and up to 4 weeks after radiation therapy was allowed. If a patient received gemcitabine in the adjuvant setting, tumor recurrence must have occurred at least 6 months after completing the last dose of gemcitabine. Patients were excluded from the study if they had active brain metastases, were on therapeutic warfarin, had significant comorbid illnesses or had a history of allergy or hypersensitivity to the drug.

Dose limiting toxicities were assessed according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE), Version 3 and included Grade 4 neutropenia lasting >3 days in the absence of growth factor support, Grade 4 neutropenia associated with fever >38.5°C,any other Grade 4 hematological toxicity, Grade 3 thrombocytopenia with hemorrhage, Grade 3 or 4 nausea, vomiting or diarrhea despite prophylaxis or treatment with an optimal anti-emetic or anti-diarrhea regimen, or any other Grade 3 or

higher non-hematological toxicity attributable to the study drug, excluding alopecia and fatigue.

6 Review of Efficacy

Efficacy Summary

The primary assessment of Abraxane efficacy in metastatic pancreatic cancer is based on the endpoint of overall survival in Study CA046, the only randomized trial submitted with this application. FDA analysis of Study CA046 data confirmed that a statistically significant prolongation of overall survival (OS) was observed in patients randomized to receive the combination of Abraxane and gemcitabine: median overall survival was 8.5 months in the Abraxane arm (95% CI 7.89, 9.53) compared to 6.7 months in the gemcitabine control arm (95%CI 6.01, 7.23) with a hazard ratio of 0.72 (95% CI 0.617, 0.835) and p-value of <0.0001.

Study CA046's secondary efficacy parameters, progression-free survival and objective response rate, supported the use of Abraxane in combination with gemcitabine in the metastatic setting. The results showed a longer median PFS time observed in the Abraxane /gemcitabine arm as compared with that observed in the gemcitabine-alone arm (5.5 months vs. 3.7 months, respectively). The estimated hazard ratio for PFS was 0.69 (95% CI=0.58, 0.82) in favor of the combination arm. The objective response rate based on an independent assessment appeared to be higher in the Abraxane /gemcitabine arm as compared with the rate in the gemcitabine treated arm (23% vs. 7%, respectively, p-value < 0.0001 based on the Chi-square statistic). The median duration of response was 7.4 (95% CI=5.6, 8.5) and 7.1 (95% CI=3.8, NA) months for ABI-007/gemcitabine and gemcitabine alone arm, respectively.

Results of subset analyses conducted by FDA and the applicant were generally consistent and thus supportive of the primary analysis. FDA statistical reviewers did not cite major statistical concerns with this application, concluding that the data submitted for Study CA046 supported its achievement of the primary endpoint.

6.1   Indication

Celgene proposed the following indication for Abraxane in the original sNDA submission: - Abraxane is a microtubule inhibitor indicated for the treatment of ⁽ᵇ⁾ ⁽⁴⁾ ⁽ᵇ⁾ ⁽⁴⁾ metastatic adenocarcinoma of the pancreas as first-line treatment, in combination with gemcitabine.

Reviewers Comment: - *No patients enrolled in the pivotal study CA046 had locally advanced pancreatic cancer as these patients were excluded from the clinical trial. This reviewer recommends limiting the indication to patients with metastatic pancreatic cancer.*

6.1.1   Methods

This review focused primarily on the efficacy results of the single randomized controlled trial Study CA046. For details regarding the FDA statistical analysis of efficacy data submitted for this NDA, refer to the statistical review conducted by reviewer Dr.Shen.

Section 5.3.1 of this review describes the study design and statistical plan for study CA046. Briefly, Study CA046 was an open label, randomized multicenter international study conducted in 151 sites in 11 countries. The primary objective of the study was to evaluate the efficacy of the combination of ABI-007 and gemcitabine versus gemcitabine alone in improving overall survival in patients with metastatic adenocarcinoma of the pancreas. Overall, following Amendment 4 (see below) 842 patients were planned to be randomized in a 1:1 ratio, with 421 patients in the ABI-007/gemcitabine arm and 421 patients in the gemcitabine arm. This sample size calculation assumed an alternative hypothesis of a 30% improvement in overall survival for patients randomized to the ABI-007 plus gemcitabine compared to gemcitabine alone (HR=0.769) and patient follow up would continue until at least 608 deaths occurred. Patients were stratified by Geographic Region (Australia, Eastern Europe, North American, or Western Europe); Karnofsky performance score (70 -80 vs. 90-100); and presence of liver metastasis (yes or no).

6.1.2   Demographics

The following two tables show the baseline demographics and disease characteristics of subjects enrolled in Study CA046. 861 patients were randomized between 08 May 2009 and 17 Apr 2002 and constituted the Intent-to-Treat population. Eleven countries (151 centers) enrolled patients in the CA046 trial. As shown in Table 9, the majority of the patients were enrolled in the U.S. [476 patients (55% of the total)]. The enrollment was well balanced between the arms with respect to the countries that enrolled patients.

Table 9: Study CA046 Distribution by geographic area

COUNTRY	ABI-007 + Gemcitabine (%) N=431	Gemcitabine (%) N=430	All patients (%) N=831
USA	235 (55)	241 (56)	476 (55)
Australia	61 (14)	59 (14)	120 (14)
Russian Federation	50 (12)	50 (12)	100 (12)
Canada	33 (8)	30 (7)	63 (7)
Italy	21 (5)	16 (4)	37 (4)

COUNTRY	ABI-007 + Gemcitabine (%) N=431	Gemcitabine (%) N=430	All patients (%) N=831
Ukraine	14 (3)	12 (3)	26 (3)
Spain	6 (1)	10 (2)	16 (2)
France	4 (1)	2 (<1)	6 (1)
Germany	3 (1)	5 (1)	8 (1)
Austria	3 (1)	3 (1)	6 (1)
Belgium	1 (<1)	2 (<1)	3 (<1)

As shown in Table 10, patient demographics were balanced with respect to gender and age. The median age of patients was 63 years with a similar distribution in both arms (range 27-88 years). Forty two percent of patients randomized were 65 years of age or older and 10% were 75 years of age or older. The distribution of patients ≥65 years of age and ≥75 years was also balanced between the two treatment arms.

Table 10: Study CA046 Demographics (ITT population)

Variable	ABI 007+Gemcitabine (%) N= 431	Gemcitabine (%) N=430
Gender		
Male	245 (57%)	257 (60%)
Female	186 (43%)	173 (40%)
Age (years)		
Mean (SD)	61 (10.7)	63 (9.2)
Median	62	63
Range	27- 86	32- 88
65 years and older	177 (41%)	188 (44%)
75 years and older	41(10%)	49(11%)
Ethnicity		
White/White-Hispanic or Latino	403 (94%)	401 (93%)
African American	16(4%)	16(4%)
Asian	8(2%)	9(2%)
BSA (%)		
Mean(SD)	1.87 (0.24)	1.85 (0.23)
Median	1.88	1.85
Range	1.2-2.7	1.0-2.6

Variable	ABI 007+Gemcitabine (%) N= 431	Gemcitabine (%) N=430
Performance status (Karnofsky) (%)		
90-100	248 (58%)	268 (62%)
70-80	179 (42%)	161 (38%)
<60	2(<1%)	0
Baseline physician assessment of peripheral neuropathy (%)		
Grade 0	400 (95%)	400 (95%)
Grade 1	22 (5%)	18 (4%)
Grade 2	----	1 (<1%)

BSA=Body Surface Area

Table 10 also shows that 93% of the patients were White or White Hispanic or Latino, 4% were African American and 2% were Asian. The arms were balanced with respect to demographic variables height. weight, BMI and BSA. The median BSA was $1.87m^2$.

Most patients enrolled in the trial were above 70% Karnofsky performance status (KPS) (99%) with the majority of patients being above the KPS of ≥90% (60%). The distribution of patients was balanced with respect to baseline KPS. Two patients on the combination of Abraxane and gemcitabine had a baseline KPS of 60% however the sponsor stated that the patients' KPS was 70% on the screening visit, thus making them eligible for the trial.

Most patients enrolled in the trial had no baseline neuropathy (95% as assessed by the physicians). There was 1 patient on the gemcitabine arm that had baseline neuropathy of Grade 2 and this patient was excluded from the applicant's supportive per protocol population.

Baseline laboratory values of albumin and LDH were balanced between the two arms. Three percent of patients had a low baseline albumin and 96% had a normal albumin at baseline. Baseline LDH was high in 27% of patients and was equally distributed between the treatment arms (*Comment: this value differed slightly from the applicant's analysis, likely based on which values were considered as baseline. This difference would not be expected to alter any determinations of the safety or efficacy of treatment with Abraxane*).

Baseline CA-19-9 values were balanced between the arms.

6.1.2.1 Baseline signs and symptoms
Patients in both arms were balanced with respect to signs and symptoms at baseline including abdominal pain, nausea, weight loss, fatigue, decreased appetite and nausea. Overall, 17% of patients had a biliary stent present at screening (19% in the combination arm and 16% in the gemcitabine-alone arm).

6.1.2.2 Baseline disease status-cancer history characteristics
Seven percent of patients had previous Whipple procedure and this was equally balanced between arms. Thirty one percent of patients had their tumor in the body of the pancreas, 43% in the head of the pancreas and 25% in the tail of the pancreas. Tumor location was balanced in the two treatment arms. Three patients in the gemcitabine arm had primary tumors that were renal, gastric, and duodenal. Ninety nine percent of patients in the trial had adenocarcinoma. Nine patients in the trial had "other histologies" of which none were neuroendocrine.

A total of 80% of patients were diagnosed with metastatic disease. The most common sites of metastasis were abdomen/peritoneum (90%) and liver (84%) followed by the lung (39%). The number of patients that had lung metastases was slightly higher on the gemcitabine arm than the combination arm (43% vs. 35%).

Table 11: Baseline cancer history characteristics (ITT population)

Variable	ABI 007+Gemcitabine (%) N= 431	Gemcitabine (%) N=430
Site of pancreatic primary, N (%)		
Head	191 (44)	180 (42)
Body	132 (31)	136 (32)
Tail	105 (24)	110 (26)
Histology at diagnosis, N (%)		
Adenocarcinoma	426 (99)	425 (99)
Other[a]	5 (1)	4 (1)
Site of metastatic disease, N (%)		
Abdomen/Peritoneum	**380 (88)**	**396 (92)**
Liver	365 (85)	360 (84)
Lung/Thoracic	153 (35)	184 (43)
Bone	22 (5)	18 (4)
Pelvis	30 (7)	27 (6)
Skin/soft tissue	10 (2)	10 (2)
Supraclavicular	10 (2)	8 (2)

Variable	ABI 007+Gemcitabine (%) N= 431	Gemcitabine (%) N=430
Brain	0	0
Other	107 (25)	99 (23)
Prior Whipple procedure, N (%)		
Yes	32 (7)	30 (7)
No	399 (93)	400 (93)
Presence of Biliary Stent at Screening, N (%)		
Yes	80 (19)	68 (16)
No	351 (81)	362 (84)

a.Per the sponsor there were no neuroendocrine histologies

6.1.2.4 Prior Chemotherapy/treatments

The ITT population included 35 (4%) patients who received any prior chemotherapy: 23 (3%) patients in the Abraxane/Gemcitabine arm and 12 patients (1%) in the Gemcitabine arm (*this analysis was performed by Dr.Shen; for further details refer to statistical review of this NDA*). Overall, 3% of patients received the prior chemotherapy in the adjuvant setting and 1% in the neoadjuvant or radiation sensitizer setting.

The *final* version of the protocol for Study CA046 excluded patients who received cytotoxic doses of gemcitabine (including in the adjuvant setting). The total number of patients with any past exposure to gemcitabine adjuvant or neoadjuvant was 17 (2 %). Prior treatment with adjuvant gemcitabine in chemotherapeutic doses (not as radiation sensitizer) was not allowed in the study; however there were 17 patients (10 in the combination arm and 7 in the gemcitabine arm) who received prior adjuvant gemcitabine).

Reviewers Comment:-This reviewer notes that there was no imbalance in this number between the treatment arms and that the number of such patients was small and would not affect the overall results of the trial.

Prior radiation therapy was administered to 3% of the total ITT patients (4% in the combination arm and 3 % in the gemcitabine arm). This total included receipt of any prior radiotherapy including extra-abdominal sites. The incidence of prior abdominal radiation was approximately 2% across both arms.

6.1.2.5 Concomitant medications
More than 99% of patients took at least one class of concomitant medication. The medications that were administered to patients in the combination arm with at least a 10% difference between arms were antiemetics, corticosteroids,

antibacterials/antiinfectives (65% vs. 47%), blood products, antidiarrheals, and antihistamines. More patients also used white blood cell growth factors in the combination arm (26% versus 15%) compared to the gemcitabine alone arm.

Reviewer Comment:-*This reviewer notes that patients on the combination arm took anti-infectives and blood products more frequently compared to patients in the gemcitabine alone arm likely due to cumulative bone marrow toxicity and higher risk of infection with both agents together (refer to Section 7 below).*

6.1.3   Subject Disposition

In Study CA046, there were 861 patients randomized who constituted the Intent-to-Treat (ITT) population, with 431 patients in the Abraxane/gemcitabine arm and 430 patients in the gemcitabine arm. The first patient was randomized on 5/8/2009, and the last patient was randomized on 4/17/2012. The applicant indicated that there were two patients who were randomized twice (Patient   (b) (6) and Patient   (b) (6)); however these patients were analyzed only once using the unique subject ID that was used to record all completed study related procedures.

The Treated population consisted of 823 patients who received at least one dose of the study drug. This included 421 patients on the Abraxane/gemcitabine arm and 402 patients on the gemcitabine arm. There was one patient (Patient   (b) (6)) who was randomized to gemcitabine but received Abraxane/gemcitabine. This patient was counted on the gemcitabine arm for efficacy analyses and on the Abraxane arm for safety analyses.

The per-protocol population consisted of 771 patients who met all eligibility criteria and received the treatment assigned by randomization, 394 patients on the combination arm and 377 patients on the gemcitabine arm.

The clinical cutoff date was 9/17/2012 and all clinical data collected up to the cutoff date was used for the final analysis.

Thirty eight patients were randomized, but never treated. The most common reason of not being treated was due to withdrawal per patients' request (1% and 5% for ABI-007/gemcitabine and gemcitabine arms, respectively).   The proportions of patients treated were comparable (97% vs. 94%) between the two arms. By the time of data cutoff (9/17/2012), the majority of patients had discontinued treatment (91% for each arm). The applicant's analysis of patient disposition is shown in Table 12.

Table 12: Applicant's analysis of patient disposition

Population	ABI-007/Gemcitabine(N=431)	Gemcitabine (N=430)	All Patients (N=861)
Patients Not Treated	11 (3%)	27 (6%)	38 (4%)
Progressive Disease	1(<1%)	0	1(<1%)
Adverse Event	1 (<1%)	1 (<1%)	2 (<1%)
Physician Decision	1 (<1%)	1 (<1%)	2 (<1%)
Protocol Violation	2 (<1%)	2 (<1%)	4 (<1%)
Withdrawal by Patient	3 (1%)	21 (5%)	24 (3%)
Other	3 (1%)	2 (<1%)	5 (1%)
Patients Treated	420 (97%)	403 (94%)	823
Therapy Ongoing	26 (6%)	12 (3%)	38 (4%)
Therapy Discontinued	394 (91%)	391 (91%)	785
Reason for Discontinuation			
Progressive Disease	196 (45%)	245 (57%)	441
Adverse Events	128 (30%)	73 (17%)	201
Unacceptable Toxicity (Related to Study Drug)	86 (20%)	29 (7%)	115 (13%)
Adverse Event (Unrelated to Study Drug)	42 (10%)	44 (10%)	86 (10%)
Physician Decision	25 (6%)	18 (4%)	43 (5%)
Protocol Violation	10 (2%)	6 (1%)	16 (2%)
Lost to Follow-up	0	0	0
Withdrawal by patient	28 (6%)	39 (9%)	67 (8%)
Other	7 (2%)	10 (2%)	17 (2%)
Patients Died	333 (77%)	359 (83%)	692
Patients in Survival Follow-up	96 (22%)	66 (15%)	162
Patients Lost to Survival Follow-	2 (<1%)	5 (1%)	7 (1%)
Patients met inclusion/exclusion	399 (93%)	400 (93%)	799

6.1.4 Analysis of Primary Endpoint(s)

__Reviewer's comments:__ All efficacy analyses presented in the following sections were conducted in collaboration with the Division of Biometrics, Biologics and Therapeutics Statistical Review Staff, Dr.Yuan Li Shen, Mathematical Statistician. All statistical analyses were conducted by Dr.Shen. Please refer to her review for additional details regarding the statistical analyses.

The primary efficacy endpoint for Study CA046 was OS (overall survival) defined as the time from the date of randomization to the date of death (any cause). Patients who are

alive were censored at the last known time that the patient was alive. During the post-study treatment period, OS status was monitored on a monthly basis for 6 months and then every 3 months thereafter until death occurred, the study closed or 3 years had passed since treatment discontinuation, whichever occurred first.

Following Amendment 4, a total of 421 patients were planned to be randomized to each treatment arm (842 patients in total) for this study. Per the final version of the study protocol the statistical analysis plan required 608 deaths to detect an improvement of 30% in OS (HR=0.769) with 90% power assuming a two-sided Type I error of 0.049 adjusting for one interim analysis.

__Reviewers Comment:-__The revision in sample size as discussed above was described in Amendment 4 of the protocol and the applicant justified it as being for purposes of increasing the power of the study from 80% to 90%. Two sensitivity analyses based on different cutoff dates (original cutoff date prior to sample size re-estimation based on 455 deaths and the revised cutoff date based on 608 deaths) were performed by the statistical reviewer Dr.Shen. The corresponding treatment effect based on the hazard ratios were 0.69 and 0.7, respectively, with both the upper 95% CIs being below 1. Both results were supportive of the primary efficacy result (i.e. HR=0.72).

An interim analysis was performed after at least 200 patients were followed for at least 6 months from the date of randomization. The purpose of this interim analysis was to evaluate futility with the possibility of stopping for lack of efficacy. The data monitoring committee (DMC) reviewed progression rate, death rate and conditional power calculations in addition to the safety data. The criterion for stopping the study for futility was a conditional power of less than 10% to reject the null hypothesis of no difference in the 6-month death rate at the end of the study.

__Reviewers Comment:-__The applicant provided the minutes from the four sessions of the DMC meetings. During all four sessions the DMC was of the opinion that the risk-benefit ratio justified continuation of the study; however additional issues related to sepsis and pneumonitis were discussed and the DMC recommended protocol modifications to address these toxicities.

Results and Conclusions
At the clinical cutoff date for the final OS analysis (dated 9/17/2012) there were 333 (77%) and 359 (83%) deaths, for ABI-007/gemcitabine and gemcitabine arms, respectively. The median follow-up time in the ITT population was 7.6 and 6.1 months for ABI-007/gemcitabine and gemcitabine arm, respectively. At the data cutoff date, a statistically significant overall survival result was demonstrated with hazard ratio of 0.72 (95% CI=0.62, 0.84; p<0.0001 based on stratified log rank test) in favor of the ABI-007/gemcitabine treated arm. The median survival times were 8.5 months (95% CI=7.89, 9.53) and 6.7 months (95% CI=6.01, 7.23) for ABI-007/gemcitabine and gemcitabine arm, respectively (Table 13).

Table 13: FDA Summary of Overall Survival in the ITT population based on 9/17/2012 cutoff date *(adapted from FDA statistical review)*

	ABI-007/Gemcitabine N=431	Gemcitabine N=430
Number (%) of Subjects		
Censored Death	98 (23) 333 (77)	71(17) 359 (83)
Duration of overall survival (months)		
Median (95% CI) [a]	8.5 (7.89,9.53)	6.7 (6.01,7.23)
p-value (stratified log-rank test)[b]	<0.0001	
Hazard ratio (95% CI; stratified)[c]	0.72 (0.617, 0.835)	

CI=confidence interval;
[a] Median and percentiles are based on Kaplan-Meier survival estimates.
[b] Stratification factors include: geographic region (North America vs. Others), Karnofsky performance score (70 to 80 vs.90 to 100), and presence of liver metastasis (yes vs. no).
[c] Estimated using the stratified Cox proportional hazard model.

Reviewers Comment:-*The median overall survival on the Abraxane arm of 8.5 months was statistically significant and represented a clinically meaningful improvement over single agent gemcitabine alone. The median overall survival of 6.7 months in the control arm was similar to that observed with previous trials of single agent gemcitabine.*

Figure 3: Plots of Kaplan-Meier Estimates for Overall Survival (9/17/2012 cutoff date) *(adapted from FDA statistical review)*
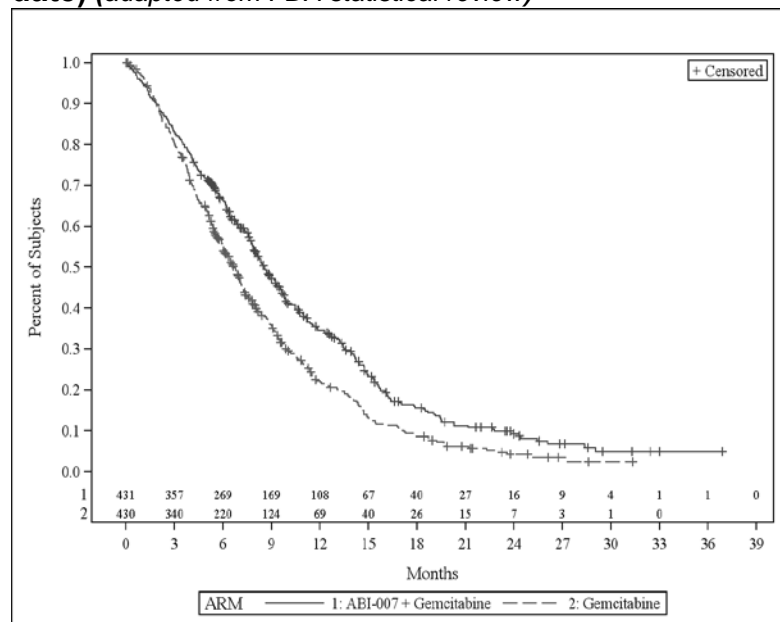
The Plots for the Kaplan-Meier estimates are presented above in Figure 3. The two curves appear to be separated.

Multiple sensitivity analysis were performed for OS and the hazard ratio estimates ranged from 0.68 to 0.74 with all the upper bound of 95% CI being below 1. These suggested that the primary analysis of OS was a robust finding. For details regarding this and other exploratory analyses please refer to the FDA statistical review for this application.

6.1.5   Analysis of Secondary Endpoints(s)

Progression Free Survival
At the time of the database cutoff date (9/17/2012), there were 277 (64%) and 265 (62%) PFS events in the ABI-007/gemcitabine and gemcitabine alone arms, respectively. The results showed a longer median PFS time observed in the ABI-007/Gemcitabine treated arm as compared with that observed in the gemcitabine alone arm (5.5 months vs. 3.7 months, respectively). The estimated hazard ratio for PFS was 0.69 (95% CI=0.58, 0.82) in favor of the ABI-007/gemcitabine arm. A summary of the PFS results is shown in the table below.

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Table 14: Summary of Progression Free Survival (based on 9/17/2012 cutoff date)
(adapted from FDA statistical review)

	ABI-007/Gemcitabine N=431	Gemcitabine N=430
Number (%) of Subjects		
Censored	154 (36)	165 (38)
Event	277 (64)	265 (62)
Death	115 (27)	109 (25)
Progressive disease	162 (38)	156 (36)
Duration of progression free survival (months) Median (95% CI) [a]	5.5 (4.47, 5.95)	3,7 (3.61, 4.04)
p-value (stratified log-rank test)[b]	<0.0001	
Hazard ratio (95% CI; stratified)[c]	0.69 (0.581, 0.821)	

a Median and percentiles are based on Kaplan-Meier survival estimates.
b Stratification factors include: geographic region (North America vs. Others), Karnofsky performance score (70 to 80 vs. 90 to 100), and presence of liver metastasis (yes vs. no).
c Estimated using the stratified Cox proportional hazard model.

Reviewers Comment:-*Please refer to the statistical review of this application for a detailed discussion on the issue of differential censoring distribution in the independent radiology review (IRR) compared to investigator-assessed PFS. In summary, the hazard ratio estimates ranged from 0.61 to 0.74 with the upper bound of the 95% CIs being below 1. The results did demonstrate robust findings for PFS based on these sensitivity analyses.*

Evaluation of Concordance and Discordance of the IRR and Investigator Assessments

Based on the 9/17/2012 cutoff date, the percentages of patients who had PD or non-PD status determined by both the IRR and investigators (concordance) are summarized below in Table 15 . The concordance rate of the IRR and investigator assessments was 79.9%.

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Table 15: Summary of Concordance/Discordance in Progressive Disease *(adapted from FDA statistical review)*

Status	If progressed	ABI-007 / Gemcitabine N=431	Gemcitabine N=430	All Patients N=861
Concordance	Progressive Disease	264 (61.3)	258 (60.0)	522 (60.6)
	Not Progressive Disease	91(21.1)	75(17.4)	166 (19.3)
Discordance	IRR progressed / INV not progressed	13 (3.0)	7 (1.6)	20 (2.3)
	INV progressed / IRR not progressed	63 (14.6)	90 (20.9)	153 (17.8)

Figure 4 shows the Kaplan-Meier curves for progression free survival.

Figure 4: Plots of Kaplan-Meier Estimates for PFS (9/17/2012 cutoff date *(adapted from FDA statistical review)*
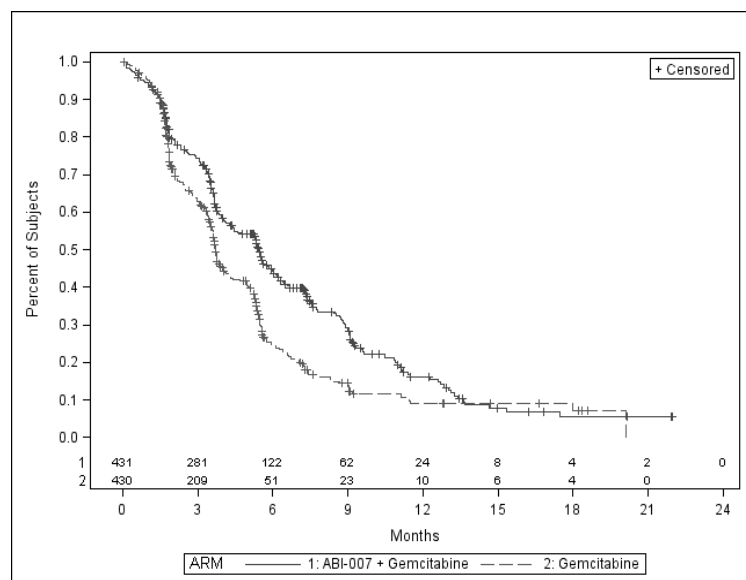
Objective Response Rate

The objective response rate based on independent assessments appeared to be higher in the ABI-007/gemcitabine arm compared to the rate in the gemcitabine arm (23% vs. 7%, respectively, p-value < 0.0001 based on the Chi-square statistic). The median durations of response were 7.4 (95% CI=5.6, 8.5) and 7.1 (95% CI=3.8, NA) months for the ABI-007/gemcitabine and gemcitabine alone arms, respectively.

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Abraxane/Nab Paclitaxel

Table 16: Summary of Objective Response Rate and Duration of Response *(adapted from FDA statistical review)*

Variable	ABI-007/Gemcitabine N=431	Gemcitabine N=430	P-value
Patients with Confirmed Complete or Partial Overall Response	99 (23%)	31 (7%)	
95% Confidence Interval	(19.1, 27.2)	(5.0, 10.1)	< 0.0001
Complete Response	1 (< 1%)	0	
Partial Response	98 (23%)	31 (7%)	
Stable Disease	118 (27%)	122 (28%)	
Progressive Disease	86 (20%)	110 (26%)	
Not Evaluable or No Post-baseline Assessment	128 (30%)	167 (39%)	
Duration of response #Progression/ # with CR or PR Median duration of response (95% CI)	10/31 (32%) 7.4 (5.552, 8.476)	47/99 (47%) 7.1 (3.745,NA)	
Hazard Ratio (95% CI)	1.07 (0.525, 2.161)		

a.   Based on a Chi-square statistic.

6.1.6 Other Endpoints
There were no additional efficacy endpoints considered for regulatory decision making from Study CA046 other than OS, PFS, ORR, and duration of response.

6.1.7   Subpopulations

Gender
The hazard ratio estimates based on OS for both male and female subgroups were equal to 0.72 with the upper bound of the 95% CIs being less than 1 which appeared to support a favorable treatment effect in the ABI-007/gemcitabine treated arm for both gender subgroups.

Reference ID: 3358410

Table 17: Subgroup analysis of OS by gender *(adapted from FDA statistical review)*

		ABI-007 / Gemcitabine N=431	Gemcitabine N=430
Male	Number of events /Total	195/245	218/257
	HR (95% CI)[a]	0.72(0.59,0.88)	
Female	Number of events /total	138/186	141/173
	HR (95% CI)[a]	0.72(0.56,0.93)	

[a] From Cox's Proportional Hazards Model, stratified by geographic region (North America vs. Others), Karnofsky performance score (70 to 80 vs. 90 to 100), and presence of liver metastasis (yes vs. no).

Race

The hazard ratio point estimates for both white and non-white subgroups were less than 1 implying favorable treatment effect in both sub-groups. The estimate was smaller for the non-white population (0.67 vs. 0.73); however, these numbers should be interpreted with caution as the number of non-white subjects in the trial was small (7%) and it was a non-randomized subgroup.

Table 18: Summary of Hazard Ratios for OS by Race *(adapted from FDA statistical review)*

		ABI-007 / Gemcitabine N=431	Gemcitabine N=430
White	Number of events/total	313/403	337/401
	HR (95% CI)[a]	0.73(0.63,0.86)	
Non-White	Number of events/total	20/28	22/29
	HR (95% CI)[a]	0.67(0.44,1.01)	

[a] From Cox's Proportional Hazards Model, stratified by geographic region (North America vs. Others), Karnofsky performance score (70 to 80 vs. 90 to 100), and presence of liver metastasis (yes vs. no).

Age

The hazard ratio estimates of OS for both age subgroups (< 65 years and ≥ 65 years) were less than 1 and showed a favorable result observed in the ABI-007/gemcitabine treated arm. The point estimate for the effect was larger in younger patients; however, these were non-randomized patient subgroups with a smaller sample size (among patients older than 65) and conclusions regarding the effect of age on efficacy should be guarded.

Table 19: Summary of Hazard Ratios for OS by Age Subgroup *(adapted from FDA statistical review)*

		ABI-007 / Gemcitabine N=431	Gemcitabine N=430
<65 years old	Number of events /total	188/254	209/242
	HR (95% CI)[a]	0.64(0.53,0.79)	
≥65 years old	Number of events /total	145/177	150/188
	HR (95% CI)[a]	0.81(0.63,1.03)	

[a] From Cox's Proportional Hazards Model, stratified by geographic region (North America vs. Others), Karnofsky performance score (70 to 80 vs. 90 to 100), and presence of liver metastasis (yes vs. no).

For a discussion on the subgroup of patients more than 75 years of age please refer to the forest plot and the discussion following it as depicted in Figure 5.

Geographic region:
The hazard ratio estimates for all four regions were all less than one. The hazard ratio estimate based on Eastern Europe was higher than the hazard ratio estimates from the other regions but since this was a small subgroup any inferences regarding this should be done with caution.

Table 20: Summary of OS results by Geographic Regions

		ABI-007 / Gemcitabine N=431	Gemcitabine N=430
Australia	Number of events /total	50/61	53/59
	HR (95% CI) [a]	0.67(0.44,1.01)	
Eastern Europe	Number of events /total	62/64	59/62
	HR (95% CI) [a]	0.84(0.58,1.23)	
Western Europe	Number of events /total	14/38	17/38
	HR (95% CI) [a]	0.72(0.35,1.47)	
North America	Number of events /total	207/268	230/271
	HR (95% CI) [a]	0.68(0.56,0.82)	

[a] From Cox's Proportional Hazards Model, stratified by geographic region (North America vs. Others), Karnofsky performance score (70 to 80 vs. 90 to 100), and presence of liver metastasis (yes vs. no).

Other Subgroup analysis

Forest plots of the hazard ratio estimates based on OS by demographic subgroups and the corresponding 95% confidence intervals are shown in Figure 5. The results of the subgroup analyses were generally consistent with the primary analysis of OS in the ITT population.

Figure 5: Forest Plot of Hazard Ratio estimates for OS by Demographic subgroups *(copied from statistical review)*
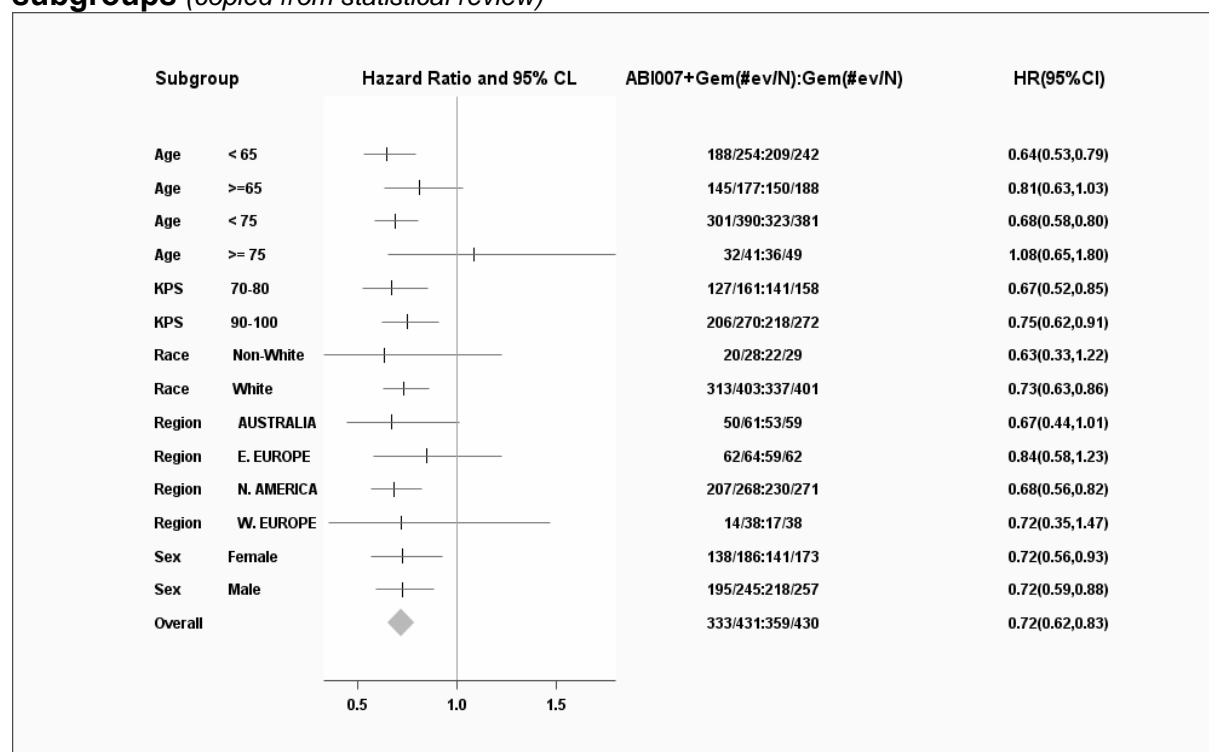
Subgroup		Hazard Ratio and 95% CL	ABI007+Gem(#ev/N):Gem(#ev/N)	HR(95%CI)
Age	< 65		188/254:209/242	0.64(0.53,0.79)
Age	>=65		145/177:150/188	0.81(0.63,1.03)
Age	< 75		301/390:323/381	0.68(0.58,0.80)
Age	>= 75		32/41:36/49	1.08(0.65,1.80)
KPS	70-80		127/161:141/158	0.67(0.52,0.85)
KPS	90-100		206/270:218/272	0.75(0.62,0.91)
Race	Non-White		20/28:22/29	0.63(0.33,1.22)
Race	White		313/403:337/401	0.73(0.63,0.86)
Region	AUSTRALIA		50/61:53/59	0.67(0.44,1.01)
Region	E. EUROPE		62/64:59/62	0.84(0.58,1.23)
Region	N. AMERICA		207/268:230/271	0.68(0.56,0.82)
Region	W. EUROPE		14/38:17/38	0.72(0.35,1.47)
Sex	Female		138/186:141/173	0.72(0.56,0.93)
Sex	Male		195/245:218/257	0.72(0.59,0.88)
Overall			333/431:359/430	0.72(0.62,0.83)

The hazard ratio estimates are based on the Cox's Proportional Hazards Model, stratified by geographic region (North America vs. Others), Karnofsky performance score (70 to 80 vs. 90 to 100), and presence of liver metastasis (yes vs. no)

Reviewers Comment:-*As seen above the hazard ratio for OS in the age group ≥75 years was 1.08, however only 10% of the overall study population belonged in this subgroup, thus accounting for the wide confidence intervals for the hazard ratio estimate. Additionally, there were potential imbalances between arms in this subgroup that may have contributed to this effect.*

Forest plot of the hazard ratio estimates based on OS by baseline characteristics is shown in Figure 6.

Reviewers Comment:-*As seen below the hazard ratio for OS in the group with a normal CA 19-9 was above one but due to the small sample size this should be interpreted with caution.*

Figure 6: Forest plots of the hazard ratio estimates for OS by baseline characteristics *(copied from statistical review)*
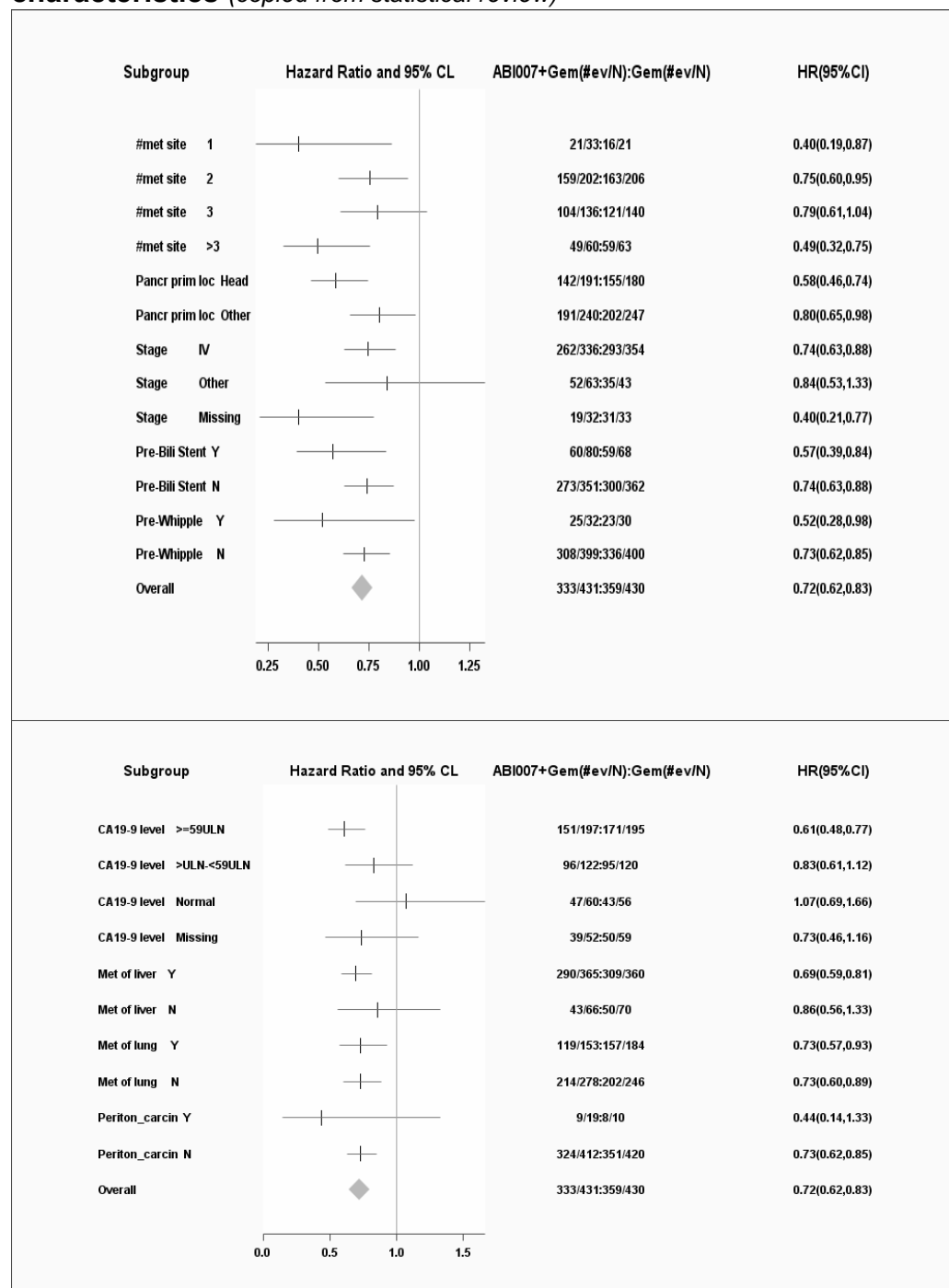
The hazard ratio estimates are based on the Cox's Proportional Hazards Model, stratified by geographic region (North America vs. Others), Karnofsky performance score (70 to 80 vs. 90 to 100), and presence of liver metastasis (yes vs. no).

Based on FDA request, Abraxis conducted analyses of overall survival on patients enrolled under each protocol amendment to explore effects of dose modification on OS. The Kaplan Meier curves separated for each of the six analyses except for the analysis based on the original protocol (this consisted of 10 patients) and the analysis based on amendment 4 (59 patients). Thus, there was no evidence that the changes to the dose modification had major effects on OS [such that the more conservative dose modification regimen (compared to the original protocol) proposed in product labeling was acceptable].

6.1.8   Analysis of Clinical Information Relevant to Dosing Recommendations

This section is not applicable as all patients received the same initial dose of Abraxane throughout study CA046.

6.1.9   Discussion of Persistence of Efficacy and/or Tolerance Effects

Refer to the analyses of OS, PFS, and duration of response in Sections 6.1.4 and 6.1.5 for a review of the persistency of efficacy effects.

6.1.10   Additional Efficacy Issues/Analyses

The applicant also submitted Study CA040 titled "A Phase I Trial of Gemcitabine (Gemzar®) Plus ABI-007 (Abraxane®) in Patients with Advanced Metastatic Pancreatic Cancer" in support of this application. The primary objective of this study was to determine the MTD and DLTs of Abraxane /gemcitabine in patients with metastatic pancreatic cancer. The secondary objectives were to obtain additional data on the antitumor activity of Abraxane /gemcitabine and to evaluate the safety and tolerability of this combination. A total of 67 patients were enrolled at 4 sites in the US and received at least one dose of study drug, including 20, 44, and 3 patients who received Abraxane 100 mg/m^2, 125 mg/m^2 and 150 mg/m^2, respectively, followed by gemcitabine 1000 mg/m^2.

The applicant's analysis of the key efficacy results from that study is summarized in Table 21.

Table 21: Key efficacy results from the Phase1/2 study CA040 *(adapted from integrated summary of efficacy report)*

Efficacy Parameter	ABI-007/Gemcitabine 1000 mg/m2			
	ABI-007 100 mg/m^2 (N = 20)	ABI-007 125 mg/m^2 (N = 44)	ABI-007 150 mg/m^2 (N = 3)	All Patients (N = 67)
Assessment of Overall Response Rate				
ORR (Confirmed CR + PR), n (%) [95% CI]	5 (25%) [8.7, 49.1]	17 (39%) [24.2, 53.0]	0 NA	22 (33%) [21.6, 44.1]
Confirmed CR, n (%) Confirmed PR, n (%)	0 5 (25%)	0 17 (39%)	0 0	0 (0) 22 (33%)
Assessment of Disease Control Rate				
Disease control, n (%) [95% CI]	11 (55%) [33.2, 76.8]	24 (55%) [39.8, 69.3]	1 (33%) [0.8, 90.6]	36 (54%) [41.8, 65.7]
Confirmed CR, n (%) Confirmed PR, n (%) SD ≥ 16 weeks	0 5 (25%) 6 (30%)	0 17 (39%) 7 (16%)	0 0 1 (33%)	0 22 (33%) 14 (21%)
Assessment of PFS[a]				
Number of Events (Death or Progression), n (%)	9 (45%)	25 (57%)	3 (100%)	37 (55%)
KM Estimated Median PFS (months) [95% CI]	6.1 [3.7, - -]	6.9 [4.8, 9.2]	1.6 [0.5, 10.0]	6.1 [5.4, 9.2]
Overall Survival[b]				
Number of deaths, n (%)	17 (85%)	38 (86%)	3 (100%)	58 (87%)
KM Estimated Median OS (months) [95% CI]	9.3 [6.6, 11.9]	12.2 [8.9, 17.9]	6.1 [0.5, 17.9]	10.3 [8.4, 13.6]

CI = confidence interval; CR = complete response; KM = Kaplan Meier; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; SD = stable disease.
[a] Progression-free survival was defined as the time from the first dose of study drug to the start of progression or patient death (whichever occurred first). Patients who did not have progression or who had not died were censored at the last known time the patient was progression-free. Patients who initiated other anticancer therapy prior to progression were censored at the time when new anticancer therapy was initiated.
[b] Patients who did not die were censored at the last known time the patient was alive.

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Reviewers Comment:-*The results of the Phase 1/2 dose finding study CA040 showed promising activity in the 125mg/m^2 dose cohort and formed the basis of the decision of the applicant to move forward with the pivotal study CA046.*

7   Review of Safety

Safety Summary
The main source of subjects for the safety analysis was the pivotal trial study CA046 which was the only randomized trial submitted in the application. Additionally, 44 patients from the Phase 1/2 study were also included in the safety database submitted by the applicant.
Among the 823 patients who constituted the safety population of study CA046, 91% of patients discontinued study treatment at the time of data cutoff. As shown in the disposition Table above, more patients discontinued gemcitabine-alone due to progression and more patients discontinued Abraxane/gemcitabine due to adverse events. The most common adverse events (by preferred term) that led to study drug discontinuation were peripheral neuropathy, fatigue, and thrombocytopenia.

The median number of treatment cycles administered was 3 in the combination arm and 2 in the gemcitabine arm. Forty one percent of patients on the Abraxane group underwent a dose reduction of Abraxane. A total of 47% of patients in the Abraxane underwent a dose reduction of gemcitabine and 33% of patients in the gemcitabine-alone arm underwent a dose reduction of gemcitabine.

The most frequently reported treatment-emergent adverse events were bone marrow suppression (anemia, neutropenia/leukopenia, thrombocytopenia), alopecia, gastrointestinal events (nausea, diarrhea, vomiting, constipation, nausea, dysgeusia), constitutional events (fatigue, asthenia, anorexia, weight loss, fever, peripheral edema, dehydration), pain-related events (headache, extremity pain, abdominal pain, arthralgia, myalgia), respiratory events (dyspnea, cough), neurologic events (insomnia, dizziness, depression, paraesthesia, and peripheral sensory neuropathy), and laboratory abnormalities (hypokalemia, ALT increased). The most common Grade 3 or greater toxicities that occurred on the Abraxane arm included hematological toxicities including neutropenia, peripheral neuropathy, fatigue, asthenia, nausea, dehydration and diarrhea.

The most common serious adverse events of Abraxane in combination with gemcitabine were pyrexia (6%), dehydration (5%), pneumonia (4%) and vomiting (4%). The most common adverse reactions resulting in dose reduction of Abraxane were neutropenia (10%) and peripheral neuropathy (6%). The most common adverse reactions leading to withholding or delay in Abraxane dosing were neutropenia (16%), thrombocytopenia (12%), fatigue (8%), peripheral neuropathy (15%), anemia (5%) and diarrhea (5%).

Adverse events of special interest included sepsis, pneumonitis and peripheral neuropathy. The incidence of interstitial lung disease was 4% on the Abraxane arm and

1% on the Gemcitabine arm. The incidence of Grade 3 or greater pneumonitis on the Abraxane arm was 2% versus 1% on the gemcitabine arm. Two patients died on the Abraxane arm due to pneumonitis.

The incidence of adverse events in the Infections and infestations SOC was 49% for the Abraxane arm and 32% for the gemcitabine arm. The incidence in the Infections and Infestations SOC for adverse events Grade 3 or greater was 16% in the Abraxane arm and 9% in the Gemcitabine arm.

The incidence of all grades of peripheral neuropathy was 54% in the Abraxane arm and 13% in the gemcitabine arm. The incidence of Grade 3 peripheral neuropathy was 17% in the Abraxane arm versus 1% in the gemcitabine arm. There were no reports of Grade 4 peripheral neuropathy in study CA046.

In addition to data from Study CA046 described above, data submitted by the applicant from study CA040 and the 120 day safety update were also reviewed. The safety results from study CA040 did not reveal any new safety signals. No changes to the proposed label were recommended based upon review of the adverse event information included in the 120-day safety update.

In general, the safety data submitted by the applicant showed that the safety profile of Abraxane used in combination with gemcitabine to treat patients with metastatic pancreatic cancer was similar to the safety profile observed in prior trials with Abraxane in breast cancer and non-small cell lung cancer. Although new safety signals of non-neutropenic sepsis and pneumonitis emerged, these risks were balanced by the robustness of the improvement in overall survival demonstrated in the pivotal study CA046.

7.1   Methods

7.1.1   Studies/Clinical Trials Used to Evaluate Safety

The primary safety data source was derived from the 823 patients (421 patients on the combination of Abraxane and gemcitabine, 402 patients on gemcitabine arm) who constituted the treated population of Study CA046 (defined as all patients randomized and who received atleast one dose of the study medication). The data sources used in the safety assessment were adequate.

7.1.2   Categorization of Adverse Events

Adverse events were analyzed by the applicant in terms of Treatment Emergent Adverse Events (TEAEs), which were defined as any AEs that began or worsened in severity by at least one (NCI CTCAE) grade after the initiation of study drug through 30 days after the last dose of study drug or end of treatment, whichever was later. The

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applicant's submission of safety data was coded using MedDRA version 15.0 and the severity of the toxicity was determined using NCI-CTCAE v 3.0. The applicant's assignment of preferred terms using verbatim terms was acceptable without apparent (major) coding errors. In addition, Case Report Forms (CRFs) for 40 patients enrolled in Study CA046 were reviewed to determine if verbatim terms, toxicity grading, intervention, and characterization of seriousness of adverse events were characterized appropriately in the CRFs and accurately entered into the database. In general, any apparent initial discrepancies between the CRFs and database entries or inaccuracies noted in the characterization of adverse events in the CRFs were resolved upon detailed review of the submitted electronic data capture forms.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The primary analysis of safety was performed using the adverse event data set (CA046-AE) from study CA046 in which 823 patients were treated. In addition there was supportive safety data for ABI-007 125 mg/m2 followed by gemcitabine 1000 mg/m2 provided from 44 patients who received this dose in the Study CA040 which was included in the ISS.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Both studies CA046 and CA040 limited enrollment to patients with metastatic disease who had a good performance status (KPS ≥70%) and adequate bone marrow, renal, and hepatic function. Additionally, the final version of study CA046 excluded patients with ≥10% decrease in KPS or ≥ 20% decrease in serum albumin level between the baseline visit and within 72 hours prior to randomization; history of connective tissue disorders (e.g., lupus, scleroderma, arteritis nodosa); history of interstitial lung disease; history of slowly progressive dyspnea and unproductive cough, sarcoidosis, silicosis, idiopathic pulmonary fibrosis, pulmonary hypersensitivity pneumonitis or multiple allergies; history of chronic leukemia (e.g., chronic lymphocytic leukemia); peripheral arterial disease; and a high cardiovascular risk, recent coronary stenting or myocardial infarction in the past year.

Reviewers Comment:-*There was inadequate data to assess the safety of Abraxane in combination with gemcitabine in patients who had one or more of the above comorbid criteria. However, some of these criteria are typical of patients enrolled in studies of other cytotoxic agents in advanced malignancies. Nevertheless, because Study CA046 demonstrated an improvement in overall survival in a population of patients with incurable cancer and a poor prognosis, the safety database submitted with this NDA contained an adequate number of patients for consideration of approval.*

7.2.2   Explorations for Dose Response

Study CA046

No formal dose-response relationships could be conducted as all patients received the same initial dose of Abraxane in Study CA046 and PK measurements were not obtained. In study CA046, patients received either gemcitabine in combination with Abraxane or gemcitabine alone until disease progression, death of the patient or discontinuation from the study for other reasons including unacceptable toxicity. Any AE that started after initial study drug administration and up to 30 days after the last dose of study drug or EOS (whichever was later) was collected. The table below compares the duration of therapy in both the groups. The median number of treatment cycles administered was 3 in the combination arm and 2 in the gemcitabine arm.

Table 22:-Duration of Therapy in Study CA046

Exposure	ABI-007 + Gemcitabine N=421 N (%)	Gemcitabine N=402 N (%)
Number of cycles completed n (%)		
1	125 (30)	176 (44)
2	37 (9)	32 (8)
3	51(12)	58 (14)
4	26 (6)	25 (6)
5	42 (10)	45 (11)
6	34 (8)	20 (5)
>6	106 (25)	46 (11)
Median number of cycles completed (range)	3 (1,23)	2(1,23)
Mean number of cycles completed (std dev)	4.4	3.3
Duration (days)		
Mean (std dev)	145.9	111.6 (92.9)
Median (min, max)	119 (4, 666)	86 (2, 654)

According to the Applicant, the median percentage of the protocol-specified Abraxane dose was 80%. The median percentage of the protocol specified gemcitabine dose was 75% in the Abraxane arm and 85% in the gemcitabine arm.

Because of the multiple changes to the dose modification section of the protocol, FDA requested that Abraxis submit exposure analyses based on the different amendments. Although, as expected (due to chance), there was some minor fluctuation in exposure by amendments, no definitive trends regarding exposure based on amendment could be ascertained. Importantly, exposure did not appreciably decrease among patients

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enrolled in Amendment 5 compared to Amendment 4 where additional changes based on day 8 and day 15 labs were instituted.

7.2.3   Special Animal and/or In Vitro Testing

No special animal studies or in vitro testing were considered necessary prior to the approval of this supplemental indication.

7.2.4   Routine Clinical Testing

See below under adverse events/laboratory analyses.

7.2.5   Metabolic, Clearance, and Interaction Workup

Sparse PK sampling for exposure-response relationships were not submitted in this application (refer to 04 Aug 2011 meeting). Additionally, FDA previously agreed that a DDI assessment was not needed based on existing information in the gemcitabine label as well as DDI assessments in non-clinical models.

7.2.6   Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Analyses of the following important adverse reactions associated with taxanes are included in other sections of this review: cytopenias, fatigue/asthenia, peripheral neuropathy, mucositis, peripheral edema.

7.3   Major Safety Results

7.3.1   Deaths

Overview of applicant's methods
Because survival was the primary end-point for study CA046, all patients were followed for survival (OS) status on a monthly basis for 6 months and then every 3 months thereafter until death occurred, the study closed or 3 years elapsed since treatment discontinuation, whichever occurred first. Any AE that started after initial study drug administration and up to 30 days after the last dose of study drug or EOS (whichever is later) was collected. The applicant provided a summary of TEAEs with an outcome of death that occurred within 30 days of the last treatment dose. The applicant also provided listings for patients that experienced a TEAE with an outcome of death. Patient narratives were provided by the applicant for patients who received at least one dose of ABI-007 and experienced a TEAE regardless of causality assessment which involved an outcome of death while on study treatment or within 30 days of treatment discontinuation (i.e., on-treatment death), resulted in discontinuation of ABI-007 or gemcitabine (for the ABI-007/gemcitabine treatment arm), or was an SAE. In addition, narratives were provided separately for patients in the ABI-007/gemcitabine arm who

received at least one dose of ABI-007 and who discontinued ABI-007 or gemcitabine (for the ABI-007/gemcitabine treatment arm) for reasons categorized as other, lost-to-follow-up, physician decision, or subject decision.

Reviewers Comment:-*The applicant's decision to analyze deaths that occurred within 30 days was acceptable. Based on the pharmacology of these drugs, most deaths due to gemcitabine or Abraxane would be expected to occur within this time-period.*

FDA review of deaths

Summary of Deaths in Study CA046 (data cut off of 17 Sep, 2012)
In study CA046, as of the data cut off of 17 Sep 2012, 692 (80%) patients died, 333 patients (77%) died in the combination arm of ABI-007 and gemcitabine and 359 patients (83%) died in the gemcitabine alone arm. The majority of the patients in the treated population died due to progressive disease, 287 on the combination arm and 291 on the gemcitabine arm. Thirty five of the 82 patients whose reported cause of death was not due to disease progression reportedly had an unknown cause of death. For the remaining 47 patients there were more deaths due to sepsis (4 versus 2 patients) and pulmonary embolism (4 versus 2 patients) in the combination arm than in the gemcitabine alone arm. Conversely deaths due to cardiorespiratory failure occurred more frequently on the gemcitabine arm compared to the Abraxane and gemcitabine arm (7 vs. 3).

Table 23: Causes of death (excluding progression of disease) other than disease progression in Study CA046 (Treated population)

Cause of Death	ABI007+Gemcitabine N=421	Gemcitabine N=402	All
Unknown	13	22	35
Cardiac/Cardiopulmonary Arrest/Failure	2	4	6
Pulmonary Embolism	4	2	6
Sepsis	4	2	6
Cerebrovascular Accident/ Cerebral Hemorrhage	2	3	5
Renal Failure	2	2	4
Gastrointestinal Hemorrhage	2	1	3
Accidental Death	1	1	2
Cardiac Failure	1	1	2
Respiratory Arrest/Failure	0	2	2
Acute Coronary Syndrome	1	0	1
Acute Respiratory Distress Syndrome	1	0	1
Diffuse Alveolar Damage	1	0	1
Hepatic Failure	1	0	1
Hypoglycemic Coma	0	1	1

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Cause of Death	ABI007+Gemcitabine N=421	Gemcitabine N=402	All
Intestinal Ischemia	0	1	1
Intestinal Perforation	1	0	1
Multi-organ Failure	0	1	1
Esophageal Hemorrhage	0	1	1
Perforated Viscus	0	1	1
Pneumonia	1	0	1

Reviewers Comment: - *The numbers of patients in most of the adverse event categories were small making it difficult to make any meaningful comparisons between the two arms with respect to causes of death.*

A higher percentage of patient deaths occurring within thirty days of therapy were attributed to progressive disease in the gemcitabine group.

There were 126 (15% of the safety analysis population) deaths that occurred within 30 days of the last dose of study drug in the treated population of which 54 (13% of 421 Abraxane treated patients) deaths occurred in the ABI-007/gemcitabine arm and 72 (18% of 402 gemcitabine-alone treated patients) deaths occurred on the gemcitabine arm (4% of data was missing). Thirty seven of these 54 patients on the combination arm died due to progressive disease whereas 53 of these 72 patients on the gemcitabine arm died due to progressive disease within 30 days of the last dose of the drug. For the rest of the patients whose cause of death was reported as other, more patients died of sepsis on the combination arm (4 versus 2).

Table 24: Analysis of Deaths Attributed to Progressive Disease by Treatment Arm within 30 days of study drug

Cause of Death	Number of Deaths within 30 days of study therapy	ABI-007+Gemcitabine N = 421		Gemcitabine N = 402	
		N	%	N	%
Other	36	18	4%	18	4%
Progressive disease	90	37	9%	53	18%

To verify the causes of death described by the applicant, narrative summaries and treatment emergent adverse event listings were reviewed.

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Table 25: Reviewer analysis of treatment emergent adverse events with an outcome of death on the ABI-007 with Gemcitabine arm *(modified from the applicant's Table 75)*

SUB ID*	Age/ Sex	Cause of Death by PT	Comorbid conditions	*Reviewer Comments*
(b) (6)	64/M	Acute coronary syndrome	Ischemic heart disease, arterial hypertension.	*Chemotherapy can increase thrombosis risk which may have been exaggerated in this patient with prior ischemic heart disease.*
	72/M	Cardiac failure congestive	Coronary artery disease, coronary artery bypass (2007), hypertension, hyperlipidemia, type 2 diabetes mellitus	*Blood transfusion with fluid overload the day prior to the event of CHF. Died in hospice. Unlikely to be related to the study drug.*
	50/M	Sepsis	Jaundice, abdominal pain, anorexia, biliary stent, sphincterotomy, duodenal obstruction, cholangitis, leukocytosis.	*Patient had disease progression on CT scan leading to duodenal obstruction, biliary compression, and cholangitis.*
	61/M	Diffuse alveolar damage	Peripheral neuropathy, bile duct stent insertion.	*Occurred in Cycle 3. Patient had no other infectious agent identified and was not neutropenic. Steroids were given.*
	47/F	Acute respiratory distress syndrome	History of radiation (site not mentioned, likely back due to spinal fracture), lung metastases/	*Occurred in cycle 3. All cultures negative. Both drugs could be considered for causality. ? Radiation recall with Gemcitabine.*

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Reference ID: 3358410

SUB ID*	Age/ Sex	Cause of Death by PT	Comorbid conditions	*Reviewer Comments*
(b) (6)	73/F	Septic shock	Diabetes mellitus type 2, acute renal failure,	*Gram negative neutropenic sepsis in cycle 1, 2 days post day 8 dose.*
	71/M	Ischemic cerebral infarction	Hypertension, lacunar infarcts, leg phlebitis, acute renal failure, left vertebral artery dissection, also atrial flutter probably embolic stroke	*Occurred in Cycle 1. Left MCA infarct two days after last dose, Followed by sepsis (gram negative rods in blood). Cause of death was probably sepsis (not cerebral infarct).*
	53/M	Sepsis	History of cholangitis, pancreatitis, diabetes mellitus type 2, biliary catheter, sacral ulcer	*Cerebral ischemia R MCA infarct 8 days after first dose of drug, enterococcus fecalis non-neutropenic sepsis, death 32 days after last dose. Cause of death sepsis not clear as patient died 3 weeks after the sepsis event which was treated*

SUB ID*	Age/ Sex	Cause of Death by PT	Comorbid conditions	*Reviewer Comments*
(b) (6)	84/M	Renal failure	Coronary artery disease, hypertension, edema peripheral, cardiac AICD insertion, prostate cancer, coronary bypass graft, angina pectoris, atrial fibrillation, superficial femoral arterial stenosis, peripheral vascular disease	*Occurred cycle 1 day 1. Pre-dose creatinine was high and with age did not meet eligibility criteria, high WBC count and hypotension suspicious for sepsis.*
	81/F	Neutropenic sepsis	Pneumonia, cholecystectomy pancreatic stent	*Occurred in cycle 4. Pseudomonas sepsis.*
	86/M	Bacterial sepsis	None	*Occurred in cycle 1. Pseudomonas and enterobacter sepsis*
	82/F	Fall	DVT, fatigue, type II diabetes mellitus, polymyalgia rheumatica, leg pain, anxiety, sarcoma excision	*Occurred in cycle 1. Accompanied by Grade 3 dehydration, rash due to gemcitabine, on lovenox for DVT, fell and resulted in intracerebral hematoma. Cause of death was hematoma due to fall while being on anticoagulants*

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SUB ID*	Age/ Sex	Cause of Death by PT	Comorbid conditions	*Reviewer Comments*
(b) (6)	54/F	Pneumonia	Diabetes mellitus, lung metastases, gastroesophageal reflux disease, deep venous thrombosis, asthma (on inhaled corticosteroids)	*Occurred in cycle 4. Cause of death may have been pneumonitis as consolidation not described on imaging and no fever. Patient not neutropenic.*
	66/M	Hepatic function abnormal	Jaundice, liver metastases, hypokalemia, bile duct stent insertion, diabetes.	*Occurred in cycle 3. Also experienced Grade 4 anemia. Fractionation results for bilirubin not provided? 3 weeks after receiving 4 units of PRBC, ALT normal AST high? Also had Grade 3 renal failure? Could not rule out microangiopathic hemolytic anemia based on the report,*
	53/F	Upper GI hemorrhage	History of upper GI hemorrhage, peptic ulcer, pancreatitis, anastomotic ulcer, was on warfarin for atrial fibrillation, esophagitis, gallstones, carcinoma breast, gastric bypass.	*Received only one dose of study drugs. Cause of hemorrhage was anastomotic ulcer.*
	67/M	Multi-organ failure	Hypertension, diabetes mellitus, atrial fibrillation, deep vein thrombosis	*Occurred after cycle 2 while off study and on capecitabine, associated with ascites.*

SUB ID*	Age/ Sex	Cause of Death by PT	Comorbid conditions	*Reviewer Comments*
(b) (6)	75/F	General physical health deterioration	Type 2 diabetes mellitus, hypertension	*Occurred after 1 dose of study medication, associated with Grade 4 decrease in vision and confusional state*
	60/F	Intestinal perforation	None	*Occurred in cycle 1, investigator felt that perforation was due to disease*

*Last 4 numbers only

Reviewer Conclusions Regarding Deaths in Study CA046
In study CA046, most of the deaths in both arms (occurring within 30 days of drug treatment and thereafter) were attributed to progressive disease. Nevertheless, this regimen can cause severe and life-threatening toxicities and the Warnings section of the label should include information in regards to severe and potentially fatal sepsis.

7.3.2 Nonfatal Serious Adverse Events

Table 26 summarizes the overall incidence of AEs and SAEs that were reported during the CA046 trial. The table shows that SAEs and ≥ Grade 3 events occurred more frequently among Abraxane-treated patients.

Table 26: Summary of Treatment Emergent Adverse Events (TEAE)

Subject description	ABI-007 + Gemcitabine N=421	Gemcitabine N=402
Subjects who experienced at least one AE*	417 (99%)	395 (98%)
Subjects who experienced at least one Treatment Related AE	403 (96%)	371 (92%)
Subjects who experienced at least one SAE‡	212 (50%)	172 (43%)
Subjects who experienced at least one Treatment Related SAE	121 (29%)	53 (13%)
Subjects who experienced at least one AE Grade 3 or higher	374 (89%)	303 (75%)
Subjects with at least one AE Leading to Treatment Discontinuation	149 (35%)	95 (24%)
Subjects with at least one AE	18 (4%)	18 (4%)

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Subject description	ABI-007 + Gemcitabine N=421	Gemcitabine N=402
Leading to Death		

[‡]SAE=Serious AE
[*]AE=Adverse event

Adverse events were analyzed by the applicant in terms of TEAEs, which were defined as any AEs that began or worsened in severity after the start of study drug through 30 days after the last dose of study drug or end of treatment, whichever was later. All AEs were coded using MedDRA V15.0.

The applicant defined serious adverse event (SAE) in the protocol as any adverse event that met the following criteria:

- Fatal;
- Life-threatening
- Resulted in persistent or significant disability or incapacity;
- Required in-patient hospitalization or prolongs an existing hospitalization. (Exception: Hospitalization for elective treatment of a pre-existing condition that did not worsen during the study was not considered an adverse event.
- Was a congenital anomaly/birth defect in the offspring of a patient who received medication
- Conditions not included in the above definitions that may have jeopardized the patient or required intervention to prevent one of the outcomes listed above unless clearly related to the patient's underlying disease.

This definition of SAE was in accordance with ICH E6 Good Clinical Practice Guidelines.

Two hundred and twelve patients (50%) in the Abraxane/Gemcitabine arm and 172 (43%) patients on the Gemcitabine arm experienced a total of 772 SAE's. Table 27 and Table 28 below display the SAE's experienced by SOC and PT.

Table 27:-SAE incidence by MedDRA SOC and Treatment Arm (per-patient analysis) arranged in order of increasing Risk Difference (RD)

MedDRA.v.15.0	ABI-007/Gemcitabine (N = 421)			Gemcitabine (N = 402)			ABI-007/Gemcitabine vs. Gemcitabine		
SOC*	Events	N	%	Events	N	%	RD	RR	OR
Infections and infestations	85	66	15.7	44	35	8.7	7.0	1.8	1.9
Blood and lymphatic system disorders	34	32	7.6	11	10	2.5	5.1	3.1	3.2
Gastrointestinal disorders	102	67	15.9	71	45	11.2	4.7	1.4	1.5
General disorders and administration site conditions	51	42	10.0	36	27	6.7	3.3	1.5	1.5
Metabolism and nutrition disorders	33	29	6.9	23	17	4.2	2.7	1.6	1.7
Hepatobiliary disorders	31	24	5.7	18	16	4.0	1.7	1.4	1.5
Skin and subcutaneous tissue disorders	2	2	0.5	0	0	0.0	0.5	4.8	4.8
Eye disorders	1	1	0.2	0	0	0.0	0.2	2.9	2.9
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4	4	1.0	3	3	0.8	0.2	1.3	1.3
Respiratory, thoracic and mediastinal disorders	37	34	8.1	33	32	8.0	0.1	1.0	1.0
Musculoskeletal and connective tissue disorders	3	3	0.7	4	3	0.8	0.0	1.0	1.0
Injury, poisoning and procedural complications	4	4	1.0	4	4	1.0	0.0	1.0	1.0
Investigations	9	5	1.2	7	5	1.2	-0.1	1.0	1.0
Psychiatric	6	6	1.4	6	6	1.5	-0.1	1.0	1.0

MedDRA.v.15.0	ABI-007/Gemcitabine (N = 421)			Gemcitabine (N = 402)			ABI-007/Gemcitabine vs. Gemcitabine		
SOC*	Events	N	%	Events	N	%	RD	RR	OR
disorders									
Renal and urinary disorders	6	6	1.4	9	7	1.7	-0.3	0.8	0.8
Cardiac disorders	11	9	2.1	12	12	3.0	-0.9	0.7	0.7
Nervous system disorders	15	13	3.1	20	16	4.0	-0.9	0.8	0.8
Vascular disorders	14	14	3.3	23	21	5.2	-1.9	0.6	0.6

*Secondary preferred terms excluded
RD=Risk Difference
OR=Odds ratio
RR=Relative Risk

Reviewers Comment:-*A higher proportion of patients in the Abraxane arm experienced SAE's in the Gastrointestinal (15.9%) and Infections and Infestations (15.7%) SOCs. The SOC that had the greatest risk difference between the arms was also the Infections and infestations SOC indicating higher susceptibility to infections on the Abraxane arm. The PTs that constituted this difference in this SOC pneumonia, cellulitis, urinary tract infection, sepsis and septic shock.*

Table 28: SAEs by Preferred Term with a per-patient incidence of more than 1% by arm

MedDRA.v.15.0	ABI-007/Gemcitabine (N = 421)			Gemcitabine (N = 402)			ABI-007/Gemcitabine vs. Gemcitabine		
Preferred Term	Events	N	%	Events	N	%	RD	RR	OR
Pyrexia	30	27	6.4	10	9	2.2	4.2	2.9	3.0
Dehydration	20	20	4.8	12	12	3.0	1.8	1.6	1.6
Vomiting	23	18	4.3	13	12	3.0	1.3	1.4	1.5
Pneumonia	18	17	4.0	11	11	2.7	1.3	1.5	1.5
Pulmonary embolism	13	13	3.1	20	20	5.0	-1.9	0.6	0.6
Febrile neutropenia	11	11	2.6	2	2	0.5	2.1	5.3	5.4
Nausea	15	11	2.6	8	8	2.0	0.6	1.3	1.3
Abdominal pain	13	11	2.6	13	10	2.5	0.1	1.1	1.1
Cholangitis	12	10	2.4	5	5	1.2	1.1	1.9	1.9

MedDRA.v.15.0	ABI-007/Gemcitabine (N = 421)			Gemcitabine (N = 402)			ABI-007/Gemcitabine vs. Gemcitabine		
Preferred Term	Events	N	%	Events	N	%	RD	RR	OR
Anemia	9	9	2.1	2	2	0.5	1.6	4.3	4.4
Diarrhea	9	9	2.1	3	3	0.8	1.4	2.9	2.9
Deep vein thrombosis	9	9	2.1	13	12	3.0	-0.9	0.7	0.7
Cellulitis	9	8	1.9	5	5	1.2	0.7	1.5	1.5
Pleural effusion	7	7	1.7	5	5	1.2	0.4	1.3	1.3
Urinary tract infection	9	6	1.4	1	1	0.3	1.2	5.7	5.8
Edema peripheral	6	6	1.4	3	3	0.8	0.7	1.9	1.9
Decreased appetite	5	5	1.2	0	0	0.0	1.2	10.5	10.6
Dyspnea	5	5	1.2	2	2	0.5	0.7	2.4	2.4
Constipation	5	5	1.2	6	6	1.5	-0.3	0.8	0.8
Sepsis	5	5	1.2	7	5	1.2	-0.1	1.0	1.0
Intestinal obstruction	4	4	1.0	1	1	0.3	0.7	3.8	3.8
Jaundice	4	4	1.0	1	1	0.3	0.7	3.8	3.8
Neutropenia	4	4	1.0	1	1	0.3	0.7	3.8	3.8
Pneumonitis	4	4	1.0	1	1	0.3	0.7	3.8	3.8
Small intestinal obstruction	4	4	1.0	2	1	0.3	0.7	3.8	3.8
Interstitial lung disease	4	4	1.0	2	2	0.5	0.5	1.9	1.9
Ascites	4	4	1.0	5	5	1.2	-0.3	0.8	0.8
Septic shock	4	4	1.0	5	5	1.2	-0.3	0.8	0.8
Bile duct obstruction	5	4	1.0	3	3	0.8	0.2	1.3	1.3
Jaundice cholestatic	4	4	1.0	3	3	0.8	0.2	1.3	1.3

RD=Risk Difference
OR=Odds ratio
RR=Relative Risk

_Reviewers Comment:-__The most frequently reported SAE on the Abraxane arm was Pyrexia (6.4%). The SAEs that had the greatest difference in incidence between the two arms were pyrexia, febrile neutropenia, dehydration, anemia, diarrhea, pneumonia and vomiting._

7.3.3   Dropouts and/or Discontinuations

Study CA046
The analysis dataset ADAE was used to analyze the adverse events that led to Abraxane discontinuation. Overall the reasons for drug discontinuation on both arms are summarized in Table 29.

Table 29: Reasons for Patient Discontinuation in Study CA046

Reason for Drug Discontinuation	ABI-007/Gemcitabine (N=421)		Gemcitabine (N=402)	
	N	%	N	%
Adverse event	42	11%	44	11%
Other	7	2%	10	3%
Physician decision	25	6%	18	5%
Progressive disease	196	50%	245	63%
Protocol violation	10	3%	6	2%
Unacceptable toxicity	86	22%	29	7%
Withdrawal by subject	29	7%	38	10%

In both arms, the majority of the patients discontinued therapy due to disease progression with a higher proportion of patients discontinuing due to disease progression on the gemcitabine arm. Despite the results presented in the table above, a higher proportion of patients in the Abraxane arm discontinued therapy due to adverse events or unacceptable toxicity according to the disposition datasets.

Reviewers Comment:-*The difference in the percentage of patients who discontinued drug due to toxicity between the study arms suggests that this is a regimen that has real side effects and results in considerable morbidity compared to single agent gemcitabine alone.*

An analysis of the specific MedDRA PT's that were associated with study drug discontinuation on either arm is shown in Table 30.

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*Reviewers Comment:-*As seen below the most common adverse event that led to the permanent discontinuation of Abraxane was peripheral neuropathy (8% of the treated population).

Table 30: Adverse events analyzed by MedDRA PT that led to drug discontinuation in >1% of the treated population

Reason for Drug Discontinuation (MedDRA PT)	ABI-007/Gemcitabine (N=421)		Gemcitabine(N=402)	
	N	%	N	%
Peripheral neuropathy(SMQ)	34	8	0	0
Fatigue	16	4	2	<1
Thrombocytopenia	10	2	10	2
Asthenia	6	1	3	<1
Pneumonia	6	1	3	<1
Nausea	5	1	8	2

7.3.4 Significant Adverse Events

The ICH E3 guidance recommends that marked laboratory abnormalities not meeting the definition of serious adverse events also be considered significant adverse events. These laboratory abnormalities are described in Section 7.4.2 of this review.

In addition, the ICH E3 guidance considers other potentially important abnormalities that do not meet the definition of a serious adverse event be considered potentially significant. A discussion of severe adverse events (i.e., ≥ Grade 3 by CTCAE) is included in section 7.3.5 of this review.

Using FDA MAED software, narrow scope MedDRA SMQs were analyzed to look for additional safety signals not identified through analyses of adverse events by MedDRA system organ class, high level term, or preferred term.

Table 31: Per Patient incidence of Adverse Events by Narrow scope MedDRA SMQ in Study CA046

SMQ (Narrow Search)	ABI-007 / Gemcitabine(N = 421)			Gemcitabine(N = 402)			RD (per hundred)
	Events	Number of subjects	Proportion (%)	Events	Number of subjects	Proportion (%)	
(1) Gastrointestinal nonspecific inflammation and dysfunctional conditions	1685	343	81.5	1093	303	75.4	6.1
(2) Gastrointestinal nonspecific symptoms and therapeutic procedures	1622	339	80.5	1046	300	74.6	5.9
(1) Hematopoietic cytopenias	1384	238	56.5	865	203	50.5	6.03
(1) Hemodynamic edema, effusions and fluid overload *	465	216	51.3	262	142	35.3	15.98
(2) Hematopoietic leukopenia	914	213	50.6	515	147	36.6	14.03
(1) Peripheral neuropathy	527	212	50.4	36	31	7.7	42.64
(2) Hematopoietic thrombocytopenia	463	150	35.6	341	137	34.1	1.55
(1) Hepatic disorders	318	104	24.7	257	100	24.9	-0.17
(2) Drug related hepatic disorders - comprehensive search	313	100	23.8	252	97	24.1	-0.38
(1) Hemorrhages	144	99	23.5	68	54	13.4	10.08
(2) Hemorrhage terms (excl laboratory terms) *	144	99	23.5	68	54	13.4	10.08

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SMQ (Narrow Search)	ABI-007 / Gemcitabine(N = 421)			Gemcitabine(N = 402)			
	Events	Number of subjects	Proportion (%)	Events	Number of subjects	Proportion (%)	RD (per hundred)
(3) Liver related investigations, signs and symptoms	291	91	21.6	231	87	21.6	-0.03
(1) Oropharyngeal disorders *	153	91	21.6	69	56	13.9	7.68
(1) Embolic and thrombotic events *	104	82	19.5	121	82	20.4	-0.92
(1) Taste and smell disorders *	89	69	16.4	40	33	8.2	8.18
(2) Oropharyngeal lesions, non-neoplastic, non-infectious and non-allergic *	97	64	15.2	44	39	9.7	5.5
(2) Embolic and thrombotic events, venous *	81	63	15.0	87	62	15.4	-0.46
(1) Depression and suicide/self-injury	60	53	12.6	24	24	6.0	6.62
(2) Depression (excl suicide and self-injury)	59	52	12.4	24	24	6.0	6.38
(1) Biliary disorders	98	50	11.9	103	49	12.2	-0.31
(2) Functional, inflammatory and gallstone related biliary disorders	97	49	11.6	102	48	11.9	-0.3
(2) Gastrointestinal nonspecific dysfunction	54	48	11.4	42	39	9.7	1.7
(1) Gastrointestinal perforation, ulceration, hemorrhage or	60	47	11.2	39	29	7.2	3.95

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SMQ (Narrow Search)	ABI-007 / Gemcitabine(N = 421)			Gemcitabine(N = 402)			RD (per hundred)
	Events	Number of subjects	Proportion (%)	Events	Number of subjects	Proportion (%)	
obstruction							
(2) Oropharyngeal infections *	54	42	10.0	23	20	5.0	5

The applicant identified adverse events of interest all of which are described in submission specific adverse events in Section 7.3.5.

7.3.5   Submission Specific Primary Safety Concerns

The applicant's definition of adverse events of interest included adverse events "that were selected for further analysis because of their frequency of occurrence or severity and association with treatment in patients with other types of cancer, gemcitabine treatment, or the underlying disease state."

Neutropenia
The applicant reported events of neutropenia as adverse events (by MedDRA PT) and Grade 3 and 4 neutropenia based on central laboratory values.

Neutropenia was reported as the HLT of "neutropenias" (including the preferred terms of neutropenia, febrile neutropenia and agranulocytosis) in 43% of patients on the Abraxane arm and 30% of patients on the gemcitabine-alone arm. These events were Grade 3 or higher in 35% of subjects in the Abraxane/gemcitabine arm and in 22% of patients in the gemcitabine-alone arm. Less than 1% of patients on both arms had drug permanently discontinued due to neutropenia. The incidence of patients who had dose delays for neutropenia was higher for both drugs on the combination arm (16% for Abraxane and 18% for gemcitabine) than the gemcitabine arm (11 %). Dose reductions for neutropenia for Abraxane were reported for 10% of patients on the combination arm. Dose reductions for neutropenia for gemcitabine was reported in 19% of patients on the combination arm and 13% on the gemcitabine alone arm.

Reviewers Comment:-*This reviewer feels that the incidence of neutropenia is better represented by the central laboratory value analysis and hence these incidence rates have been included in the adverse reactions section of the label. Please see Section 7.4.2 for a discussion on the incidence of neutropenia based on central laboratory values.*

Febrile neutropenia
Febrile neutropenia was reported as a MedDRA PT in 3% of patients on the combination arm and 1% of patients on the gemcitabine alone arm. These events were

Grade 3 in 2% of patients and Grade 4 in 1% of patients on the Abraxane arm. There were no deaths attributed to the PT of febrile neutropenia although one death did occur due to neutropenic sepsis on the Abraxane arm and is discussed in the section of sepsis below.

__Reviewers Comment:-__This reviewer notes that the applicant was using an older version of the NCI-CTCAE for toxicity grading for study CA046. Per the latest version of the CTCAE v 4.0 febrile neutropenia is by definition grade 3 or higher.

Thrombocytopenia
The incidence of the PT of thrombocytopenia was 30% for all grades on the Abraxane arm and 29% on the gemcitabine arm. The incidence of Grade 3 and higher thrombocytopenia was 13% on the combination arm vs. 8% on the gemcitabine-alone arm.

__Reviewers Comment: -__ This reviewer feels that the incidence of thrombocytopenia is better represented by the central laboratory value analysis and hence these incidence rates have been included in the adverse reactions section of the label. Please see Section 7.4.2 for a discussion on the incidence of thrombocytopenia based on central laboratory values.

Bleeding Events
The incidence of bleeding events was analyzed by the applicant grouping several preferred terms across SOC's. The incidence of bleeding events (all grades) was 23% on the combination arm vs.13% on the gemcitabine arm. The incidence of grade 3 and higher hemorrhagic events using the narrow scope MedDRA SMQ was 3% on either arm.

__Reviewers Comment:-__This reviewer preferred to analyze this adverse event using the narrow scope MedDRA SMQ. The rates were similar to those obtained by the applicant. In this reviewer's opinion, the higher rates of hemorrhagic events for all grades was probably due to the higher rates of grade 1 and 2 epistaxis reported in the Abraxane arm. This might be a result of the dryness and congestion of the nasal mucosa that can occur following the use of taxanes.

<u>Sepsis:</u>
The applicant utilized a collection of 87 preferred terms in MedDRA.v.15.0 for the search strategy for this adverse event. The incidence of adverse events in the Infections and infestations SOC was 49% for the Abraxane arm and 32% for the gemcitabine arm. The incidence in the Infections and Infestations SOC for adverse events Grade 3 and higher was 16% in the Abraxane arm and 9% in the Gemcitabine arm.

__Reviewers Comment:-__This reviewer agrees that the applicant's search strategy appeared comprehensive. Nevertheless, sepsis is a broad term and was not defined.

For the purposes of this review, this reviewer conducted a sensitivity analysis and analyzed the cases of sepsis as defined in CTCAE V 4.0 (i.e., Grade 4 with Life-threatening consequences; urgent intervention indicated). The table below gives a listing of all the infection PT's and their per-patient incidence. Shaded PT's represent those with a Grade 4 event, representing a case that potentially satisfied the CTCAE definition of sepsis.

Table 32: Incidence of sepsis related events

Preferred Term	Abraxane +Gem All grades		Gem All grades		Abraxane +Gem (Grade 4)	Gem (Grade 4)
	N	%	N	%	N	%
Urinary tract infection	40	10	15	4	0	0
Oral candidiasis	34	8	15	4	0	0
Pneumonia	28	7	19	5	1	0
Cellulitis	28	7	18	4	0	0
Upper respiratory tract infection	20	5	10	2	0	0
Sinusitis	18	4	5	1	0	0
Nasopharyngitis	11	3	7	2	0	0
Lower respiratory tract infection	10	2	7	2	0	0
Rhinitis	9	2	8	2	0	0
Device related infection	9	2	1	<1	0	0
Sepsis	7	2	7	2	0	2
Oral herpes	7	2	4	1	0	0
Clostridial infection	6	1	2	<1	0	0
Catheter site infection	5	1	3	1	0	0
Bronchitis	5	1	3	1	0	0
Liver abscess	4	1	5	1	0	0
Septic shock	4	1	5	1	3	2
Cystitis	4	1	5	1	0	0
Clostridium difficile colitis	4	1	3	1	0	0
Influenza	4	1	2	<1	0	0
Lung infection	4	1	0	0	0	0

Preferred Term	Abraxane +Gem All grades		Gem All grades		Abraxane +Gem (Grade 4)	Gem (Grade 4)
	N	%	N	%	N	%
Respiratory tract infection	3	1	6	1	0	0
Pharyngitis	3	1	1	<1	0	0
Folliculitis	3	1	0	0	0	0
Tooth infection	3	1	0	0	0	0
Bacterial sepsis	3	1	0	0	0	0
Gastroenteritis	2	<1	2	<1	0	0
Diverticulitis	2	<1	1	<1	0	0
Skin infection	2	<1	1	<1	0	0
Erysipelas	2	<1	1	<1	0	0
Onychomycosis	2	<1	0	0	0	0
Klebsiella bacteremia	2	<1	0	0	0	0
Neutropenic sepsis	2	<1	0	0	1	0
Urosepsis	2	<1	0	0	0	0
Rash pustular	2	<1	0	0	0	0
Laryngitis	2	<1	0	0	0	0
Respiratory tract infection viral	1	<1	2	<1	0	0
Vulvovaginal candidiasis	1	<1	1	<1	0	0
Vulvovaginal mycotic infection	1	<1	1	<1	0	0
Infection	1	<1	1	<1	0	0
Furuncle	1	<1	1	<1	0	0
Staphylococcal infection	1	<1	1	<1	0	0
Tinea pedis	1	<1	1	<1	0	0
Tracheobronchit is	1	<1	1	<1	0	0
Infectious peritonitis	1	<1	0	0	0	0
Pancreatic abscess	1	<1	0	0	0	0
Perihepatic abscess	1	<1	0	0	0	0

Preferred Term	Abraxane +Gem All grades		Gem All grades		Abraxane +Gem (Grade 4)	Gem (Grade 4)
	N	%	N	%	N	%
Perirectal abscess	1	<1	0	0	0	0
Catheter site cellulitis	1	<1	0	0	0	0
Cellulitis of male external genital organ	1	<1	0	0	0	0
Pneumonia bacterial	1	<1	0	0	0	0
Skin bacterial infection	1	<1	0	0	0	0
Urinary tract infection bacterial	1	<1	0	0	0	0
Osteomyelitis	1	<1	0	0	0	0
Hepatic candidiasis	1	<1	0	0	0	0
Tooth abscess	1	<1	0	0	0	0
Ear infection	1	<1	0	0	0	0
Otitis media	1	<1	0	0	0	0
Enterococcal infection	1	0	0	0	0	0
Urinary tract infection enterococcal	1	<1	0	0	0	0
Escherichia bacteremia	1	<1	0	0	0	0
Eyelid infection	1	<1	0	0	0	0
Hordeolum	1	<1	0	0	0	0
Vaginal infection	1	<1	0	0	0	0
Fungal skin infection	1	<1	0	0	0	0
Biliary sepsis	1	<1	0	0	0	0

Preferred Term	Abraxane +Gem All grades		Gem All grades		Abraxane +Gem (Grade 4)	Gem (Grade 4)
	N	%	N	%	N	%
Localized infection	1	<1	0	0	0	0
Postoperative wound infection	1	<1	0	0	0	0
Legionella infection	1	<1	0	0	0	0
Bronchopneumo nia	1	<1	0	0	0	0
Pneumonia primary atypical	1	<1	0	0	0	0
Orchitis	1	<1	0	0	0	0
Pneumocystis jiroveci pneumonia	1	<1	0	0	0	0
Pseudomonal sepsis	1	<1	0	0	0	0
Salmonellosis	1	<1	0	0	0	0
Bacteremia	1	<1	0	0	0	0
Erysipeloid	1	<1	0	0	0	0
Nail bed infection	1	<1	0	0	0	0
Nail infection	1	<1	0	0	0	0
Soft tissue infection	1	<1	0	0	0	0
Wound infection staphylococcal	1	<1	0	0	0	0
Tinea cruris	1	<1	0	0	0	0
Chronic sinusitis	1	<1	0	0	0	0
Gastroenteritis viral	1	<1	0	0	0	0
Gastrointestinal viral infection	1	<1	0	0	0	0

Preferred Term	Abraxane +Gem All grades		Gem All grades		Abraxane +Gem (Grade 4)	Gem (Grade 4)
	N	%	N	%	N	%
Vestibular neuronitis	1	<1	0	0	0	0

The most common infection/sepsis-related events were urinary tract infection, oral candidiasis, pneumonia, cellulitis, upper respiratory tract infection, sinusitis, nasopharyngitis, lower respiratory tract infection, rhinitis, device related infection, sepsis, oral herpes. The infection events that were associated with Grade 4 severity included pneumonia, septic shock and neutropenic sepsis.

Reviewers Comment:-*This reviewer notes that these three shaded preferred terms were included in the applicant's calculation of the incidence of sepsis and was included in the proposed label (as a Warning under the term sepsis).*

There were 7 patients who died due to sepsis (5 on the Abraxane arm and 2 on the Gemcitabine arm). There were two deaths due to sepsis and one death, each due to the terms bacterial sepsis, neutropenic sepsis and septic shock on the Abraxane arm. The two patients on the Gemcitabine arm died of septic shock. Based on these events, the sponsor made revisions to the protocol intended to decrease the incidence and severity of sepsis (refer to Section 5.3.1.10 of this review).

Pneumonitis
The sponsor analyzed pneumonitis using the broad scope SMQ for interstitial lung disease.

The incidence of interstitial lung disease was 4% on the Abraxane arm and 1% on the gemcitabine arm-alone. The incidence of Grade 3 or higher pneumonitis on the Abraxane arm was 2% versus 1% on the gemcitabine arm. Two patients died on the Abraxane arm due to pneumonitis (narratives and reviewer comments are in Table 25).

Reviewers Comment:-*In addition this reviewer feels that pneumonitis may have contributed to the death of one additional patient (patient* (b) (6) *in Table 25). The sponsor also described one additional patient on the Abraxane arm that died due to progressive disease who had ongoing pneumonitis.*

Peripheral neuropathy
The events related to peripheral neuropathy were analyzed using the peripheral neuropathy SMQ MedDRA v15.0 and included the terms burning sensation, dysesthesia, gait disturbance, hypoesthesia, hyporeflexia, muscle atrophy, muscular

weakness, and neuralgia neuropathy peripheral, neurotoxicity, paraesthesia, peripheral motor neuropathy peripheral sensorimotor neuropathy, peripheral sensory neuropathy, peroneal nerve palsy, polyneuropathy, sensory loss, and skin burning sensation.

Neuropathy is an important safety concern with Abraxane and has been observed in previous trials that have been conducted with Abraxane in the already approved indications of breast cancer and non-small cell lung cancer. Peripheral neuropathy SMQ was the most common adverse event leading to study drug discontinuation in study CA046 (8% of patients). The incidence of all grades of peripheral neuropathy was 54% in the Abraxane arm and 13% in the gemcitabine arm. The incidence of Grade 3 peripheral neuropathy was 17% in the Abraxane arm vs. 1% in the gemcitabine arm. There were no reports of Grade 4 peripheral neuropathy in study CA046.

The incidence of peripheral neuropathy was related to the cumulative exposure to Abraxane. The incidence of Grade 3 neuropathy in patients who received up to 3 cycles of Abraxane was 7% and increased to 12% for patients who received up to 6 cycles.

The applicant performed an analysis of the time to first occurrence of Grade 3 neuropathy and the time to improvement after the occurrence of Grade 3 neuropathy. The time to occurrence of first Grade 3 neuropathy was 140 days on the Abraxane arm and the time to improvement in the Grade 3 neuropathy to Grade 1 or better was seen in 43% of patients with a median time to improvement of 29 days.

Table 33: Applicant's analysis of time to first occurrence of Grade 3 neuropathy and time to improvement

	ABI-007/ Gemcitabine (N=421)	Gemcitabine (N=402)
Number of Patients with at least one Grade 3 Peripheral Neuropathy[a]	70 (17%)	3 (1%)
Time to First Grade 3 Peripheral Neuropathy (Days)[b]		
Number of patients	70	3
Mean	142.5	117.7
STDEV	76.86	65.13
Median	140.0	113.0
Min, Max	9, 336	55, 185
Time to Improvement by at Least 1 Grade[c]		
Number of Patients	44 (63%)	1 (33%)
Median Time to Improvement (days)	21.0	29.0

	ABI-007/ Gemcitabine (N=421)	Gemcitabine (N=402)
95% Confidence Interval	17.00, 28.00	NE
Time to Improvement to Grade 1 or Better[d]		
Number of Patients	30 (43%)	0
Median Time to Improvement (days)	29.0	-
95% Confidence Interval	22.00, 86.00	NE

[a] There were no reports of >Grade 3 peripheral neuropathy AEs. [b] Time to onset was defined as the time from the first dose of study drug to the first occurrence of Grade 3 peripheral neuropathy [c] Time to improvement was defined as the time from the first occurrence of Grade 3 peripheral neuropathy to improvement by at least 1 grade. Patients not experiencing improvement were censored at the last time the patients were evaluated for adverse events [d] Time to improvement was defined as the time from the first occurrence of Grade 3 or higher peripheral neuropathy to improvement to Grade1 or better. Patients not experiencing improvement to Grade 1 or better were censored at the last time the patients were evaluated for adverse events.

Cranial nerve palsies: There were two patients in study CA046 who developed facial nerve paralysis that was reported using the preferred terms of facial nerve disorder and seventh nerve paralysis (patient _____ (b) (6) and patient _____ (b) (6)).

Gastrointestinal Adverse Events

The applicant selected certain preferred terms to be used to analyze under this heading that included nausea, diarrhea, vomiting, small intestinal obstruction, colitis, retching, and regurgitation.

Reviewers Comment:-This reviewer preferred to analyze all the preferred terms under this SOC instead of selecting within the SOC.

The total incidence of these preferred terms for all grades was 73% in the Abraxane arm and 62% in the gemcitabine arm. The incidence of Grade 3 and 4 events of these selected PT's under this SOC was 15% on the Abraxane arm and 7% on the gemcitabine arm. The overall incidence of adverse events under this SOC was 84% on the Abraxane arm and 78% on the gemcitabine arm. The PT's that occurred with the highest frequency under this SOC were nausea, vomiting, diarrhea and constipation, similar to those seen with previous clinical trials of Abraxane. No deaths on either arm were attributed to gastrointestinal AE's. The incidence of Grade 3 and 4 diarrhea was higher in the Abraxane arm (6% vs. 1%). Consequently, the incidence of dehydration and the use of antidiarrheals and intravenous fluids were also higher on the Abraxane arm. However, the incidence of the other common PT's of nausea and vomiting was similar in both arms.

Myalgia and Arthralgia

A well-recognized taxane related toxicity, the incidence of arthralgia was higher on the Abraxane arm than the gemcitabine arm (11% vs. 3%). However the incidence of grade 3 and 4 arthralgia was low in both arms (1%). There was only one patient who had arthralgia that was considered an SAE and was of CTCAE Grade2. However, per the applicants report this patient recovered completely and the adverse event was thought by the investigator to not be related to the study drug.

Reviewers Comment:-*Although this patient had an SAE related to arthralgia the CTCAE grade was only grade 2. Hence, this event could be considered an isolated event.*

Depression

Depression has been associated with the diagnosis of pancreatic cancer and its dismal prognosis. The applicant did not analyze this preferred term separately although there was a difference of 6% in the incidence rates between the two treatment arms for all grades. This preferred term was included in the label. However, there was only one patient who had a grade 3 or higher event of depression and this patient was on the Abraxane arm. Hence, there was not a significant difference in the incidence of Grade 3 and higher depression events.

Hypersensitivity Reaction

There were no episodes of hypersensitivity reactions to the drug reported by the applicant in the study report of study CA046.

Cardiotoxicity

The incidence of cardiotoxicity adverse events was similar between the two treatment arms (5% vs.4%). The most frequently reported cardiac adverse event on the Abraxane arm was tachycardia (4%).

Stevens- Johnson Syndrome or Toxic Epidermal Necrolysis

There were no occurrences of Stevens-Johnson syndrome reported among the 823 patients enrolled in the trial.

Peripheral Edema, Generalized Edema, and Edema

This adverse event occurs with taxanes and the incidence of the HLT edema NEC was 46% on the Abraxane arm vs. 31% on the gemcitabine arm. There was also a 4% incidence of Grade 3 and 4 events under this HLT on the Abraxane arm.

Hepatotoxicity

Both treatment arms reported adverse events of alanine aminotransferase increased (11% in the ABI-007/gemcitabine arm and 9% in the gemcitabine-alone arm) and an increased aspartate aminotransferase (9% in both arms). The incidence of the HLGT hepatic and hepatobiliary disorders was 8% on the Abraxane arm and 10% on the

gemcitabine arm. The rates of Grade 3 and 4 events in the hepatobiliary disorders SOC was 7% on the Abraxane arm and 8% on the gemcitabine arm.

Renal Toxicity
The incidence of adverse events under the SOC of renal and urinary disorders was 11% on both the arms. The incidence of the HLT Renal failure and impairment was also similar between the two arms (3% vs. 2 %). The rates of Grade 3 and 4 events under this HLT were also similar (2%) on both study arms.

Hemolytic Uremic Syndrome
There were two patients who were reported to have an adverse event of hemolytic uremic syndrome (PT) on the Abraxane arm versus one patient on the gemcitabine arm.

__Reviewers Comment:-__HUS is a labeled adverse reaction following the use of gemcitabine. One additional case in the Abraxane arm was not sufficient to conclude that this event was likely to be related to Abraxane (in the setting of concomitant gemcitabine treatment).

Cystoid Macular Edema
There was one patient who developed cystoid macular edema in Study CA046 on the Abraxane arm; no patients on the gemcitabine arm were reported to have this adverse event.

__Reviewers Comment:-__This rare adverse event was included in product labeling in the pancreatic cancer section because cystoid macular edema is listed as an adverse reaction in the post-marketing setting.

7.4   Supportive Safety Results

7.4.1   Common Adverse Events

In Study CA046, the treated population consisted of 823 patients excluding the 38 patients who did not receive the study drugs. These patients were included in the ITT analysis but excluded from the safety analysis.

In this review, common adverse events were evaluated in the treated population based upon preferred term, high level term, and high level group term levels of the MedDRA hierarchy. The most common adverse events (>10%) on the combination arm were bone marrow suppression (anemia, neutropenia/leukopenia, thrombocytopenia), alopecia, gastrointestinal events (nausea, diarrhea, vomiting, constipation, nausea,dysgeusia), constitutional events (fatigue, asthenia, anorexia, weight loss, fever, peripheral edema, dehydration), pain-related events (headache, extremity pain, abdominal pain, arthralgia, myalgia), respiratory events (dyspnea, cough), neurologic

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events (insomnia, dizziness, depression, paraesthesia, and peripheral sensory neuropathy), and laboratory abnormalities (hypokalemia, ALT increased).

_Reviewers Comment:-__In the proposed label for Abraxane, the applicant used the SMQ for peripheral neuropathy (Broad scope MedDRA V 15.0) to summarize the AE._

In study CA046, a total of 16,437 events were analyzed from 823 patients in the treated population. There were 16,381 treatment emergent events. Fifty six events in the database were considered non-treatment emergent by the applicant. Five of the 56 non-treatment emergent events occurred prior to the first dose of study drug. Fifty one adverse events were reported by the applicant to have occurred after 30 days of the last dose of the study drug and hence were considered non-TEAEs. Twenty seven of these events occurred in patients receiving Abraxane and gemcitabine and twenty four occurred in patients receiving gemcitabine alone. Non-TEAEs in the database that were ≥ Grade 3 in severity (by MedDRA PT associated) are shown in Table 34.

Table 34: Adverse Events of ≥ Grade 3 Severity Occurring More Than 30 days After Cessation of ABI-007/Gemcitabine Therapy (Classified as Non-treatment Emergent by the Applicant)

USUBJID*	MedDRA PT	Days since last Abraxane dose	CTCAE Grade	Outcome	Considered related by investigator
(b) (6)	Clostridium difficile colitis	33	3	Recovered / Resolved	No
	Liver abscess	35	3	Recovered / Resolved	No
	Hypoglycemia	37	4	Recovered / Resolved	No
	Renal failure acute	36	3	Recovered / Resolved	No
	Dehydration	58	3	Ongoing at time of death	No
	Failure to thrive	58	5	Fatal	No

*Last four digits

_Reviewers Comment__:-The number of Grade 3 or greater non-TEAE events were few and included only two adverse events ongoing at the time of a patient's death. In this reviewer's opinion, it is unlikely that the omission of these six adverse events substantially impacted the analysis of safety._

Table 35 lists the common adverse events that were reported from Study CA046. The label proposed by the applicant lists the common adverse events by MedDRA preferred term with an incidence of ≥10% (per patient incidence) by system organ class. The applicant also proposed a separate listing for hematological toxicities. The events

related to peripheral neuropathy were analyzed using the peripheral neuropathy SMQ MedDRA v15.0 and included the terms burning sensation, dysesthesia, gait disturbance, hypoesthesia, hyporeflexia, muscle atrophy, muscular weakness, neuralgia, neuropathy peripheral, neurotoxicity, paraesthesia, peripheral motor neuropathy peripheral sensorimotor neuropathy, peripheral sensory neuropathy, peroneal nerve palsy, polyneuropathy, sensory loss, and skin burning sensation

Reviewers Comment:-*This reviewer recommends revising the table in the proposed label to include preferred terms which occurred with a difference of ≥ 5% for all grades (1-4) or ≥ 2% for Grade 3-4 with a higher incidence rate in the ABRAXANE plus gemcitabine-treated group compared to the patients in the gemcitabine group.*

Table 35: Adverse Reactions (per-Patient incidence rate) ≥ 10% in Study CA046 by MedDRA Preferred Term.

Preferred Term	ABI-007+Gemcitabine(N=421)				Gemcitabine(N=402)			
	All Grades		Severe[a]		All Grades		Severe[a]	
	N	%	N	%	N	%	N	%
Fatigue	248	59	77	18	183	46	37	9
Nausea	228	54	27	6	192	48	14	3
Alopecia	212	50	6	1	21	5	0	0
Edema peripheral	194	46	13	3	123	31	12	3
Diarrhea	184	44	26	6	96	24	6	1
Anemia	177	42	49	12	133	33	32	8
Neutropenia	175	42	138	33	122	30	85	21
Pyrexia	171	41	12	3	115	29	4	1
Decreased appetite	152	36	23	5	104	26	8	2
Vomiting	151	36	25	6	114	28	16	4
Thrombocytopenia	128	30	53	13	117	29	33	8
Constipation	126	30	12	3	111	28	7	2
Rash	117	28	7	2	39	10	2	0
Neuropathy peripheral	116	28	32	8	11	3	0	0
Peripheral sensory neuropathy	107	25	34	8	17	4	1	0
Abdominal pain	98	23	27	6	91	23	32	8
Dehydration	88	21	32	8	45	11	10	2
Asthenia	79	19	29	7	54	13	17	4

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Preferred Term	ABI-007+Gemcitabine(N=421)				Gemcitabine(N=402)			
	All Grades		Severe[a]		All Grades		Severe[a]	
	N	%	N	%	N	%	N	%
Dyspnea	73	17	12	3	62	15	11	3
Cough	72	17	0	0	30	7	0	0
Dysgeusia	68	16	0	0	33	8	0	0
Insomnia	64	15	0	0	46	11	3	1
Epistaxis	64	15	1	0	14	3	1	0
Headache	61	14	1	0	38	9	1	0
Leukopenia	59	14	39	9	39	10	15	4
Weight decreased	57	14	1	0	48	12	2	0
Hypokalemia	52	12	18	4	29	7	6	1
Depression	52	12	1	0	24	6	0	0
Chills	49	12	0	0	35	9	0	0
Pain in extremity	48	11	3	1	24	6	3	1
Dizziness	48	11	3	1	34	8	0	0
Arthralgia	47	11	3	1	13	3	1	0
Alanine aminotransferase increased	46	11	13	3	37	9	15	4
Myalgia	44	10	4	1	15	4	0	0
Abdominal pain upper	43	10	10	2	28	7	3	1
Mucosal inflammation	42	10	6	1	16	4	1	0
Hemoglobin decreased	41	10	11	3	29	7	8	2
Back pain	41	10	3	1	41	10	6	1
Urinary tract infection	40	10	8	2	15	4	1	0

[a] Includes ≥ Grade 3 adverse reactions

Reviewers Comment: - *Mucosal inflammation was not included in the proposed label although the incidence was 10% in the Abraxane arm and is a well-recognized taxane related toxicity. This preferred term was recommended by DOP2 for inclusion in the label. This reviewer also recommends combining the terms abdominal pain and upper abdominal pain and also using the SMQ to analyze the incidence of Peripheral neuropathy which has been included in the label. The final label included all the adverse*

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reactions by SOC and preferred term with a risk difference of greater than 5 %(all grades) or 2% (Grade 3 and higher) in the Abraxane arm.

Table 36 (all Grades) and Table 37 (Grades 3 and higher) represent the analyses of adverse events by MedDRA preferred term using the MAED analysis. Shaded entries represent odds ratios that were greater than 1.75. Note that the proportions are rounded in the tables (the ratio values were obtained from un-rounded analyses). *The MAED tool also uses a small correction for risk-ratios if the value 0 is in the denominator.*

Table 36: Adverse Events all grades with a Per-patient incidence of ≥5% in the Abraxane Treatment Arm by MedDRA Preferred Term (MAED analysis)

Preferred Term	ABI-007/Gemcitabine (N = 421)			Gemcitabine (N = 402)			ABI-007/Gemcitabine vs. Gemcitabine		
MedDRA V 15.0	Events	Subjects	%	Event	subjects	%	RD	RR	OR
Fatigue	563	248	59	308	183	46	13.4	1.3	1.7
Nausea	465	228	54	319	192	48	6.4	1.1	1.3
Alopecia	255	212	50	22	21	5	45.1	9.6	18.4
Edema peripheral	382	194	46	180	123	31	15.5	1.5	1.9
Diarrhea	381	184	44	149	96	24	19.8	1.8	2.5
Anemia	426	177	42	283	133	33	9.0	1.3	1.5
Neutropenia	546	175	42	333	122	30	11.2	1.4	1.6
Pyrexia	375	171	41	204	115	29	12.0	1.4	1.7
Decreased appetite	235	152	36	125	104	26	10.2	1.4	1.6
Vomiting	322	151	36	187	114	28	7.5	1.3	1.4
Thrombocytopenia	373	128	30	271	117	29	1.3	1.0	1.1
Constipation	177	126	30	141	111	28	2.3	1.1	1.1
Rash	178	117	28	46	39	10	18.1	2.9	3.6
Neuropathy peripheral	291	116	28	11	11	3	24.8	10.1	13.5
Peripheral sensory neuropathy	219	107	25	21	17	4	21.2	6.0	7.7
Abdominal pain	148	98	23	139	91	23	0.6	1.0	1.0

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Preferred Term	ABI-007/Gemcitabine (N = 421)			Gemcitabine (N = 402)			ABI-007/Gemcitabine vs. Gemcitabine		
MedDRA V 15.0	Events	Subjects	%	Event	subjects	%	RD	RR	OR
Dehydration	127	88	21	50	45	11	9.7	1.9	2.1
Asthenia	180	79	19	89	54	13	5.3	1.4	1.5
Dyspnea	99	73	17	80	62	15	1.9	1.1	1.2
Cough	83	72	17	32	30	7	9.6	2.3	2.6
Dysgeusia	88	68	16	39	33	8	7.9	2.0	2.2
Epistaxis	80	64	15	16	14	3	11.7	4.4	5.0
Insomnia	70	64	15	51	46	11	3.8	1.3	1.4
Headache	80	61	14	45	38	9	5.0	1.5	1.6
Leukopenia	174	59	14	98	39	10	4.3	1.4	1.5
Weight decreased	74	57	14	55	48	12	1.6	1.1	1.2
Depression	59	52	12	24	24	6	6.4	2.1	2.2
Hypokalemia	79	52	12	41	29	7	5.1	1.7	1.8
Chills	77	49	12	50	35	9	2.9	1.3	1.4
Pain in extremity	70	48	11	30	24	6	5.4	1.9	2.0
Dizziness	64	48	11	36	34	8	2.9	1.3	1.4
Arthralgia	75	47	11	27	13	3	7.9	3.5	3.8
Alanine aminotransferase increased	110	46	11	63	37	9	1.7	1.2	1.2
Myalgia	66	44	10	16	15	4	6.7	2.8	3.0
Abdominal pain upper	60	43	10	35	28	7	3.3	1.5	1.5
Mucosal inflammation	59	42	10	16	16	4	6.0	2.5	2.7 0.00094
Hemoglobin decreased	121	41	10	55	29	7	2.5	1.4	1.4
Back pain	50	41	10	60	41	10	-0.5	1.0	1.0
Urinary tract	60	40	10	17	15	4	5.8	2.5	2.7

Preferred Term	ABI-007/Gemcitabine (N = 421)			Gemcitabine (N = 402)			ABI-007/Gemcitabine vs. Gemcitabine		
MedDRA V 15.0	Events	Subjects	%	Event	subjects	%	RD	RR	OR
infection									
Hypotension	45	39	9	32	27	7	2.6	1.4	1.4
Aspartate aminotransferase increased	78	38	9	61	35	9	0.3	1.0	1.0
Deep vein thrombosis	41	36	9	37	33	8	0.3	1.0	1.0
Anxiety	40	35	8	56	45	11	-2.9	0.7	0.7
Oral candidiasis	43	34	8	15	15	4	4.3	2.2	2.3
Pruritus	42	34	8	32	20	5	3.1	1.6	1.7
Dyspepsia	38	34	8	29	28	7	1.1	1.2	1.2
Platelet count decreased	90	33	8	70	25	6	1.6	1.3	1.3
Stomatitis	47	31	7	14	14	3	3.9	2.1	2.2
Cellulitis	48	28	7	33	18	4	2.2	1.5	1.5
Pneumonia	33	28	7	22	19	5	1.9	1.4	1.4
Neutrophil count decreased	95	26	6	50	19	5	1.5	1.3	1.3
Dyspnea exertional	29	25	6	17	13	3	2.7	1.8	1.9
Hypoalbuminemia	38	25	6	24	18	4	1.5	1.3	1.3
Bone pain	28	24	6	8	8	2	3.7	2.9	3.0
Dry skin	25	24	6	10	9	2	3.5	2.5	2.6
Pain	28	24	6	12	9	2	3.5	2.5	2.6
Erythema	31	24	6	15	13	3	2.5	1.8	1.8
Hyperglycemia	34	23	5	23	18	4	1.0	1.2	1.2
Blood alkaline phosphatase increased	44	22	5	53	30	7	-2.2	0.7	0.7

Preferred Term	ABI-007/Gemcitabine (N = 421)			Gemcitabine (N = 402)			ABI-007/Gemcitabine vs. Gemcitabine		
MedDRA V 15.0	Events	Subjects	%	Event	subjects	%	RD	RR	OR
Pulmonary embolism	25	22	5	35	28	7	-1.7	0.8	0.7
Hyponatremia	32	22	5	22	17	4	1.0	1.2	1.2

OR=Odds ratio
RR=Relative Risk

Reviewers Comment: - *Adverse events with a risk difference of greater than 5% were recommended for inclusion in the label. The sponsor proposed describing the incidence rate of neuropathy (including the preferred terms peripheral neuropathy and peripheral sensory neuropathy) as an SMQ rather than PT's. This was acceptable. Most of the toxicities observed during the clinical trial were adverse events that were observed in prior clinical trials with Abraxane (e.g., alopecia, fatigue, peripheral neuropathy, diarrhea, rash, peripheral edema, fatigue, neutropenia, decreased appetite, arthralgia). The higher rates of epistaxis on the Abraxane arm may have been due to the generalized mucosal dryness and inflammation that has been well recognized with the use of other taxanes and in prior trials of Abraxane.*

Table 37: Adverse Events (Grade 3 and higher) (Per-patient incidence>1%) in the Abraxane Treatment Arm by MedDRA Preferred Term (MAED analysis)

Preferred Term	ABI-007/Gemcitabine (N = 421)			Gemcitabine (N = 402)			ABI-007/Gemcitabine vs. Gemcitabine		
MedDRA V 15.0	Events	Subjects	%	Events	Subjects	%	RD	RR	OR
Neutropenia	327	138	33	165	85	21	11.6	1.6	1.8
Fatigue	96	77	18	43	37	9	9.1	2.0	2.2
Thrombocytopenia	87	53	13	50	33	8	4.4	1.5	1.6
Anemia	65	49	12	48	32	8	3.7	1.5	1.5
Leukopenia	74	39	9	25	15	4	5.5	2.5	2.6
Peripheral sensory neuropathy	36	34	8	1	1	0	7.8	32.5	35.2
Neuropathy peripheral	45	32	8	0	0	0	7.6	62.1	67.2

Preferred Term	ABI-007/Gemcitabine (N = 421)			Gemcitabine (N = 402)			ABI-007/Gemcitabine vs. Gemcitabine		
MedDRA V 15.0	Events	Subjects	%	Events	Subjects	%	RD	RR	OR
Dehydration	32	32	8	10	10	2	5.1	3.1	3.2
Asthenia	35	29	7	20	17	4	2.7	1.6	1.7
Nausea	28	27	6	15	14	3	2.9	1.8	1.9
Abdominal pain	31	27	6	41	32	8	-1.6	0.8	0.8
Diarrhea	30	26	6	8	6	1	4.7	4.1	4.3
Vomiting	27	25	6	17	16	4	2.0	1.5	1.5
Decreased appetite	24	23	5	8	8	2	3.5	2.7	2.8
Deep vein thrombosis	22	21	5	25	22	5	-0.5	0.9	0.9
Neutrophil count decreased	59	19	5	29	15	4	0.8	1.2	1.2
Pulmonary embolism	20	19	5	30	26	6	-2.0	0.7	0.7
Hypokalemia	21	18	4	7	6	1	2.8	2.9	2.9
White blood cell count decreased	21	15	4	2	2	1	3.1	7.2	7.4
Pneumonia	16	15	4	9	9	2	1.3	1.6	1.6
Febrile neutropenia	13	13	3	8	6	1	1.6	2.1	2.1
Hyponatremia	14	13	3	9	8	2	1.1	1.6	1.6
Edema peripheral	20	13	3	13	12	3	0.1	1.0	1.0
Alanine aminotransferase increased	17	13	3	18	15	4	-0.6	0.8	0.8
Pyrexia	14	12	3	4	4	1	1.9	2.9	2.9
Constipation	12	12	3	7	7	2	1.1	1.6	1.7
Dyspnea	14	12	3	12	11	3	0.1	1.0	1.0
Hemoglobin decreased	13	11	3	10	8	2	0.6	1.3	1.3
Abdominal pain upper	10	10	2	3	3	1	1.6	3.2	3.2
Hyperglycemia	14	10	2	7	5	1	1.1	1.9	1.9

Preferred Term	ABI-007/Gemcitabine (N = 421)			Gemcitabine (N = 402)			ABI-007/Gemcitabine vs. Gemcitabine		
MedDRA V 15.0	Events	Subjects	%	Events	Subjects	%	RD	RR	OR
Cholangitis	12	10	2	6	6	1	0.9	1.6	1.6
Cellulitis	11	9	2	9	8	2	0.2	1.1	1.1
Urinary tract infection	12	8	2	1	1	0	1.7	7.6	7.8
Platelet count decreased	12	8	2	14	8	2	-0.1	1.0	1.0
Blood alkaline phosphatase increased	9	8	2	12	11	3	-0.8	0.7	0.7
Hyperbilirubinemia	9	8	2	16	13	3	-1.3	0.6	0.6
Aspartate aminotransferase increased	8	8	2	17	14	3	-1.6	0.5	0.5
Rash	7	7	2	2	2	1	1.2	3.3	3.4
Hypotension	7	7	2	5	5	1	0.4	1.3	1.3
Alopecia	7	6	1	0	0	0	1.4	12.4	12.6
Mucosal inflammation	8	6	1	1	1	0	1.2	5.7	5.8
Bile duct obstruction	8	6	1	5	5	1	0.2	1.1	1.1
General physical health deterioration	5	5	1	2	2	1	0.7	2.4	2.4
Hypertension	6	5	1	4	3	1	0.4	1.6	1.6
Hypoalbuminemia	5	5	1	3	3	1	0.4	1.6	1.6
Blood bilirubin increased	5	5	1	5	5	1	-0.1	1.0	1.0
Sepsis	5	5	1	9	7	2	-0.6	0.7	0.7
Ascites	6	5	1	15	13	3	-2.1	0.4	0.4
Catheter site infection	4	4	1	0	0	0	1.0	8.6	8.7
Myalgia	4	4	1	0	0	0	1.0	8.6	8.7
Stomatitis	5	4	1	0	0	0	1.0	8.6	8.7
Small intestinal	4	4	1	1	1	0	0.7	3.8	3.8

Clinical Review
Abhilasha Nair,MD
NDA 21660/Supplement-37
Abraxane/Nab Paclitaxel

Preferred Term	ABI-007/Gemcitabine (N = 421)			Gemcitabine (N = 402)			ABI-007/Gemcitabine vs. Gemcitabine		
MedDRA V 15.0	Events	Subjects	%	Events	Subjects	%	RD	RR	OR
obstruction									
Gamma-glutamyltransferase increased	4	4	1	2	2	1	0.5	1.9	1.9
Intestinal obstruction	4	4	1	2	2	1	0.5	1.9	1.9
Jaundice	4	4	1	2	2	1	0.5	1.9	1.9
Pneumonitis	5	4	1	2	2	1	0.5	1.9	1.9
Syncope	7	4	1	4	4	1	0.0	1.0	1.0
Renal failure	4	4	1	6	5	1	-0.3	0.8	0.8
Septic shock	4	4	1	5	5	1	-0.3	0.8	0.8
Cardiac failure congestive	3	3	1	0	0	0	0.7	6.7	6.7
Dizziness	3	3	1	0	0	0	0.7	6.7	6.7
Pancytopenia	3	3	1	0	0	0	0.7	6.7	6.7
Upper gastrointestinal hemorrhage	3	3	1	0	0	0	0.7	6.7	6.7
Arthralgia	4	3	1	1	1	0	0.5	2.9	2.9
Clostridium difficile colitis	4	3	1	1	1	0	0.5	2.9	2.9
Device related infection	3	3	1	1	1	0	0.5	2.9	2.9
Hepatic enzyme increased	4	3	1	1	1	0	0.5	2.9	2.9
Hypocalcaemia	3	3	1	1	1	0	0.5	2.9	2.9
Duodenal obstruction	4	3	1	2	2	1	0.2	1.4	1.4
Failure to thrive	3	3	1	2	2	1	0.2	1.4	1.4
Muscular weakness	3	3	1	2	2	1	0.2	1.4	1.4
Jaundice cholestatic	3	3	1	3	3	1	0.0	1.0	1.0
Lower respiratory tract	3	3	1	3	3	1	0.0	1.0	1.0

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Preferred Term	ABI-007/Gemcitabine (N = 421)			Gemcitabine (N = 402)			ABI-007/Gemcitabine vs. Gemcitabine		
MedDRA V 15.0	Events	Subjects	%	Events	Subjects	%	RD	RR	OR
infection									
Pain in extremity	4	3	1	3	3	1	0.0	1.0	1.0
Atrial fibrillation	3	3	1	4	4	1	-0.3	0.7	0.7
Liver abscess	3	3	1	4	4	1	-0.3	0.7	0.7
Renal failure acute	4	3	1	6	5	1	-0.5	0.6	0.6
Back pain	3	3	1	8	6	1	-0.8	0.5	0.5
Pleural effusion	3	3	1	6	6	1	-0.8	0.5	0.5

Reviewers Comment: - _Grade 3 or greater adverse events with a risk difference of more than 2% between the arms were recommended for inclusion in the label. Most of these preferred terms were discussed in more detail in the serious adverse events section of this review. The most common Grade 3 or greater toxicities that occurred on the Abraxane arm included hematological toxicities including neutropenia, peripheral neuropathy, fatigue, asthenia, nausea, dehydration and diarrhea._

The table below shows the listing of HLT's observed in trial CA046 that had an incidence of more than 10% on the Abraxane arm. This reviewer analyzed those HLT's that had a more than 5% risk difference between the arms or had an OR of more than 1.5 (shaded entries).

Table 38: Adverse event listing by MedDRA HLT with a per patient incidence of more than 10 %(MAED analysis)

MedDRA V 15.0	ABI-007/Gemcitabine (N = 421)			Gemcitabine (N = 402)			ABI-007/Gemcitabine vs. Gemcitabine		
HLT	Events	Subjects	%	Events	Subjects	%	RD	RR	OR
Asthenic conditions	749	294	69.8	401	223	55.5	14.4	1.3	1.9
Nausea and vomiting symptoms	792	255	60.6	510	224	55.7	4.9	1.1	1.2
Alopecias	255	212	50.4	22	21	5.2	45.1	9.6	18.4

Peripheral neuropathies NEC	518	208	49.4	34	29	7.2	42.2	6.8	12.6
Edema NEC	402	195	46.3	193	124	30.9	15.5	1.5	1.9
Diarrhea (excl infective)	381	184	43.7	149	96	23.9	19.8	1.8	2.5
Neutropenias	570	182	43.2	341	124	30.9	12.4	1.4	1.7
Anemias NEC	428	178	42.3	283	133	33.1	9.2	1.3	1.5
Febrile disorders	375	171	40.6	204	115	28.6	12.0	1.4	1.7
Appetite disorders	238	153	36.3	125	104	25.9	10.5	1.4	1.6
Gastrointestinal atonic and hypomotility disorders NEC	195	135	32.1	155	118	29.4	2.7	1.1	1.1
Gastrointestinal and abdominal pains (excl oral and throat)	223	131	31.1	182	115	28.6	2.5	1.1	1.1
Thrombocytopenias	374	129	30.6	272	118	29.4	1.3	1.0	1.1
Rashes, eruptions and exanthems NEC	203	128	30.4	53	45	11.2	19.2	2.7	3.5
Musculoskeletal and connective tissue pain and discomfort	167	96	22.8	134	77	19.2	3.7	1.2	1.2
Breathing abnormalities	129	95	22.6	98	74	18.4	4.2	1.2	1.3
Total fluid volume decreased	129	89	21.1	51	46	11.4	9.7	1.8	2.1
Coughing and associated symptoms	95	79	18.8	41	35	8.7	10.1	2.2	2.4
Sensory abnormalities NEC	109	76	18.1	50	42	10.5	7.6	1.7	1.9
Liver function analyses	232	68	16.2	147	51	12.7	3.5	1.3	1.3
Physical examination procedures and organ system status	93	68	16.2	68	59	14.7	1.5	1.1	1.1
Nasal disorders NEC	82	64	15.2	16	14	3.5	11.7	4.4	5.0
Headaches NEC	81	62	14.7	48	38	9.5	5.3	1.6	1.7
Leukopenias NEC	189	62	14.7	108	42	10.5	4.3	1.4	1.5
Potassium imbalance	83	55	13.1	62	42	10.5	2.6	1.3	1.3
Joint related signs and symptoms	85	54	12.8	31	16	4.0	8.9	3.2	3.6

Upper respiratory tract infections	81	53	12.6	34	30	7.5	5.1	1.7	1.8
Feelings and sensations NEC	84	53	12.6	55	39	9.7	2.9	1.3	1.3
Depressive disorders	59	52	12.4	24	24	6.0	6.4	2.1	2.2
Neurological signs and symptoms NEC	67	51	12.1	41	39	9.7	2.4	1.2	1.3
Lower respiratory tract and lung infections	57	45	10.7	34	29	7.2	3.5	1.5	1.5
Muscle pains	66	44	10.5	16	15	3.7	6.7	2.8	3.0
Urinary tract infections	64	44	10.5	24	20	5.0	5.5	2.1	2.2
Vascular hypotensive disorders	51	43	10.2	33	28	7.0	3.3	1.5	1.5

Note: Secondary preferred terms have been excluded.

Analysis of selected HLT's with a per patient incidence of more than 10%:

Asthenic Conditions: This was the HLT with the highest incidence and includes the PT's of asthenia, fatigue and malaise. Both "asthenia" and "fatigue" are included in the proposed adverse event table in the label. The delta (difference) between the events was driven primarily by the term fatigue.

Alopecias: The incidence of this HLT was similar to the PT of "alopecia" (50%) described in the label.

Peripheral neuropathies NEC: This HLT has a lower incidence than the SMQ of peripheral neuropathy since it did not encompass some PT's that were included in the HLT of sensory abnormalities NEC.

Edema NEC: This HLT was similar in incidence to the PT of "peripheral edema" that was included in the label and is a known taxane related toxicity.

Diarrhea (excl infective): The incidence was similar to the preferred term "diarrhea" (44%) was included in the label.

Neutropenias: A higher percentage is indicated by the preferred term "neutropenia" (73%) on the table in the label since it included only patients that had a post baseline value that had been verified by the central laboratory (hence the denominator was 405 patients as opposed to 421 patients).

Febrile disorders: The incidence of this HLT was similar to the preferred term "pyrexia" that was included in the label.

Appetite disorders: This HLT was included under the preferred term of "decreased appetite" in the label with a similar incidence.

Rashes, eruptions and exanthems NEC: The incidence rate of this HLT was higher than the PT of "rash" included in the label. Hence the PT has been replaced by the HLT in the label to reflect this.

Total fluid volume decreased: This HLT is reflected by the PT "dehydration" (21%) that better describes the term and is included in the label.

Coughing and associated symptoms: This HLT includes the PT's of cough, hemoptysis and productive cough. The incidence of this HLT was almost similar to the PT "cough" that has been included in the label.

Sensory abnormalities NEC: This HLT encompasses disparate terms such as "Dysgeusia" and "hypoesthesia". In this reviewer's opinion, these terms refer to disparate concepts better described by the respective PT's.

Nasal disorders NEC: This HLT includes PT's of "epistaxis" (main PT),"nasal dryness" and "nasal ulcer". This reviewer feels that since the high rates of epistaxis was mainly due to the nasal dryness related to the drug, the PT of "epistaxis" should be used to describe these events and has been included in the label.

Headaches NEC: The incidence of this HLT is similar to the PT of "headache" included in the label.

Leukopenias NEC: This HLT primarily reflects the preferred term "Leukopenia" (14%). Because low white blood cell counts caused by Abraxane are primarily due to neutropenia, which is described in the proposed label, including the preferred term "leucopenia" would not add substantive information. The other preferred term included in this HLT, "lymphopenia", had a low incidence rate (1%).

Joint related signs and symptoms: This HLT includes the PT's of arthralgia, joint range of motion decreased, joint stiffness, joint swelling. The majority of the events in this HLT occurred in the PT "arthralgia" that was included in the label.

Upper respiratory tract infections: The majority of the events under this HLT were under the PT of "upper respiratory tract infection" (5%). The other PT's under this HLT with events included nasopharyngitis, sinusitis and rhinitis. The incidence rates of all these PT's were less than 5% and hence these were not included in the proposed label.

Depressive disorders: This HLT includes the PT of "depression" which was included in the label

Lower respiratory tract and lung infections: The PT's that were included in this HLT were bronchitis, bronchopneumonia, lower respiratory tract infection, lung infection, pneumonia (majority=7%), pneumonia primary atypical. Given that the difference between the arms for this HLT is less than 5% this HLT was not included in the label. However a detailed analysis of sepsis events is described in Section 7.3.4 of this review which includes an analysis of pneumonia cases.

Muscle pains: The incidence of this HLT is identical to the incidence of the preferred term "myalgia". "Myalgia" is included in the product label.

Urinary tract infections: This HLT has been included under the term sepsis and has been included in the label

Vascular hypotensive disorders: The majority of the events under this HLT were of the PT "hypotension" which in most of the cases occurred in the context of sepsis which is described separately in the label.

7.4.2   Laboratory Findings

Hematology
The different parameters of anemia, neutropenia and thrombocytopenia were analyzed by the worst grade experienced by a patient on the trial. Only patients who had at least one post baseline central laboratory value recorded were used as the denominator. The rates of anemia (all Grades and Grade 3-4) were comparable between the treatment arms and hence were excluded from the label.

Reviewers Comment:-*The rates of neutropenia and thrombocytopenia differed between the arms and were included in the label.*

Table 39: Incidence of Hematologic Laboratory-Detected Abnormalities by Worst CTCAE Grade during treatment

Laboratory Value	Abraxane / Gemcitabine[d]		Gemcitabine	
	Grades 1-4 (%)	Grade 3-4 (%)	Grades 1-4 (%)	Grade 3-4 (%)
Neutropenia [a,b]	73	38	58	27
Thrombocytopenia[b,c]	74	13	70	9

Anemia	97	13	96	12

[a] 405 patients assessed in Abraxane /gemcitabine-treated group
[b] 388 patients assessed in gemcitabine-treated group
[c] 404 patients assessed in Abraxane /gemcitabine-treated group
[d] Neutrophil growth factors were administered to 26% of patients in the Abraxane / gemcitabine group

Biochemistry

The schedule of assessments in study CA046 indicated that serum biochemistry parameters (to include, but not limited to, sodium, potassium, chloride, glucose, BUN, alkaline phosphatase, AST/SGOT, ALT/SGPT, serum albumin, and total bilirubin and creatinine) were performed at screening and then on Cycle1 Day 1, Day 29 and Day 1 from Cycle 2 onwards and at end of study (EOS). Toxicity grades were assigned to each laboratory measurement based upon NCI CTCAE version 3.0 criteria.

For the purposes of this discussion, laboratory data is expressed using SI units.

**Hepatic function parameters**

The incidence of Grade 3/4 alanine aminotransferase and Grade 3/4 aspartate aminotransferase increase was low (≤2% in both treatment arms) and in general, deviations from baseline were comparable between arms.

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Figure 7: Graphical representation of the maximum change from baseline for hepatic parameters
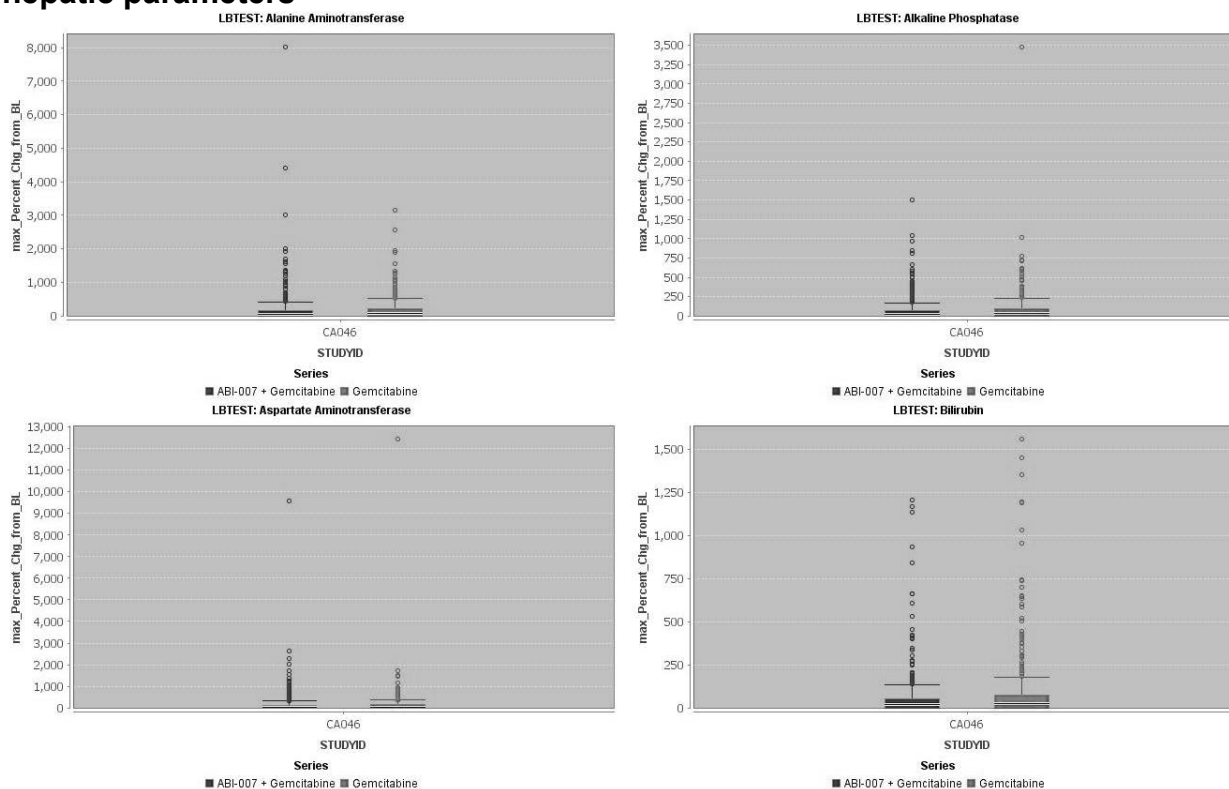
Reviewers Comment:-This reviewer feels that these results should be interpreted with caution as pancreatic cancer frequently metastasizes to the liver and hence a change in the hepatic parameters often cannot be attributed to study drugs alone. Also, 17% of the patients had biliary stents placed at baseline to relieve biliary obstruction which can alter the hepatic function.

Figure 8: Graphical depiction of possible Hy's Law cases (ALT/Bilirubin)
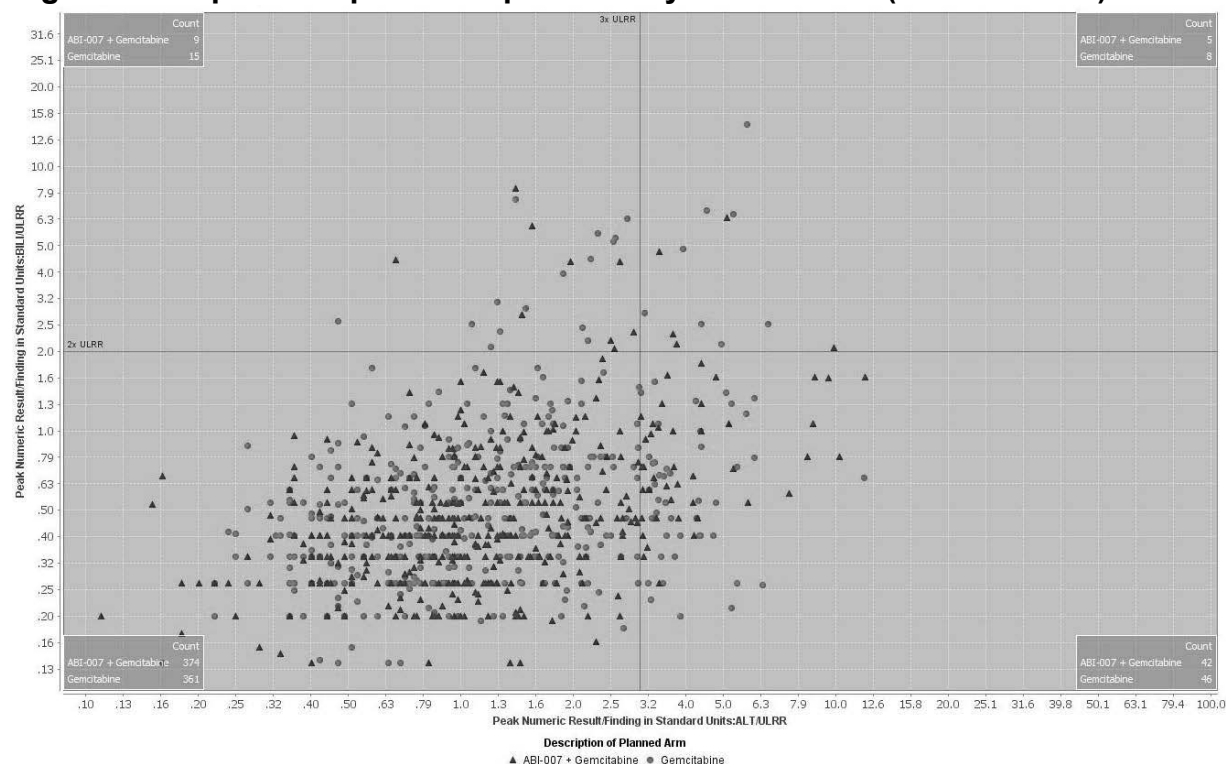
Reviewers Comment:-*The graph above of possible cases of Hy's Law should be interpreted with caution for the same reasons stated above that are unique to the pancreatic cancer population: high incidence of liver metastasis, biliary obstruction due to the primary tumor, presence of biliary stent.*

Renal function parameters

Based on central laboratory values, there were no reported cases of Grade 3 or 4 elevations of creatinine in the Abraxane arm as shown in the figure below.

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Figure 9: Scatter plot of renal function parameters (max change from baseline)
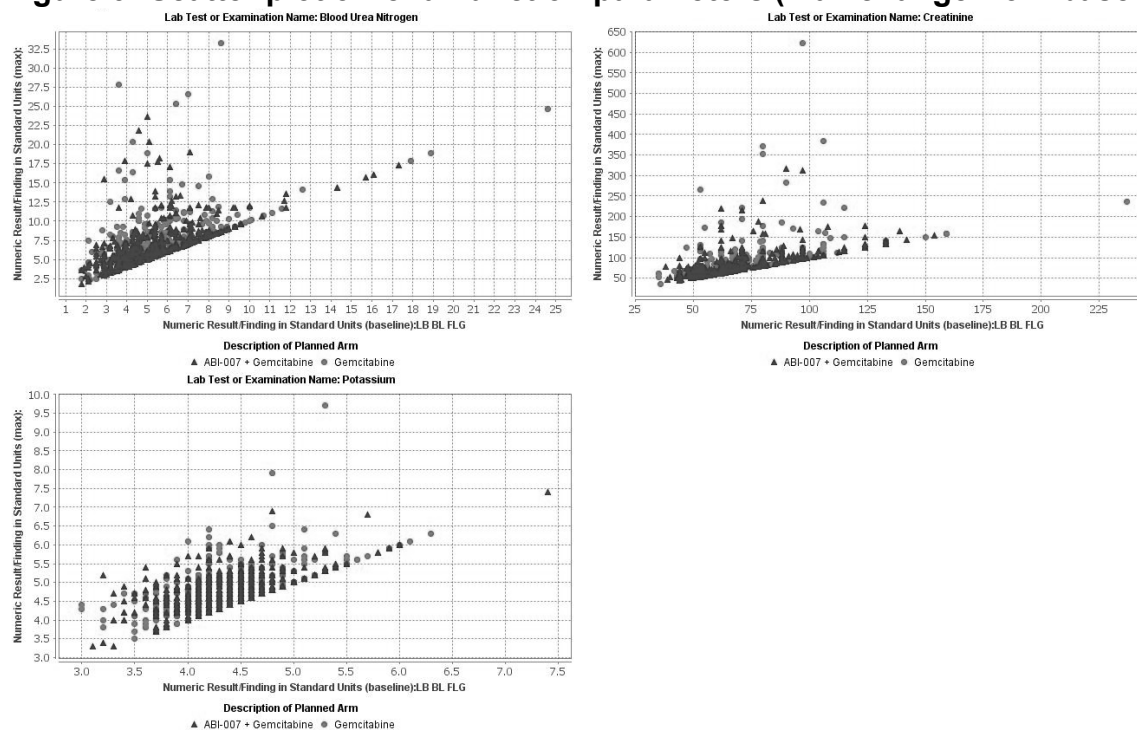
7.4.3   Vital Signs

The applicant did not provide datasets for vital signs except a listing of body weight measurements. Other physical examination findings were reported by the applicant as adverse events if found to be clinically significant by the investigator.

7.4.4   Electrocardiograms (ECGs)

There were no serial ECG data collected by the applicant included in this application.

7.4.5   Special Safety Studies/Clinical Trials

No specific special safety studies were submitted in this efficacy supplement.

7.4.6   Immunogenicity

This section is not applicable to this efficacy supplement for Abraxane.

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7.5   Other Safety Explorations

7.5.1   Dose Dependency for Adverse Events

This section is not applicable. All patients received the same starting dose of Abraxane in pivotal trial CA046.

7.5.2   Time Dependency for Adverse Events

The time dependency to development of neutropenia and neuropathy were reviewed in Section 7.3.5.

7.5.3   Drug-Demographic Interactions

Race
Because 94% of the Abraxane-treated group were White, explorations of difference in adverse events based on race would not be informative.

Gender
In general, there were no major difference in the incidence and distribution of adverse events between men and women in study CA046. In the Abraxane arm, neutropenia, anemia, vomiting and urinary tract infection were reported more often (>10% difference) by women than men whereas cough was reported more by men than women. In the gemcitabine arm, women reported more anemia and men reported more fatigue than their counterparts.

Age
Patients with age ≥ 65 years vs. less than 65 years
In the safety evaluable population, there were 175 patients who were ≥ 65 years of age in the Abraxane arm and 177 patients in the gemcitabine arm who experienced TEAE's in Study CA046. An analysis of AEs between groups showed that the PT's diarrhea, decreased appetite, dehydration and epistaxis had a higher incidence in the Abraxane arm in the age group more than or equal to 65 years. On the contrary, alopecia was reported more frequently in the Abraxane arm by patients younger than 65 years of age.

Table 40: Incidence of adverse events by MedDRA PT in patient's ≥ 65 years of age

PT	Abraxane/Gem (%)	Gem (%)	RD (per hundred)
Fatigue	62	51	11
Nausea	53	45	8
Diarrhea	51	25	27

PT	Abraxane/Gem (%)	Gem (%)	RD (per hundred)
Edema peripheral	48	33	15
Neutropenia	45	30	15
Anemia	45	40	6
Alopecia	42	5	38
Decreased appetite	42	28	13
Pyrexia	37	31	6
Constipation	34	31	4
Thrombocytopenia	34	35	-1
Vomiting	32	24	8
Rash	29	9	20
Dehydration	26	14	13
Neuropathy peripheral	25	3	22
Abdominal pain	23	20	3
Peripheral sensory neuropathy	22	4	18
Epistaxis	22	4	18
Asthenia	19	13	6
Dyspnea	18	20	-2
Cough	18	7	11
Dysgeusia	16	10	6
Hypokalemia	15	8	7
Insomnia	14	15	-1
Leukopenia	14	11	2
Oral candidiasis	13	3	10

PT	Abraxane/Gem (%)	Gem (%)	RD (per hundred)
Urinary tract infection	12	4	8
Hypotension	12	11	1
Mucosal inflammation	11	3	8
Depression	11	8	4
Dizziness	11	8	2
Headache	11	9	2
Weight decreased	11	11	0
Deep vein thrombosis	10	5	5
Pain in extremity	10	5	5
Hemoglobin decreased	10	10	0

Age ≥ 75 years vs. < 75 years
There were 40 patients in the Abraxane arm and 44 patients in the gemcitabine arm who were ≥ 75 years in Study CA046. Due to these small numbers, any conclusions based on subgroup analyses will have to be guarded. In the Abraxane arm, patients ≥ 75 years had a higher incidence of the MedDRA PT's of dry mouth, diarrhea, confusional state and hypotension while the PT's of alopecia and nausea were higher in patients younger than 75 years of age. Incidences of peripheral neuropathy SMQ and neutropenia remained the same in the ≥ 75 years age group. Of the 40 patients, there were five patients on the Abraxane arm who had an adverse event that resulted in death and Figure 10 shows the associated MedDRA PT's and their onset.

Figure 10: MedDRA PT's with an outcome of death in the ≥ 75 age group

MedDRA PT with outcome of death
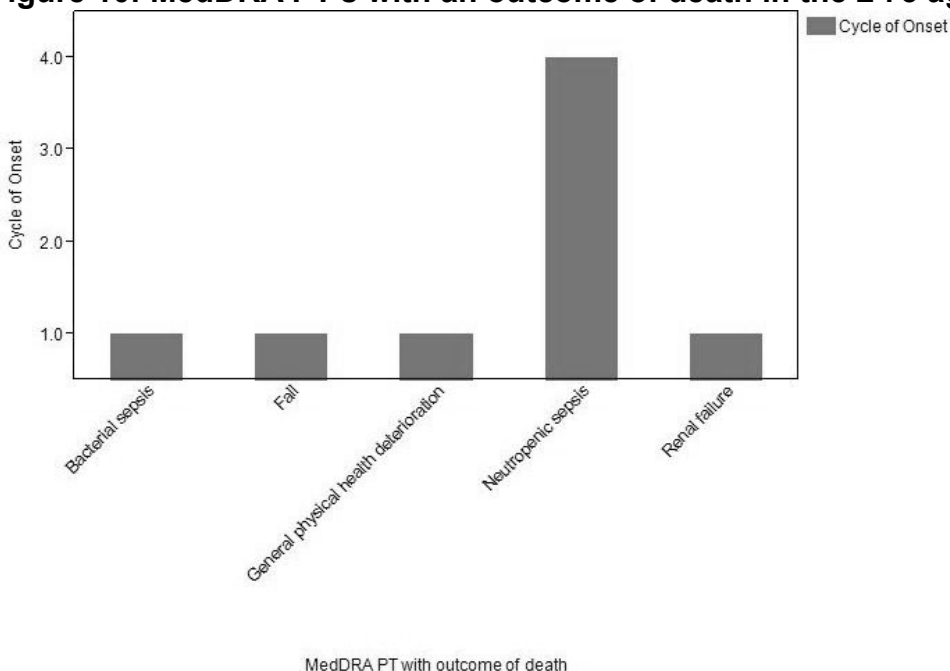
Of the 44 patients on the gemcitabine arm, 3 patients had an adverse event with an outcome of death. In patient's ≥ 75 years, more patients discontinued Abraxane and gemcitabine due to an adverse event compared to the overall population on the Abraxane/Gemcitabine arm.

Reviewers Comment:-*The applicant included a warning in the label with respect to the use of Abraxane in patients who were ≥ 75 years. Since this group represented a small subgroup of patients in the trial and there was no increase in the incidence of fatal adverse events, there was inadequate data to restrict its use to patients younger than 75 years of age. Additionally, as described above, the HR of ~ 1 in this group for OS may have been explained by imbalances in prognostic factors. Any physician planning to start any patient irrespective of age on this regimen of Abraxane/gemcitabine should weigh the risks and benefits, carefully considering bone marrow reserve (as a boxed warning exists for neutropenia) and other comorbidities including the presence of a biliary stent.*

7.5.4   Drug-Disease Interactions

No specific drug-disease interaction studies were conducted. All patients in the pivotal trial had life-threatening metastatic pancreatic cancer.

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7.5.5   Drug-Drug Interactions

No drug-drug interaction studies were submitted in this efficacy supplement.

7.6   Additional Safety Evaluations

7.6.1   Human Carcinogenicity

No specific carcinogenicity study was conducted for this application. The proposed use in this application is for the treatment of patients with a life-threatening malignancy. The label states that the carcinogenic potential of Abraxane has not been studied.

7.6.2   Human Reproduction and Pregnancy Data

Abraxane has been designated Pregnancy Category D based upon findings of embryo fetal toxicity and teratogenicity animal studies. There are no clinical studies of Abraxane in pregnant or lactating women. Such studies are usually not required for drugs intended to treat patients with advanced cancer.

Administration of paclitaxel protein-bound particles to rats during pregnancy, on gestation days 7 to 17 at doses of 6 mg/m^2 (approximately 2% of the daily maximum recommended human dose on a mg/m^2 basis) caused embryofetal toxicities, as indicated by intrauterine mortality, increased resorptions (up to 5-fold), reduced numbers of litters and live fetuses, reduction in fetal body weight and increase in fetal anomalies. Fetal anomalies included soft tissue and skeletal malformations, such as eye bulge, folded retina, microphthalmia, and dilation of brain ventricles. A lower incidence of soft tissue and skeletal malformations were also exhibited at 3 mg/m^2 (approximately 1% of the daily maximum recommended human dose on a mg/m^2 basis).

7.6.3   Pediatrics and Assessment of Effects on Growth

This section is not applicable to this application. Pancreatic cancer is rare in children. Abraxane was granted orphan designation in September 2009 and hence the Pediatric Research Equity Act (PREA) is not applicable and a waiver for pediatric studies was not required.

7.6.4   Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is no expected drug abuse potential for Abraxane. There were no events of overdose in the trials submitted. There is no known antidote for ABI-007 overdosage.

7.7   Additional Submissions / Safety Issues

Summary of Safety data from Study CA040

Study CA040 was a single-arm, multicenter, Phase 1/2 dose-escalation study designed to determine the MTD and DLTs of ABI-007 in combination with gemcitabine in patients with metastatic pancreatic cancer. Supportive safety data for ABI-007 125 mg/m^2 followed by gemcitabine 1000 mg/m^2 was provided from 44 patients who received this dose in the Study CA040. Review of the datasets submitted and the study report submitted by the applicant revealed that the most frequently reported adverse events were fatigue (89%), alopecia (80%), anemia (70%), nausea (66%), peripheral neuropathy (66%), peripheral edema (61%), thrombocytopenia (61%), neutropenia (59%), and diarrhea (55%). The most common TEAE's grade 3 or higher were neutropenia (59%), fatigue (32%), leukopenia (27%), and thrombocytopenia (27%). The most common SAEs were pyrexia and dehydration, which each occurred in 7% of patients. The most common treatment-related AEs that resulted in study treatment discontinuation were peripheral neuropathy (9%), fatigue (7%), and thrombocytopenia (7%).

Reviewers Comment:-*The safety results from study CA040 did not reveal any new safety signals. The incidences of individual adverse events were higher in this dose finding study likely related to the study design and smaller size of the study. Since the majority of the safety data was from the pivotal study CA046, the final adverse event incidence numbers included in the label were an accurate representation of the actual incidence rates in this reviewer's opinion.*

Four Month Safety Update

The applicant provided updated safety data (disposition, extent of exposure, adverse events, death, serious adverse events, and adverse events of special interest) for Study CA046 using a clinical data cut-off date of 31 Jan 2013. Study CA040 was completed at the time of the original sNDA submission and no new information was submitted regarding this study.

The applicant submitted updated safety information regarding 38 patients in study CA046 who had therapy ongoing at the time of the initial cut-off date of 17 Sep 2012. Based on the analysis of the adverse events and the datasets submitted there was no new safety concerns identified and there were no changes to the frequency or severity of the known adverse events previously reported. There were no changes in the incidence of adverse events of interest of myelosuppression and peripheral neuropathy and no new cases of pneumonitis. There was one new case of sepsis reported that was non-fatal. No patient experienced a TEAE that had an outcome of death in the 4 month safety update. As of April 1 2013, the applicant also terminated Study CA046 because the primary (overall survival) and secondary (progression free survival and overall response rate) endpoints were met.

Reviewers Comment: *No changes to the proposed label are recommended based upon review of the adverse event information included in the 120-day safety update.*

8   Postmarket Experience

Please refer to product labeling for listing of adverse reactions described in the post marketing setting (*Section 6.4*).

9   Appendices

9.1   Literature Review/References

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Moore, M. J., et al. "Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group." Journal of clinical oncology 25.15 (2007): 1960-66.

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Product labeling for Abraxane®, Gemzar®, Taxol® available at:
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/

Von Hoff, DD , et al, "Gemcitabine plus nab-paclitaxel is an active regimen in patients with advanced pancreatic cancer: a phase I/II trial." Journal of Clinical Oncology.(2011) ;29(34):4548-54.

9.2   Labeling Recommendations

At the time of completion of this review, text for the proposed label had not been finalized. This section of the review will focus on high-level labeling recommendations. All pertinent sections (i.e., sections related to pancreatic cancer) of the proposed label and patient package insert were revised for clarity, brevity, and consistency. Only clinically-relevant, substantive content changes will be discussed in this section.

Clinical Review
Abhilasha Nair,MD
NDA 21660/Supplement-37
Abraxane/Nab Paclitaxel

9.2.1   Indications and Usage

At the time of the NDA submission, the label proposed by the applicant stated that Abraxane was indicated for the first-line treatment of patients with ⬛ (b) (4) ⬛ (b) (4) metastatic adenocarcinoma of the pancreas, in combination with gemcitabine. ⬛ (b) (4)

9.2.2   Dosage and Administration Section

Dosing recommendations in patients with hepatic impairment as outlined in Table 5 of the label were based on predicted exposure in patients with hepatic impairment; patients with bilirubin levels above the upper limit of normal were excluded from clinical trials for pancreatic cancer. Hence language was added to the label to state that in moderate or severe hepatic impairment the use of Abraxane was not recommended.

The dose modification tables (Tables 4 and 5) for hematologic and other toxicities were modified so that the regimen can be consistently applied in the community setting. .

9.2.3   Warnings and Precautions Section

At the time of the original label submission the applicant proposed ⬛ (b) (4)

FDA recommended (in the filing letter) that Celgene either delete this ⬛ (b) (4)

9.2.4   Adverse Reactions Section

The tables of common adverse events (Tables 9 and 10) were modified to reflect adverse reactions with a higher incidence on the combination of Abraxane and gemcitabine for all grades of toxicity. This reviewer noted that the original label did not include mucositis, a known taxane related toxicity and hence this adverse reaction was added to Table 10.

9.2.5   Clinical Studies Section

This section was modified based on an OPDP recommendation to remove ⬛ (b) (4) ⬛ (b) (4)

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Clinical Review
Abhilasha Nair,MD
NDA 21660/Supplement-37
Abraxane/Nab Paclitaxel

(b) (4) Recommendations were also made to
remove (b) (4)

Reviewers Comment:-*As labeling negotiations were underway at the time of this
review submission the above material may not reflect the final changes agreed upon by
the agency.*

9.3   Advisory Committee Meeting

Patients in study CA046 randomized to the combination of Abraxane and gemcitabine
experienced a clinically meaningful, statistically significant improvement in overall
survival. Hence, advice from the Oncology Drugs Advisory Committee (ODAC) was not
necessary in order to render a regulatory decision.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21660Orig1s037

<u>PRODUCT QUALITY REVIEW(S)</u>

Office of New Drug Quality Assessment
Division of New Drug Quality Assessment I (Branch III)
Review of Chemistry, Manufacturing, and Controls

1. **NDA number: 21660**

2. **Submission(s) Being Reviewed**

Supplement Number	DARRTS SD Number	Submission Date	CDER Stamp Date	Assigned Date	PDUFA Goal Date	Review Date
S- 037 (efficacy supplement)	519	21-Mar-2013	21-Mar-2013	11-Apr-2013	21-Sep-2013	08-Aug-2013
Amendment	536	03-Jun-2013	03-Jun-2013	03-June-2013		
Amendment	541	10-Jun-2013	10-Jun-2013	10-Jun-2013		

3. **Proposed Changes:** This efficacy supplement proposes to add a new indication for first-line treatment of patients with metastatic adenocarcinoma of the pancreas, in combination with gemcitabine.

4. **Review #:** 1

5. **Clinical Review Division:** Division of Oncology Products 2

6. **Name and Address of Applicant:**
   Abraxis BioScience, LLC, a wholly-owned subsidiary of Celgene Corporation
   c/o Celgene Corporation
   9225 Indian Creek Parkway, Suite 900
   Overland Park, KS, 66210

7. **Drug Product:**

Drug Name	Dosage Form	Strength	Route of Administration	Rx or OTC
Abraxane® for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) (albumin-bound)	lyophilized powder for injectable suspension	100 mg of paclitaxel	intravenous infusion	Rx

8. Chemical name and structure of drug substance:

	USAN: Paclitaxel **Chemical name:** 5β,20-Epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2R,3S)-N-benzoyl-3-phenylisoserine **Molecular formula:** $C_{47}H_{51}NO_{14}$ **MW:** 853.91

9. Pharmacological Category/Indication: a microtubule inhibitor approved for the indications of metastatic breast cancer and locally advanced or metastatic non-small cell lung cancer (NSCLC)

10. Supporting/Relating Document: N/A

11. Consults: N/A

12. Summary/Remarks

This efficacy supplement proposes to add a new indication for first-line treatment of patients with metastatic adenocarcinoma of the pancreas, in combination with gemcitabine.
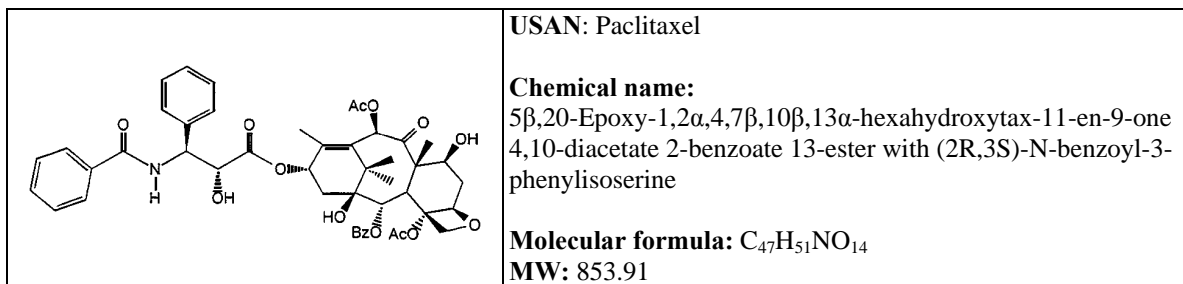
There are no proposed CMC changes in this supplement.

A categorical exclusion from the preparation of an environmental assessment (EA) was requested under 21 CFR 25.31(b), which has been reviewed and found acceptable.

Although container labels and carton labeling are included in this supplement, the applicant states that these container labels and carton labeling are the same as what are currently approved, except an update to patent numbers.

For the package insert, there are no proposed changes to the CMC-related sections. However, this reviewer suggested minor changes to the "Dosage Form and Strengths" and "Description" sections to be consistent with the current labeling review policy. The suggested changes were incorporated into the FDA recommended version of the package insert, which was sent by the project manager to the applicant on 8/6/13.

13. Conclusions & Recommendations:

This supplement is recommended for approval from the CMC perspective.

14. Comments/Deficiencies to be Conveyed to Applicant: none

15. Primary Reviewer: Sue-Ching Lin, CMC reviewer, ONDQA

Secondary Reviewer: Hasmukh Patel, Ph.D., Branch Chief, Branch III, Division of New Drug Quality Assessment I (DNDQA I), ONDQA

(See appended electronic signature page)

CMC Assessment

I. Background Information

The drug product, Abraxane for Injectable Suspension, is an albumin-bound form of paclitaxel with a mean particle size of approximately 130 nanometers. Paclitaxel exists in the particles in a non-crystalline, amorphous state.

The drug product is currently marked for the treatment of metastatic breast cancer and non-small cell lung cancer.

II. Proposed Changes

This prior-approval efficacy supplement proposes to add a new indication for first-line treatment of patients with metastatic adenocarcinoma of the pancreas, in combination with gemcitabine.

III. Data Submitted to Support the Proposed Changes

This supplement does not propose CMC changes. Therefore, the original S-037 supplement submission did not include Module 3. However, in response to this reviewer's questions, the applicant submitted the 6/3/13 and 6/10/13 amendments to update Sections 3.2.P.3.1 and 3.2.P.5.1 respectively to provide current information in e-CTD submissions. Pleas see below for further discussions.

A. Updates to Module 3

During the review of this supplement, in order to confirm that there were no changes to the manufacturing sites, this reviewer compared the establishment information submitted in Form 356h of this supplement with the information in Section 3.2.P.3.1, using "current view" in GlobalSubmit. This reviewer discovered that there were three different 3.2.P sections, two for Abraxis Bioscience and one for   (b) (4)   Accordingly, there were three 3.2.P.3.1 sections for "Manufacturers." These three sections were not completely the same, with some common and some different manufacturers. This also happened to Section 3.2.P.5.1, where there were two different sets of drug product specifications under two different 3.2.P sections, both were shown as "current."

Based on this reviewer's previous experience, the above issues may be related to how e-CTD information was updated, as sometimes changes were submitted in NDA amendments during NDA review or submitted in a supplement or its amendments but the corresponding Module 3 sections were not updated. Therefore, this reviewer consulted Ms. Valerie Gooding, who is FDA expert on e-CTD submissions. Ms. Gooding conveyed my comments, as shown below, to the applicant via 5/21/13 and 6/7/13 e-mails:

Please see reviewer's concerns below:

Trying to find out whether there are any changes to the current drug product manufacturing sites for supplement 37 as compared to the currently approved sites.

(b) (4)

In response, the applicant submitted the 6/3/13 amendment to update three 3.2.P.3.1 sections so that all are consistent with the manufacturers' information as what was submitted in the 3/6/13 annual report for approved sites. In conclusion, this supplement proposes no changes to the manufacture sites.

In addition, the applicant submitted the 6/10/13 amendment to update the drug product specification sections to show consistent information among the three 3.2.P.3 sections. There was no change to the approved specification.

In response to this reviewer's questions about why there are two Abraxis Bioscience 3.2.P sections, the applicant responded in a 6/10/13 e-mail the following:

The two 3.2.P sections for NDA 021660 is a legacy situation from when Celgene Corporation acquired Abraxis BioScience LLC.
(b) (4)

Evaluation: The changes submitted in the 6/3/13 and 6/10/13 amendments provide clarifications regarding manufacturing sites. As stated by the applicant, there are no changes to the current manufacturing sites. As the drug product is currently marketed for approved indications, this efficacy supplement does not require an inspection of the approved manufacturing and control facilities.

B. Environmental Assessment: Claim of Categorical Exclusion

A categorical exclusion from the preparation of an environmental assessment (EA) was requested under 21 CFR 25.31(b). This exclusion is based on the calculation that a worst-case Expected Introductory Concentration (EIC) of the active moiety (paclitaxel) into the waters of the United States would be approximately ___(b) (4)___ ppb, more than ___(b) (4)___ fold less than the 1 ppb level established by FDA. In addition, the paclitaxel used in the formulation of Abraxane is obtained through the semi-synthetic mechanism. Non-cultivated plants are not used in any part of the formulation of Abraxane.

Evaluation: The claim of categorical exclusion is acceptable.

C. Container Labels and Carton labeling

This supplement includes container labels and carton labeling in Section 1.14.1. Ms. Meredith Libeg, the project manager for this supplement, requested the applicant to confirm that there is no change to the currently approved container label and carton labeling. In response, the applicant stated in a 5/15/13 e-mail that the container labels and carton labeling included in supplement 37 are the current approved carton label and container labeling and the only change is to the patent numbers listed, which have been updated to match the changes to the patent numbers in the proposed package insert.

D. Package Insert

For the package insert, there are no proposed changes to the CMC-related sections. However, this reviewer suggested minor changes, which were conveyed to the project manager via an e-mail on 6/20/13:

****

- "Dosage form and strengths" in Highlights and Full Prescribing Information Sections: changed to read:

  For injectable suspension: lyophilized powder containing 100 mg of paclitaxel in single-use vial for reconstitution

  See pages 10 and 20 of the Labeling Review Tool , September 2012, for the format of these sections:

  http://inside.fda.gov:9003/downloads/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/UCM321175.doc

  The reason for the edits is that the information in the current labeling, as shown below, does not contain dosage form:

  Single use vial containing 100 mg of paclitaxel. (3)

- Section 11, Description: The proprietary name should be followed by the nonproprietary name as per 21CFR 201.57(c)(12) and 201.10.(g)(1). Therefore, please see my suggested text in red below for the first sentence of this section:

  ABRAXANE for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension), (b) (4) is an albumin-bound form of paclitaxel with a mean particle size of approximately 130 nanometers.....

  The second sentence:

  The active agent in ABRAXANE is paclitaxel, a microtubule inhibitor. The chemical name for paclitaxel is....

  ****

  Since this NDA was previously approved in Division of Oncology Products 1 (DOP1), the revisions would need approval from that division. Dr. Bob Justice, DOP1 Director, responded in his e-mail dated 8/6/13 that the above revisions are fine. Accordingly, the above revisions were incorporated into the FDA recommended version of the package insert that was sent by the project manager to the applicant on 8/6/13.

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

/s/

SUE CHING LIN
08/09/2013

HASMUKH B PATEL
08/09/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21660Orig1s037

<u>STATISTICAL REVIEW(S)</u>

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	21660
Supplement #:	S-37 (SDN 519)
Drug Name:	ABRAXANE® (paclitaxel protein-bound particles for injectable suspension)
Indication(s):	[b) (4)] metastatic adenocarcinoma of the pancreas
Applicant:	Abraxis Bioscience a wholly owned subsidiary of Celgene Corporation
Receipt Date:	March 21, 2013
PDUFA Goal Date:	September 21, 2013
Review Priority:	Priority
Biometrics Division:	V
Statistical Reviewer:	Yuan-Li Shen
Concurring Reviewers:	Kun He
	Rajeshwari Sridhara
Medical Division:	Oncology Products 2
Clinical Team:	Abhilasha Nair
	Steve Lemery
	Patricia Keegan
Project Manager:	Meredith Libeg

Keywords:

Log-rank test, hazard ratio, Cox model

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1   EXECUTIVE SUMMARY

The applicant submitted Study CA046 to seek a first-line indication for the treatment of patients with [(b) (4)] metastatic adenocarcinoma of the pancreas.

Based on study CA046, the results demonstrated statistically significant improvement based on the overall survival in favor of the ABI-007/gemcitabine treatment. The median OS time was 8.5 months (95% CI=7.9, 9.5) for the ABI-007/gemcitabine treated arm and 6.7 months (95% CI=6.0, 7.2) for the gemcitabine alone arm. The hazard ratio estimate was 0.72 (95% CI=0.62, 0.84; p-value<0.0001). The favorable results from the ABI-007/gemcitabine treated arm were robust based on various sensitivity analyses including the analyses using different database cut-off dates. The overall survival results were also consistent across different demographic and baseline disease characteristic subgroups. The result based on the independent assessment of progression free survival also demonstrated statistically significant improvement in favor of the ABI-007/gemcitabine treated arm (HR=0.69, 95% CI=0.58, 0.82; median PFS time were 5.5 months [95% CI=4.5, 6.0] for the ABI-007/gemcitabine arm and 3.7 [95% CI=3.6, 4.0] months for the gemcitabine alone arm; p-value <0.0001). In addition, the objective response rate also showed statistically significant results in favor of the ABI-007/gemcitabine treated arm (ORR=23% [95% CI=5.6, 8.5] for the ABI-007/gemcitabine treated arm vs. 7% [95% CI=3.8, NA] for the gemcitabine alone arm; p-value <0.0001).

In conclusion, this statistical reviewer confirms the applicant's efficacy results submitted. Whether the results demonstrate an overall favorable benefit to risk ratio in supporting an indication of the ABI-007/gemcitabine treatment in patients with [(b) (4)] [(b) (4)] metastatic adenocarcinoma of the pancreas will be deferred to the clinical review team.

2   INTRODUCTION

2.1   Overview

The applicant submitted study CA046, a phase 3 multicenter, international, randomized, controlled, open-label study of ABI-007 followed by gemcitabine versus gemcitabine alone, to support this application. The proposed indication statement in the patient package insert is:

ABRAXANE is indicated for the first-line treatment of patients with (b) (4)
(b) (4) *metastatic adenocarcinoma of the pancreas, in combination with gemcitabine.*

The primary objective of study CA046 was the overall survival (OS). The secondary objectives were to evaluate the progression free survival (PFS) and objective response rate (ORR). The first patient was enrolled on 5/8/2009 and the last patient was randomized on 4/17/2012. This multicenter study was conducted by investigators in 11 countries and randomized patients at a total of 151 sites. ABI-007 is currently approved under the trade name ABRAXANE in the US. ABRAXANE will be referred as ABI-007 through out this statistical review.

Some key information for the supporting study is summarized in the following table:

Table 1   Summaries of the Key Information for the Supporting Phase III tries

	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
CA046	Randomized, open-label, phase III study	Treatment Period: The treatment cycle length in both arms was 56 days during Cycle 1, and 28 days from Cycle 2 onward. Treatment was continued until the patient experienced PD or unacceptable toxicity , required palliative radiotherapy, withdrew consent, or the patient's physician recommendation.	Post-study treatment, OS status was monitored on a monthly basis for 6 months and then every 3 months thereafter until death occurred, the study closed or 3 years had elapsed since treatment discontinuation, whichever happened first. The median follow-up time : ABI-007+gemcitabine: 7.6 months; gemcitabine : 6.1 months	ABI-007+gemcitabine: : 431; gemcitabine : 430	patients diagnosed with metastatic adenocarcinoma of the pancreas

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2.2   Data Sources

The application's data (including raw and analysis datasets) from the original submission for study CA046 is located in the following link:
\\Cdsesub1\evsprod\NDA021660\0257\m5\datasets\ca046.

The SAS programs that were used to derive the analysis datasets and perform the analysis were also included in the link shown above.

The clinical study reports and the statistical analysis plan for this study are located in the following link:

\\Cdsesub1\evsprod\NDA021660\0257\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pancreaticadenocarcinoma\5351-stud-rep-contr\ca046

3   STATISTICAL EVALUATION

The original protocol was finalized on 11/12/2008 and subsequently has undergone 6 amendments. The items that were revised and may affect the efficacy evaluation are listed below:

Amendment 1 (3/20/ 2009)

- Added an interim analysis to evaluate futility and the evaluation of the interim analysis by an independent DMC.
- Clarified the primary efficacy endpoint hypotheses and modified the CI of OS HR to account for the interim efficacy analysis.

Amendment 2 (11/17/2009)

- Added language on the randomization stratification categories: geographic region, Karnofsky Performance Status (KPS: 70 to 80 versus 90 to 100), and presence of liver metastasis (yes or no). *Note: Randomization was stratified by these 3 factors as indicated in the Randomization Authorization Form since the original protocol, so it is not a new addition.*

- Modified the statistical procedure for testing the secondary efficacy endpoints (PFS and ORR) from the Hochberg procedure to a sequential step-down procedure. The PFS was tested first and ORR was tested only if PFS was statistically significant.
- Clarified the analysis population for tumor response and the analysis of correlation analysis between ORR and tumor response by PET (Positron Emission Tomography) scans,

Amendment 3 (4/19/2010)
- Modified texts to allow for additional patients with PET scans to be included beyond the first 200 patients.
- Revise the time frame of baseline assessments and starting treatment with respect to the randomization date, i.e. Randomization will occur within 14 days of Baseline assessments, and treatment will begin within 3 days of randomization, to ensure the rapid initiation of active drug treatment.

Amendment 4 (9/30/2010)
- Revised the sample size (increased the number of deaths to at least 608, and enrolled patients up to 842) and allow for an increase in statistical power from 80% to 90%.

- Revised to reflect that patients enrolled after the date of this protocol amendment would not receive baseline or follow-up PET scans. Patients who had obtained a baseline scan and who were still receiving treatment would no longer obtain follow-up PET scans after week 16. All sites were notified on 10/8/2010 to stop collection of additional PETs scans on new patients.

Amendment 5 (1/12/2011)
- Clarified that follow-up data may still be collected for patients who discontinue treatment.
- Added requirement for pelvic CT scan at Baseline (within 14 days, every 8 weeks regardless of arm, and EOS [End of Study]).
- Defined stratification by geographic region (Australia, Western Europe, Eastern Europe or North America).

Amendment 6 (11/12/2011)
- Post-study, overall survival status will be monitored on a monthly basis for 6 months and then every 3 months thereafter until death, the study close or 3 years have elapsed since patient discontinuation from treatment.

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The statistical analysis plan (SAP) was signed off by the applicant on 10/11/2012. The SAP appears to be finalized before the final data base lock and any data analysis had begun.

Reviewer's comment:
According to the applicant's response received on 6/11/2013, region was a stratification factor specified in the original Randomization Authorization Form before the first patient was enrolled (5/8/09). In this original randomization plan, the levels for the region were <u>North America, Australia/New Zealand, Eastern Europe, Western Europe, Asia/Pacific, Additional Region 1 and Additional Region 2</u>*. Protocol amendment 5 (1/12/2011) specified the relevant geographic regions as Australia, Eastern Europe, North America, or Western Europe because by that time all of the study sites were located in one of these 4 regions. It is noted that even though the randomization appears to be based on the same levels of region through out the study, the region levels had not been specified in the protocol until amendment 5. Because the levels of the region have been used throughout the study, we consider the stratified analyses based on the SAP specified levels of region are pre-specified.*

3.1   Data and Analysis Quality

The applicant submitted raw datasets in SDTM (Study Data Tabulation Model) and analysis data sets in ADaM (Analysis Data Model Implementation) formats, the defined files for the variables and the corresponding SAS programs for the primary ADaM data derivation to document the analysis results. The documentation for the derived variables appears to be easy to follow. The reviewer was able to duplicate the analysis results based on the SDTM dataset as well as based on the ADaM datasets.

3.2   Evaluation of Efficacy

3.2.1   Study Design and Endpoints

This study was an open-label, randomized, international, multicenter, Phase 3 study designed to compare ABI-007 in combination with gemcitabine administered weekly to standard treatment (gemcitabine monotherapy) in patients diagnosed with metastatic adenocarcinoma of the pancreas.

Patients who had definitive histologically or cytologically confirmed metastatic adenocarcinoma of the pancreas, had the initial diagnosis of metastatic disease ≤6 weeks prior to randomization, were at least 18 years of age (should be non-pregnant and non-lactating for women), should not

have received previous radiotherapy, surgery, chemotherapy or investigational therapy for the treatment of metastatic disease, had adequate laboratory results (shown in the inclusion criteria), had a Karnofsky performance status (KPS) ≥70, was asymptomatic for jaundice prior to day 1 and had significant or symptomatic amounts of ascites drained prior to Day 1, etc, were allowed to be enrolled into the study.

Patients who had known brain metastases (except some exceptions shown in the protocol), had locally advanced disease, had experienced a ≥10% decrease in KPS between baseline visit and within 72 hours prior to randomization, had unacceptable laboratory results (shown in the exclusion criteria), had history of malignancy in the last 5 years, who used Coumadin, had active, uncontrolled bacterial, viral or fungal infections required systemic therapy, had major or diagnostic surgery, had history of some adverse events (indicated in the exclusion criteria), was enrolled in any other clinical trial or unwilling or unable to comply with study procedures or was planning to take vacation for 7 or more consecutive days during the study were excluded from the study.

Patients were randomized in a 1:1 ratio and the randomization was stratified by the following:
- Geographic Region (Australia versus Eastern Europe versus Western Europe versus North America);
- Karnofsky Performance Status (70 to 80 versus 90 to 100);
- Presence of liver metastases (yes versus no).

The randomization schedule used a block size of 2 patients. Patients were randomized within 14 days of starting their baseline assessments. All patients were to begin treatment within 3 days after randomization.

Reviewer's comment:
A randomization schedule with block size of 2 patients is usually not sufficient for blinding purpose. However, since the trial had the primary endpoint OS which is a more objective measure and the distribution of the potential prognostic factors appear to be balanced in the trial, no further exploration has been performed to evaluate the impact.

This multicenter study was conducted by investigators in 11 countries (United States [US], Australia, Russian Federation, Italy, Canada, Ukraine, Spain, Germany, Austria, France, and Belgium) and randomized patients at a total of 151 sites. After the acquisition of Abraxis

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BioScience, Inc by Celgene Corporation, the applicant made the decision to gain Western European experience by adding centers in Italy, Spain, Germany, Austria, France and Belgium (76 patients), and by limiting the enrollment of Eastern European countries to 15% (126 patients) of the intended sample size of 842 patients.

Patients were randomized to receive ABI-007 followed by gemcitabine and gemcitabine alone in 1:1 ratio:

ABI-007 125 mg/m^2 followed by gemcitabine 1000 mg/ m^2 administered on Days 1, 8, 15 and 29, 36, 43 of a 56-day cycle in Cycle 1 only (i.e. weekly for 3 weeks with a 1-week rest x 2) and subsequently administered on Days 1, 8 and 15 of a 28-day cycle in Cycle 2 and onwards.

Or

Gemcitabine 1000 mg/ m^2 administered on Days 1, 8, 15, 22, 29, 36, 43 of a 56-day cycle in Cycle 1 (i.e. weekly for 7 weeks and a 1-week rest period) and subsequently administered on Days 1, 8 and 15 of a 28-day cycle in Cycle 2 and onwards.

Treatment was continued until the patient had progressive disease (PD, based on the investigators' assessment) or unacceptable toxicity, required palliative radiotherapy, withdrew consent or the patient's physician felt it was no longer in the best interest of the patient to continue on treatment.

The primary objective of this study was to evaluate the overall survival. The secondary objectives of this study were to:
- Evaluate PFS based on RECIST guidelines, v1.0 by independent radiological review (IRR);
- Evaluate the objective response rate (ORR) according to RECIST guidelines by IRR;
- Evaluate the safety and tolerability.

Tumor response assessment was performed based on IRR of CT scans (or MRI scans) every 8 weeks. The investigator determination of PD was used to determine the treatment duration.

Crossover to the combination arm was not allowed per protocol.

During post-study treatment period, OS status was monitored on a monthly basis for 6 months and then every 3 months thereafter until death occurred, the study closed or 3 years had passed since treatment discontinuation, whichever occurred first.

Sample Size Calculation

A total of 421 patients were planned to be randomized to each treatment arm (842 patients in total) for this study. The study requires 608 deaths to detect an improvement of 30% in OS (HR=0.769) with 90% power assuming a two-sided Type I error of 0.049 adjusting for one interim analysis.

Reviewer's comment:

It is noted that the sample size (including the number of deaths) have been revised. Prior to amendment 4 (9/30/2010), the required number of deaths was 455 and a total of 630 patients were expected to be randomized. The applicant indicates that the change of sample size was based on independent source of information, not from the current trial data. The purpose of the sample size revision is to gain more statistical power for various subgroup analyses.

Interim Analysis

An interim analysis was performed after at least 200 patients had been followed for at least 6 months from the date of randomization. The purpose of this interim analysis was to evaluate futility with the possibility of stopping for lack of efficacy. DMC reviewed progression rate, death rate and conditional power calculations in addition to the safety data. The criterion for stopping the study for futility was conditional power of less than 10% to reject the null hypothesis of no difference in the 6-month death rate at the end of the study.

Even though the interim analysis was not designed to stop the study early for efficacy, an alpha spending function was utilized to control the overall study-wise Type 1 error at the 5% level. The study allocated an alpha of 0.001 and 0.049 at the interim and final analyses, respectively (Haybittle, 1971; Peto, 1977).

Primary Efficacy Endpoint

The primary endpoint of this study was the overall survival

Secondary Efficacy Endpoint

The secondary efficacy endpoints included:

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- Progression-free survival (PFS)
- Overall response rate based on CT or MRI scans (ORR).

The assessments of PFS and ORR endpoints were completed by IRR of CT (or MRI) scans at the centralized facility with radiologic reviewers who were blinded to treatment assignment (2 reviewers with a third reviewer for adjudication).

Other Supportive Secondary Efficacy Endpoints:
- Time to response and response duration (duration of response [DOR]) according to RECIST guidelines;
- Disease control rate (i.e., SD for ≥16 weeks or confirmed CR or PR);
- Time to treatment failure (TTF);
- Changes in serum CA19-9;
- Tumor response based on PET scans evaluated according to EORTC (European Organization for Research and Treatment of Cancer) criteria;
- Determine whether a correlation exists between ORR based on CT or MRI scans (evaluated according to RECIST guidelines) and tumor response based on PET scans (evaluated according to the EORTC criteria);
- Changes in plasma SPARC (Secreted Protein Acidic and Rich in Cysteine [Osteonectin]) levels;
- Determine whether a correlation exists between the expression of molecular markers and efficacy outcomes;
- Determine whether correlations exist between ORR by CT or MRI scan, tumor response by PET scan, changes in serum CA19-9, and OS;
- Determine whether correlations exist between ORR by CT or MRI scan, tumor response by PET, PFS, OS, and expression of tumor markers (e.g., SPARC; nucleoside transporters).

3.2.2 Patient Disposition, Demographic and Baseline Characteristics

The first patient was randomized on 5/8/2009, and the last patient was randomized on 4/17/2012. The clinical cutoff date was 9/17/2012 and all clinical data collected up to the cutoff date will be used for the final analysis.

There were 431 and 430 patients in ABI-007/gemcitabine and gemcitabine arm, respectively, based on the intent-to-treat population. One patient who was randomized to the gemcitabine arm

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was treated with ABI-007/gemcitabine. Among the all randomized population, 98% and 93% were treated in ABI-007/gemcitabine and gemcitabine arm, respectively and 90% were in per-protocol population in both arms. The following table summarizes patient populations:

Table 2   Applicant's Summary of Patient Population

Population	ABI-007/Gemcitabine N=431	Gemcitabine N=430	All Patients N=861
Intent-to-treat Population [a]	431	430	861
Treated Population [b]	421 (98%)	402 (93%)	823 (96%)
Treated as Randomized	420 (97%)	402 (93%)	822 (95%)
Treated Not as Randomized	1 (<1%)	0	1 (<1%)
Per-protocol Population [c]	394 (91%)	377 (88%)	771 (90%)

a An intent-to-treat population included all randomized patients.
b Treated population included all randomized patients who received at least one dose of study drug .
c Per-protocol population included all patients who were treated as randomized and met all eligibility criteria.

Thirty eight patients were randomized, but were never treated. The most common reason of not being treated was due to withdrawal per patients' request (1% and 5% for ABI-007/gemcitabine and gemcitabine arm, respectively).   The proportions of patients treated between treatment arms are comparable (97% and 94% for ABI-008/gemcitabine and gemcitabine, respectively). By the time of data cutoff (9/17/2012), the majority of patients had discontinued treatment (91% for each arm). The most common reasons for treatment discontinuation were due to progressive disease (51%) and adverse events (23%). More patients who discontinued treatment early in gemcitabine arm were due to progressive disease (45% and 57% for ABI-007/gemcitabine and gemcitabine arm, respectively) and more patients discontinued treatment early in ABI-007/gemcitabine arm were due to adverse events (30% and 17% for ABI-007/gemcitabine and gemcitabine arm, respectively). In general, the percentage of patients met the inclusion/exclusion criteria in both arms are comparable (93% for each arm). There were more patients in ABI-007/gemcitabine arm still under survival follow-up (22% and 15% for ABI-007/gemcitabine and gemcitabine arm, respectively). A summary of the patient disposition is shown in the following table:

Table 3   Applicant's Summary of Patient Disposition

Population	ABI-007/Gemcitabine N=431	Gemcitabine N=430	All Patients N=861
Patients Not Treated	11 (3%)	27 (6%)	38 (4%)
Progressive Disease	1(<1%)	0	1(<1%)
Adverse Event	1 (<1%)	1 (<1%)	2 (<1%)
Physician Decision	1 (<1%)	1 (<1%)	2 (<1%)

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Protocol Violation	2 (<1%)	2 (<1%)	4 (<1%)
Withdrawal by Patient	3 (1%)	21 (5%)	24 (3%)
Other	3 (1%)	2 (<1%)	5 (1%)
Patients Treated	420 (97%)	403 (94%)	823 (96%)
Therapy Ongoing	26 (6%)	12 (3%)	38 (4%)
Therapy Discontinued	394 (91%)	391 (91%)	785 (91%)
Reason for Therapy Discontinuation			
Progressive Disease	196 (45%)	245 (57%)	441 (51%)
Adverse Events	128 (30%)	73 (17%)	201 (23%)
Unacceptable Toxicity (Related to Study Drug)	86 (20%)	29 (7%)	115 (13%)
Adverse Event (Unrelated to Study Drug)	42 (10%)	44 (10%)	86 (10%)
Physician Decision	25 (6%)	18 (4%)	43 (5%)
Protocol Violation	10 (2%)	6 (1%)	16 (2%)
Lost to Follow-up	0	0	0
Withdrawal by patient	28 (6%)	39 (9%)	67 (8%)
Other	7 (2%)	10 (2%)	17 (2%)
Patient Died	333 (77%)	359 (83%)	692 (80%)
Patients in Survival Follow-up	96 (22%)	66 (15%)	162 (19%)
Patients Lost to Survival Follow-up	2 (<1%)	5 (1%)	7 (1%)
Patients met inclusion/exclusion criteria	399 (93%)	400 (93%)	799 (93%)

In general, the distribution of the demographic characteristics, including region, gender, race, age and KPS appears to be comparable between treatment arms (shown in the following table). The majority of patients were from North America (63%). There were more patients less than 65 years old than patients aged 65 years or older (58% vs. 42%) and more men than women (58% vs. 42%) in this study. Approximately, ninety three percent of patients were White and 60% of the patients had KPS in 90-100 range.

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Table 4   **Reviewer's Summary of Demographic Characteristics**

	ABI-007/Gemcitabine N=431	Gemcitabine N=430	All Patients N=861
Region n	431	430	861
Australia	61 (14)	59 (14)	120 (14)
Eastern Europe	64 (25)	62 (14)	126 (15)
North America	268 (62)	271 (63)	539 (63)
Western Europe	39 (9)	38 (9)	76 (9)
Age (years)			
n	431	430	861
Mean (STDEV)	61.4 (10.70)	63.0 (9.27)	62.2 (10.04)
Median (Max, Min)	62.0 (27, 86)	63.0 (32, 88)	63.0 (27, 88)
< 65 Years	254 (59)	242 (56)	496 (58)
>= 65 Years	177 (41)	188 (44)	365 (42)
Sex n	431	430	861
Female	186 (43)	173 (40)	359 (42)
Male	245 (57)	257 (60)	502 (58)
Race n	431	430	861
White	403 (94)	401 (93)	804 (93)
Non-White	28 (6)	29 (7)	57 (7)
Karnofsky Performance Status n [a]	429	429	858
90 - 100	248 (58)	268 (62)	516 (60)
70 - 80	179 (42)	161 (38)	340 (40)
<70	2 (<1)	0	2 (<1)

Max = maximum; Min = minimum; STDEV = standard deviation.
Note: The percentage for each category was calculated using the total number of patients with non-missing values for the corresponding variables as a denominator.
[a] KPS data was based on CRF form.

In general, the distribution of baseline disease characteristics also appears to be balanced between treatment arms. A summary of baseline disease characteristics are presented in the following two tables. The median time from primary diagnosis to randomization was approximately 0.85 and 0.92 months for ABI-007/gemcitabine and gemcitabine alone arm, respectively. The majority of patients had stage IV at primary diagnosis (~80%) and at current diagnosis (>99%). The pancreatic primary locations are mainly on head (43%) and body (31%). The Majority of patients did not have biliary stent at screening (83%) and did not have previous Whipple procedure (93%).

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Table 5   Applicant's Summary of Baseline Disease Characteristics (1)

	ABI-007/Gemcitabine N=431	Gemcitabine N=430	All Patients N=861
Time from Primary Diagnosis to randomization (Mon)			
n	431	430	861
Mean (Stdev)	2.00 (4.51)	2.04(6.67)	2.02(5.69)
Median (Min, Max)	0.85(0.1,41.0)	0.92(0.1,109.4)	0.89(0.1,109.4)
Stage at Primary Diagnosis , n	431	430	861
I	10 (2)	9 (2)	19 (2)
II	28 (6)	16 (4)	44 (5)
III	25 (6)	18 (4)	43 (5)
IV	336 (78)	354 (82)	690 (80)
Unknown	32 (7)	33 (8)	65 (8)
Anatomic Site of Primary Diagnosis, n	431	430	861
Pancreas	431 (100)	427 (99)	858 (>99)
Other	0	3 (1)	3 (<1)
Stage at Current Diagnosis, n	431	430	861
I, II, or III	0	0	0
IV	431 (100)	429 (>99)	860 (>99)
Unknown	0	1 (<1)	1 (<1)
Pancreatic Primary Location, n	431	427	858
Head	191 (44)	180 (42)	371 (43)
Body	132 (31)	136 (32)	268 (31)
Tail	105 (24)	110 (26)	215 (25)
Unknown	3 (1)	1 (<1)	4 (<1)
Presence of Biliary Stent at Screening, n	431	430	861
Yes	80 (19)	68 (16)	148 (17)
No	351 (81)	362 (84)	713 (83)
Previous Whipple Procedure, n	431	430	861
Yes	32 (7)	30 (7)	62 (7)
No	399 (93)	400 (93)	799 (93)

Max = maximum; Min = minimum; STDEV = standard deviation.
Note: The percentage for each category was calculated using the total number of patients with non-missing values for the corresponding variables as a denominator.

Approximately, 76% of the patients had more than 5 targeted or non-targeted lesions in each treatment arm. The median sums of the longest target lesions were comparable between treatment arms (~12.2 cm). The most frequent occurred sites of metastasis were abdomen/peritoneum (90%), liver (84%) and lung/thoracic (39%). The proportions of metastasis in abdomen/peritoneum and liver appear to be balanced between treatment arms.

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However, metastasis in lung/thoracic was observed more often in the gemcitabine arm than that in ABI-007/gemcitabine arm (43% vs. 35%). The distribution of the CA19-9 levels appears to be comparable between treatment arms. The majority of patients had CA19-9 level $\geq$ 59x ULN level (46%).

Table 6   Applicant's Summary of Baseline Disease Characteristics (2)

	ABI-007/Gemcitabine N=431	Gemcitabine N=430	All Patients N=861
Number of Lesions (Targeted + non-targeted) [a] n	361	345	706
1	1 (<1%)	0	1 (<1%)
2	32 (9%)	25 (7%)	57 (8%)
3	7 (2%)	7 (2%)	14 (2%)
4	37 (10%)	43 (12%)	80 (11%)
5	8 (2%)	8 (2%)	16 (2%)
> 5	276 (76%)	262 (76%)	538 (76%)
Sum of the longest target lesion (cm) [a] n	359	344	703
Mean (Stdev)	12.93 (6.767)	13.33(7.137)	13.12(6.949)
Median (Min, Max)	12.10(1.8,35.1)	12.25(1.4,40.2)	12.20(1.4,40.2)
Current Site(s) of Metastasis [b], n	431	430	861
CNS/Brain	0	0	0
Breast	1 (<1)	0	1 (<1)
Skin/Soft Tissue	10 (2)	10 (2)	20 (2)
Supraclavicular	10 (2)	8 (2)	18 (2)
Axilla	4 (1)	8 (2)	12 (1)
Groin	1 (<1)	0	1 (<1)
Bone	22 (5)	18 (4)	40 (5)
Lung/Thoracic	153 (35)	184 (43)	337 (39)
Liver	365 (85)	360 (84)	725 (84)
Peritoneal Carcinomatosis	19 (4)	10 (2)	29 (3)
Abdomen/Peritoneum	380 (88)	396 (92)	776 (90)
Pelvis	30 (7)	27 (6)	57 (7)
Other	107 (25)	99 (23)	206 (24)
CA19-9 (U/mL) n	379 (88%)	371 (86%)	750 (87%)
Number of Patients with Normal CA19-9	60 (14%)	56 (13%)	116 (13%)
Number of Patients with CA19-9 > ULN but < 59x ULN	122 (28%)	120 (28%)	242 (28%)

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Number of Patients with CA19-9 ≥ 59x ULN	197 (46%)	195 (45%)	392 (46%)
Unknown	52 (12%)	59 (14%)	111 (13%)

Max = maximum; Min = minimum; STDEV = standard deviation.
a Based on independent radiological review.,
b   Patients can be in multiple current sites of metastasis categories.
 Note: The percentage for each category was calculated using the total number of patients with non-missing values for the corresponding variables as a denominator.

3.2.3   Statistical Methodologies

<u>**Analysis Population**</u>

There were three analysis populations specified in the protocol:

- The Intent-to-treat (ITT) population: included all randomized patients.   All efficacy analyses were based on the ITT population unless otherwise specified.

- The treated population: included all randomized patients who received at least one dose of study drug. The patient was assigned to the treatment arm that the patient actually received during the study. All safety analyses were based on the treated population.

- The Per-protocol population: included all treated patients who met all eligibility criteria and received the same treatment as assigned by randomization. The primary and secondary efficacy analyses were also conducted based on the Per-protocol population.

<u>**Primary efficacy Analysis**</u>

The primary analysis of OS was performed based on the stratified log rank test. The type I error was controlled at 0.049 level by taking consideration of one interim analysis. The stratification factors include:

- Geographic Region (North America vs. others);
- Baseline KPS (70-80 and 90-100);
- Presence of liver metastases (yes and no).

The associated hazard ratio (HR) and two-sided 95% CI were estimated using a stratified Cox proportional hazard model. The median survival time and its corresponding 95% CI were obtained from the Kaplan-Meier method.

<u>**Sensitivity Analyses for the Overall Survival**</u>

To assess the potential influence of the effect of the prognostic factors on the primary efficacy endpoint of OS, the following factors were specified in the SAP and were evaluated using the multivariate Cox proportional hazards model adjusted for these factors:

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1. Geographic Region (Australia, Eastern Europe, Western Europe, North America);
2. Age (< 65 years, ≥ 65 to < 75 years, and ≥ 75 years);
3. KPS (70 to 80 and 90 to 100);
4. Gender (male and female);
5. Pancreatic cancer primary location (head and other);
6. Stage at diagnosis (IV and other)
7. Level of CA19-9 (within normal limit [WNL], ULN to < 59 x ULN, ≥ 59 x ULN);
8. Presence of liver metastases (yes and no);
9. Peritoneal carcinomatosis (yes and no);
10. Previous Whipple procedure (yes and no);
11. Presence of biliary stent (yes and no) at Baseline;
12. Presence of pulmonary metastases (yes and no); and
13. Number of metastatic sites (1, 2, 3 and above).

It is noted that the geographic region, baseline KPS and presence of liver metastases were based on the clinical data, not the randomization data. The potential factors were identified using a stepwise selection procedure with the significance level of 0.20 for entry and the significance level of 0.10 for stay.

Subgroup analyses were also performed and presented based on a forest plot of the hazards ratio (HRs) for each subgroup (note: the list of subgroups was similar to the list for the prognostic factors).

An additional stratified analysis of OS was conducted using stratification factors based on the clinical database and not as randomized.

The other sensitivity analysis was conducted by censoring patients who started a new anticancer therapy at the initiation date of the new chemotherapy. Non-stratified analyses based on a Cox's model and a log rank test for OS was also performed.

Secondary Efficacy Analysis

Statistical tests for the secondary efficacy endpoints (in the order of PFS and then ORR) were to be performed at a 2-sided $\alpha = 0.050$ level only if the primary efficacy endpoint of OS showed a statistically significant result.

Progression-free Survival

PFS was analyzed based on the similar statistical analysis methods as those described for the primary analysis of OS. PFS was defined as the time from the date of randomization to the date of disease progression or death on or prior to the clinical cutoff date, whichever occurred first. The censoring strategies described in the SAP are listed below:

1. Patients who did not have disease progression or who were alive were censored at the date of last tumor assessment that the patient was progression-free on or prior to the clinical cutoff date.
2. Patients who dropped out early without any post baseline tumor assessment and/or died more than 120 days after the randomization were censored on the date of randomization.
3. If a patient began a new anticancer chemotherapy prior to documented progression (or death), the patient was censored at the date of last assessment when the patient was documented as progression free prior to the intervention.
4. Patients with two or more consecutive missing response assessments prior to a visit with documented progression (or death) were censored at the last date of tumor assessment when the patient was documented to be progression free.

The subgroup analyses and multivariate analyses based on Cox's model for PFS were also performed using similar subgroups/prognostic factors as described in the Sensitivity Analyses for the OS. Non-stratified analyses based on a Cox's model and a log rank test for PFS was also performed.

Objective Response Rate

Overall response rate based on IRR was summarized by the number and percentage of patients who achieved a confirmed CR or PR. The difference in tumor response rates between treatment arms was tested using the Chi-square test.

Duration of response (DOR)

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Based on the SAP, DOR was calculated by the applicant as time from the earliest date of documented response (CR or PR) to the earliest date when disease progression was confirmed. Patients who are non-responders were excluded from this analysis. If a patient had disease progression, then the date of disease progression would be the event date. For a patient who did not have disease progression, then the patient would be censored on the date of last tumor assessment. If a patient died, then the patient would be censored on the date of death. If patient started new anti-cancer therapy, then the patient was censored on the last tumor assessment date on or prior to the start date of new anti-cancer therapy. The analysis methods used for OS were used for the analysis of DOR.

Reviewer's comments: The applicant's defined DOR considered deaths as being censored and did not consider patients who had an event after missing tumor assessment for more than 120 days as being censored (as those defined for censoring in the PFS analysis). This reviewer calculated the DOR as time from the date of observing a CR or PR to the PFS events occurred time. The censoring strategy for DOR is similar to those described for the PFS. Formal comparison of DOR in the 2 treatment arms is not valid as DOR is calculated only in responders.

3.2.4 Results and Conclusions

The efficacy results for study CA046 will be described in this section.

3.2.4.1 Efficacy Endpoint Analyses

<u>**Overall Survival**</u>

There were 333 (77%) and 359 (83%) deaths, for ABI-007/gemcitabine and gemcitabine arm, respectively, at the clinical cutoff date for the final OS analysis (dated 9/17/2012). The median follow-up time in the ITT population was 7.6 and 6.1 months for ABI-007/gemcitabine and gemcitabine arm, respectively. At the data cutoff date, a statistical significant overall survival result was demonstrated with hazard ratio of 0.72 (95% CI=0.62, 0.84; p<0.0001 based on stratified log rank test) in favor of the ABI-007/gemcitabine treated arm. The median survival times were 8.5 months (95% CI=7.89, 9.53) and 6.7 months (95% CI=6.01, 7.23) for ABI-007/gemcitabine and gemcitabine arm, respectively.

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Table 7   Reviewer's Summary of Overall Survival (based on 9/17/2012 cutoff date)

	ABI-007/Gemcitabine N=431	Gemcitabine N=430
Number (%) of Subjects		
Censored	98 (23)	71(17)
Death	333 (77)	359 (83)
Duration of overall survival (months)		
Median (95% CI) [a]	8.5(7.89,9.53)	6.7(6.01,7.23)
p-value (stratified log-rank test)[b]	<0.0001	
Hazard ratio (95% CI; stratified)[c]	0.72 (0.617, 0.835)	

CI=confidence interval;
a Median and percentiles are based on Kaplan-Meier survival estimates.
b Stratification factors include: geographic region (North America vs. Others), Karnofsky performance score (70 to 80 vs.90 to 100), and presence of liver metastasis (yes vs. no).
c Estimated using the stratified Cox proportional hazard model.

Reviewer's Comments:

- *There was no differential censoring distribution observed between treatment arms for overall survival based on a stratified Cox's proportional hazards model including a treatment indicator in the model and using a reversed censoring indicator for the model (hazard ratio=0.93, 95% CI=0.67, 1.27).*

Sensitivity Analyses for OS

Sensitivity analyses for OS were performed and the results were shown in the following table. The hazard ratio estimates ranged from 0.68 to 0.74 with all the upper bound of 95% CI being below 1. The results demonstrate robust findings based on these sensitivity analyses.

Table 8   Reviewer's Sensitivity Analyses for OS

Analysis #	#event/total ABI-007+Gem vs. Gem	Hazard Ratio [a]	Median (months) (95% CI) ABI-007+Gem	Median (months) (95% CI) Gemcitabine	Difference in median (months) (ABI-007+Gem-Gem)
1. Primary (strata data are from IVRS)	333/431:359/430	0.72(0.62,0.83)	8.5(7.9,9.5)	6.7(6.0,7.2)	1.87
2.Strata data based on CRF	333/431:359/430	0.69(0.59,0.80)	8.5(7.9,9.5)	6.7(6.0,7.2)	1.87
3. Unstratified analysis	333/431:359/430	0.74(0.63,0.85)	8.5(7.9,9.5)	6.7(6.0,7.2)	1.87

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4. use 4-level of region in the stratified analysis	333/431:359/430	0.70(0.60,0.82)	8.5(7.9,9.5)	6.7(6.0,7.2)	1.87
5. Censored for patients who took anti-CA	210/431:218/430	0.68(0.56,0.82)	9.4(8.4,11.4)	6.8(6.0,7.5)	2.60
6.Per-protocol	309/394:315/377	0.72(0.61,0.84)	8.6(7.9,9.6)	6.8(6.0,7.3)	1.77
7.Cutoff at 455 deaths (prior to 9/30/2010)	212/431:243/430	0.69(0.58,0.84)	8.6(7.9,9.7)	6.6(5.6,7.4)	1.94
8.Cutoff at 608 deaths (9/30/2010)	293/431:315/430	0.73(0.62,0.86)	8.6(7.9,9.7)	6.8(6.0,7.3)	1.77

[a] Estimated using the stratified Cox proportional hazard model

Reviewer's comments:

- *A sensitivity analysis using the stratification data recorded on the CRF form was performed (sensitivity analyses #2). The hazard ratio was equal to 0.69 (95% CI=0.59, 0.80) which supports the primary efficacy result.*

- *The result based on an unstratified Cox's model appears to be supportive of the primary results (HR=0.74, 95% CI=0.63, 0.8).*

- *In the SAP, the levels for the geographic region for the efficacy analyses was specified as North America vs. others instead of using the 4 regions (Australia, Eastern Europe, Western Europe, North America). If the stratification factor based on 4 region was used in the analysis, the hazard ratio=0.70 (95% % CI=0.60, 0.82) which is consistent with the primary finding.*

- *Two sensitivity analyses based on different cutoff dates (original cutoff date prior to sample size re-estimation based on 455 deaths and the revised cutoff date based on 608 deaths, in analyses #7 and #8, respectively) were presented in the table. The corresponding treatment effect based on the hazard ratios were 0.69 and 0.7, respectively, with both the upper 95% CIs being below 1. Both results are supportive to the primary efficacy result (i.e. HR=0.72).*

- *An additional sensitivity analysis which censored patients who took the other anti-cancer therapy at the last assessment time was also performed (sensitivity analysis #5). The hazard ratio=0.68 (95% CI=0.56, 0.82) which further supports the primary efficacy result.*

Additional exploratory analyses were also performed based on the Cox's proportional hazards models including some potential prognostic factors with stepwise variable selection method. Since there are 111 patients with missing CA19-9 measurements, the inclusion of CA19-9 level

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in the model would not be based on the intent-to-treat population. Two analyses were performed based on whether CA19-9 level was included in the model or not. The hazards ratio estimates for treatment effect were 0.72 (95% CI=0.62, 0.83) and 0.70 (95% CI=0.60, 0.83) based on the model including and not including CA19-9 level, respectively. The treatment effects based on both models are both supportive to the primary finding. The factors that had been selected based on both models for the overall survival include age group, KPS status and liver metastasis status.

Table 9   Reviewer's Exploratory Analyses for OS based on Multivariate Cox's Model with Stepwise Procedure

With or without CA19-9	Covariates	Hazard Ratio (HR)	95% CI of HR	P-value
Without CA19-9	Treatment	**0.72**	0.62, 0.83	<.0001
	Age (≥65 years vs. <65 years)	1.20	1.03 1.40	0.0200
	KPS status (70- 80 vs. 90-100)	1.46	1.25 1.70	<.0001
	Eastern Europe vs. others	1.20	0.98 1.47	0.0761
	Whipple procedure (Yes vs. No)	0.74	0.55 0.99	0.0451
	Liver met.astasis (Yes vs. No)	1.78	1.42 2.22	<.0001
With CA19-9				
	Treatment	**0.70**	0.60, 0.83	<.0001
	Age (≥65 years vs. <65 years)	1.19	1.01, 1.40	0.0386
	KPS status (70 - 80 vs. 90-100)	1.45	1.23, 1.71	<.0001
	Liver metastasis (Yes vs. No)	1.80	1.42, 2.29	<.0001
	# of meta. Sites (1,2,3 and >3)	1.09	0.99, 1.19	0.0669

Note: A stepwise selection with significance level for entry of 0.20 and significance level for stay of 0.10 was used to identify potential prognostic factors.
Note: The Cox proportional hazards model included the following explanatory covariates: treatment groups, age (≥ 65 years vs. <65 years), sex, Karnofsky performance status (70 to 80 versus 90 to 100), geographic region (North America was used as the reference, include 3 d.f. for the effect from E. Europe, Australia and W. Europe), pancreatic cancer primary location (head versus other), presence of biliary stent, previous Whipple procedure, presence of liver metastases, presence of pulmonary metastases, peritoneal carcinomatosis, stage of diagnosis (IV versus other), number of metastatic sites (1,2,3, >3) and level of CA19-9.(1 = 'ULN-<59xULN';2 = 'Normal';3 = '>= 59xULN)

The Plots for the Kaplan-Meier estimates are presented below. The two curves appear to be separated.

Figure 1   Plots of Kaplan-Meier Estimates for Overall Survival (9/17/2012 cutoff date)
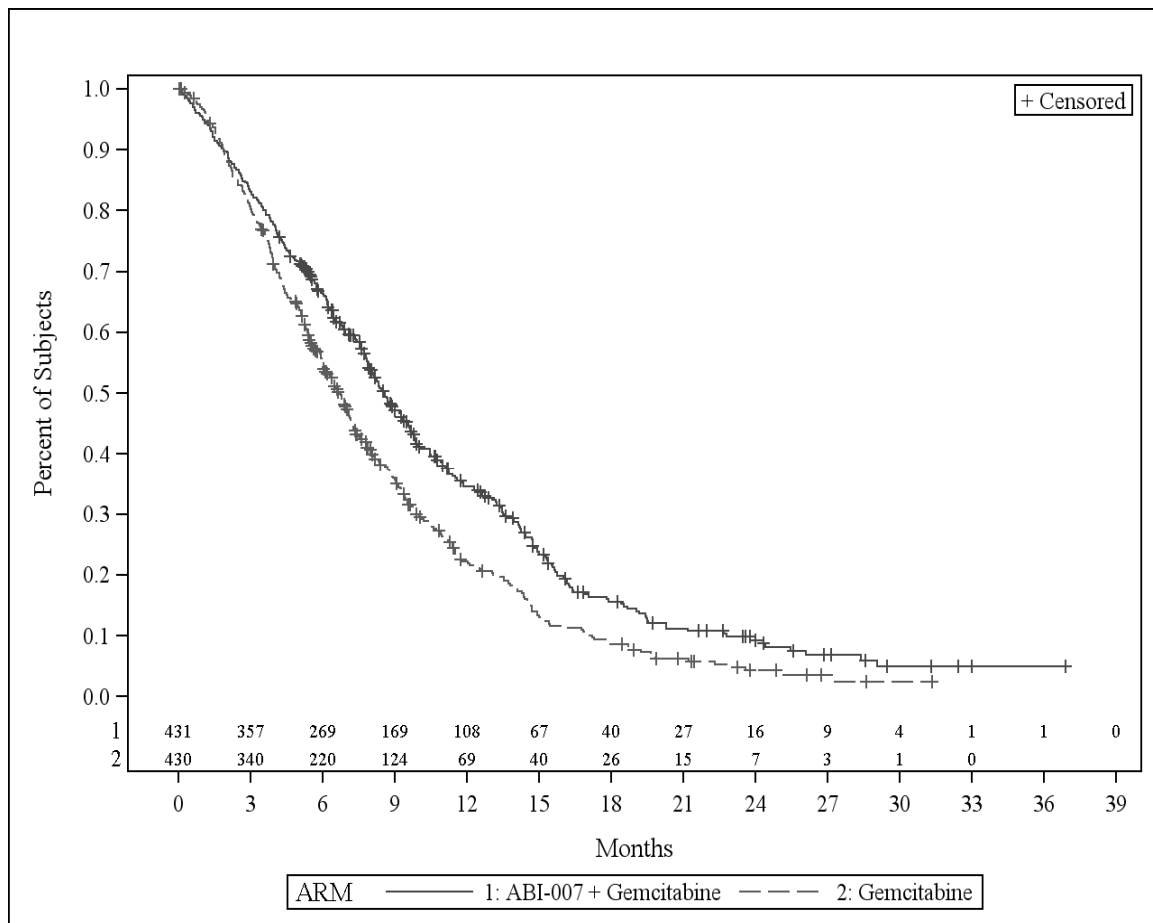
Progression Free Survival

By the time of the database cutoff date (9/17/2012), there were 277 (64%) and 265(62%) of the PFS events for the ABI-007/gemcitabine and gemcitabine alone arm, respectively. The results showed a longer median PFS time observed in the ABI-007/Gemcitabine treated arm as compared with that observed in the gemcitabine alone arm (5.5 months vs. 3.7 months, respectively).   The estimated hazard ratio for PFS was 0.69 (95% CI=0.58, 0.82) in favor of the ABI-007/gemcitabine arm. A summary of the PFS results is shown in the following table:

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Table 10   Reviewer's Summary of Progression Free Survival (based on 9/17/2012 cutoff date)

	ABI-007/Gemcitabine N=431	Gemcitabine N=430
Number (%) of Subjects		
Censored	154 (36)	165 (38)
Event	277 (64)	265 (62)
Death	115 (27)	109 (25)
Progressive disease	162 (38)	156 (36)
Duration of progression free survival (mon.) Median (95% CI) a	5.5 (4.47, 5.95)	3,7 (3.61, 4.04)
p-value (stratified log-rank test)b	<0.0001	
Hazard ratio (95% CI; stratified)c	0.69 (0.581, 0.821)	

a Median and percentiles are based on Kaplan-Meier survival estimates.
b stratification factors include: geographic region (North America vs. Others), Karnofsky performance score (70 to 80 vs. 90 to 100), and presence of liver metastasis (yes vs. no).
 c Estimated using the stratified Cox proportional hazard model.

Reviewer's comments:

- *Patients in the gemcitabine arm appear to have higher risk to be censored compared with patients in the ABI-007/gemcitabine arm. Based on a Cox's proportional hazards model including treatment indicator in the model and using a reversed censoring indicator, the median time to censor was 5.6 (95% CI=5.36,7.29) and 9.0 (95% CI=7.26, 9.49) for gemcitabine alone and ABI-007/gemcitabine arm, respectively (HR=0.59, 95% CI=0.47, 0.74). The results indicate potential differential censoring distribution in the IRR assessed PFS between treatment arms. The differential censoring may result in a biased treatment effect estimate. Such bias would possibly be against the ABI-007/gemcitabine treated arm because more patients in gemcitabine arm who had early discontinuation due to disease progression were removed early from the time-to-event analysis. Also, as pointed out in the applicant's 6/3/2013 clarification letter, the differential censoring was not observed in the investigator determined PFS (with the hazard ratio estimate 0.82 [95% CI=0.60, 1.10] for evaluation of the censoring distribution). The treatment effect based on the investigator assessed PFS (HR=0.61, 95% CI=0.52, 0.71) was smaller than that observed from the IRR assessed PFS (HR=0.69, 95% CI=0.58, 0.82).*

- *Based on the SAP, patients were censored for PFS if they took anti-cancer therapy before the PFS event or if they had a PFS event after missing more than 120 days (~ >1*

assessment time intervals). The following table summarizes the censoring distribution by censoring reasons based on the primary PFS analysis.

It is noted that a patient may have more than one incidence that met the censoring criteria. However, the calculation of the censoring distribution was based on a hierarchical order, i.e. first censored when a patients had a PFS event after missing assessment time for 120 days, then censored when a patient had a PFS event after they took anti-cancer therapy , finally censored when a patient had an assessment discontinued early by the investigator. The censoring distribution of the numbers of patients who had an event after missing assessment time for 120 days or after taking anti-cancer therapies appears to be comparable between treatment arms. However the numbers of patients who had missing post-baseline assessments (5% vs. 9%, for ABI-007/gemcitabine arm and gemcitabine alone arm, respectively) or who had disease assessment discontinued early by the investigators (16% vs. 21%, for ABI-007/gemcitabine arm and gemcitabine alone arm, respectively) appear to be higher in the gemcitabine alone arm.

Table 11   Reviewer's Summary of Censoring Distribution for the Primary PFS Analysis by Censoring Reasons (based on 9/17/2012 cutoff date)

Censoring reasons	ABI-007/Gemcitabine N=431	Gemcitabine N=430
# Patients who had either PD or died	277 (64%)	265 (62%)
#patients who had an event after missing assess. for 120 days (i.e.~>1 assessment periods)	8 (2%)	8 (2%)
#patients who took anti-cancer therapy	20(5%)	15 (3%)
#Patients who had early assessment discontinued by investigator	67 (16%)	92 (21%)
# patient who had missing post baseline assessments	21 (5%)	39 (9%)
# patients who were censored at the last assessment time	38 (9%)	11 (3%)

The corresponding plots for the Kaplan-Meier estimates are presented in the following figure. The two curves appear to be separated from each other except toward the end of the curve.

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Figure 2   Plots of Kaplan-Meier Estimates for PFS (9/17/2012 cutoff date)
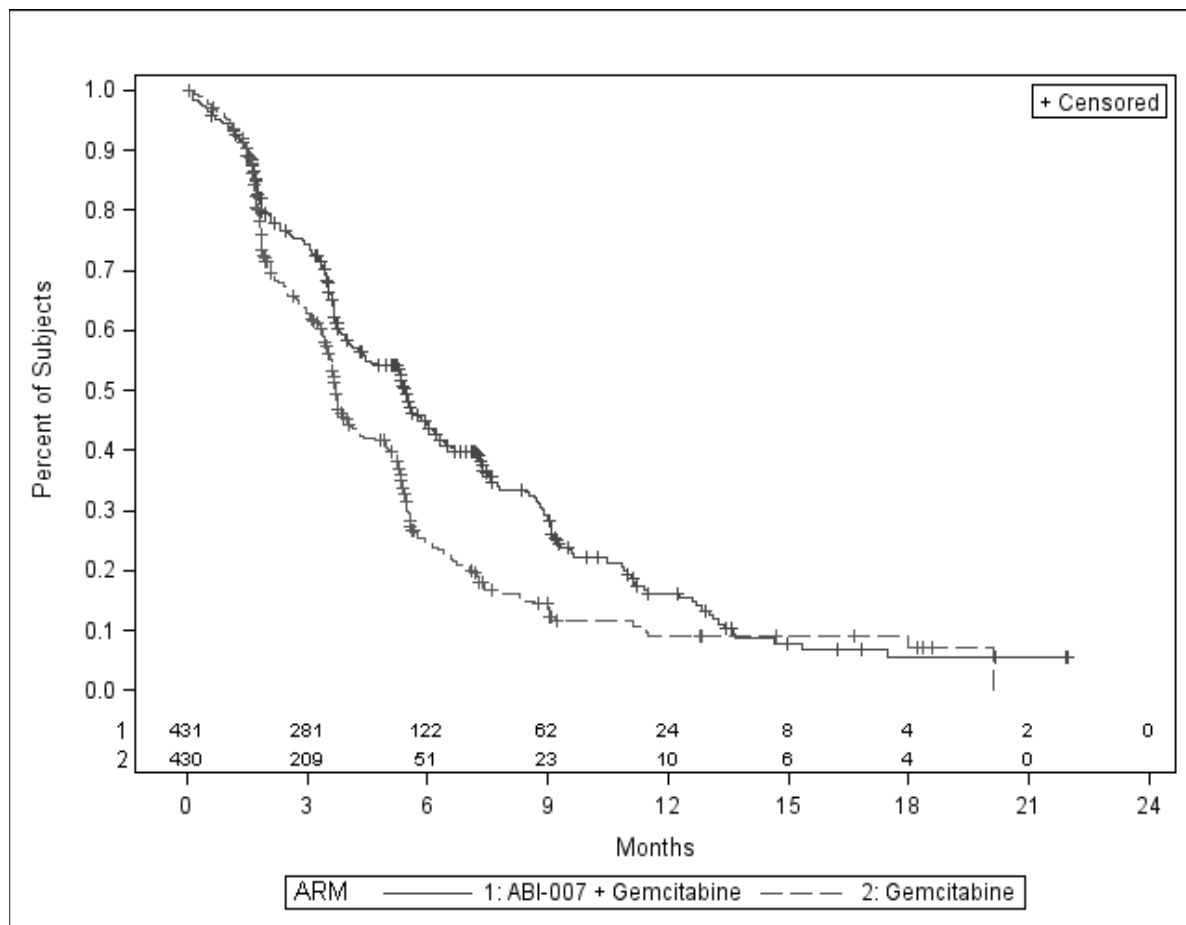
Evaluation of Concordance and Discordance of the IRR and Investigator Assessments
Based on the 9/17/2012 cutoff date, the percentages of patients who had PD or non-PD status
determined by both the IRR and investigators (concordance) are summarized below. The
concordance rate of the IRR and investigator assessments was 79.9%.

Table 12　Reviewer's Summary of Concordance/Discordance in Progressive Disease Status　(based on 9/17/2012 cutoff date)

Status	If progressed	ABI-007/Gemcitabine N=431	Gemcitabine N=430	All Patients N=861
Concordance	Progressive Disease	264 (61.3)	258 (60.0)	522 (60.6)
	Not Progressive Disease	91(21.1)	75(17.4)	166 (19.3)
Discordance	IRR progressed/INV not progressed	13 (3.0)	7 (1.6)	20 (2.3)
	INV progressed/IRR not progressed	63 (14.6)	90 (20.9)	153 (17.8)

Sensitivity Analyses for PFS

Sensitivity analyses for PFS were performed and the results were shown in the following table. The hazard ratio estimates ranged from 0.61 to 0.74 with all the upper bound of 95% CIs being below 1. The results demonstrate robust findings for PFS based on these sensitivity analyses.

Table 13　Reviewer's Sensitivity Analyses for PFS

Analysis #	#event/total ABI-007+Gem vs. Gem	Hazard Ratio [a]	Median (months) (95% CI) ABI-007+Gem	Median (months) (95% CI) Gemcitabine	Difference in median (months) (ABI-007+Gem-Gem)
1. Primary (IRC)	277/431:265/430	0.69(0.58,0.82)	5.45(4.47,5.95)	3.71(3.58,4.04)	1.74
2. Unstratified	277/431:265/430	0.69(0.58,0.82)	5.45(4.47,5.95)	3.71(3.58,4.04)	1.74
3. Censored at the last asses. time prior to anti-cancer therapy, trt discon. due to tox or miss assessment for >120days	240/431:254/430	0.65(0.54,0.78)	5.55(5.29,6.31)	3.71(3.58,4.04)	1.84
4. Censored at the last assessment Time prior to anti-cancer therapy only	308/431:304/430	0.74(0.63,0.86)	5.52(5.29,6.05)	3.88(3.68,4.99)	1.64
5. Same as primary except using Investigator assessments.	327/431:348/430	0.61(0.52,0.71)	5.45(4.47,5.95)	3.52(3.25,3.65)	1.81
6. Per protocol	260/394:242/377	0.69(0.58,0.83)	5.55(5.29,6.31)	3.75(3.61,4.34)	1.77
7. Multivariate Cox's model without baseline CA19-9 [b]	277/431:265/427	0.68(0.58,0.81)	5.45(4.47,5.95)	3.71(3.58,4.04)	1.74
8. Multivariate Cox's model including baseline CA19-9 [b]	247/379:238/371	0.68(0.57,0.81)	5.45(4.47,5.95)	3.71(3.58,4.04)	1.74

[a] Estimated using the stratified Cox proportional hazard model.

[b] Note: The Cox proportional hazards model included the following explanatory covariates: treatment groups, age ($\geq$ 65 years vs. <65 years), sex, Karnofsky performance status (70 to 80 versus 90 to 100), geographic region (North America was used as the reference, include 3 d.f. for the effect from E. Europe, Australia and W. Europe), pancreatic cancer primary location (head versus other), presence of biliary stent, previous Whipple procedure, presence of liver metastases, presence of pulmonary metastases, peritoneal carcinomatosis, stage of diagnosis (IV versus other), number of metastatic sites (1,2,3, >3) and level of CA19-9.(1 = 'ULN-<59xULN';2 = 'Normal';3 = '>= 59xULN)

Reviewer's comments:

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- *The analysis #3 considers additional censoring based on patients who had treatment discontinued due to toxicity. There were 37 and 11 additional censoring cases in the ABI-007/gemcitabine and gemcitabine arm, respectively. With this additional censoring on toxicity, the hazard ratio estimate was 0.65, (95% CI=0.54, 0.78) which supports the primary PFS analysis.*

- *Additional exploratory analyses are also performed by Cox's proportional hazards models including the potential prognostic factors with stepwise variable selection method. Two analyses were performed based on whether CA19-9 level was included in the model or not (sensitivity analyses #7 and 8). The hazards ratio estimates for treatment effect were the same (HR=0.68), based on both analyses which were also close to the primary result (i.e. HR=0.69). The factors that have been selected based on both models include KPS status and liver metastasis status.*

- *Additional sensitivity analyses (analyses #4, 5, 6 shown in the table) by censoring patients without events at the last disease assessment time, using the investigators' PFS assessments or based on per-protocol population, all provide supportive results for the primary PFS analysis.*

Best Overall Response Rate

The objective response rate based on independent assessments appears to be higher in the ABI-007/gemcitabine arm as compared with the rate in the gemcitabine treated arm (23% vs. 7%, respectively, p-value < 0.0001 based on the Chi-square statistic). The median duration of response was also longer in the ABI-007/gemcitabine arm as compared with that in the gemcitabine treated arm. The median durations of response were 7.4 (95% CI=5.6, 8.5) and 7.1 (95% CI=3.8, NA) months for ABI-007/gemcitabine and gemcitabine alone arm, respectively.

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Table 14   Reviewer's Summary of Objective Response Rate and Duration of Response

Variable	ABI-007/Gemcitabine N=431	Gemcitabine N=430	P-value[a]
Patients with Confirmed Complete or Partial Overall Response	99 (23%)	31 (7%)	
95% Confidence Interval	(19.1, 27.2)	(5.0, 10.1)	< 0.0001
Complete Response	1 (< 1%)	0	
Partial Response	98 (23%)	31 (7%)	
Stable Disease	118 (27%)	122 (28%)	
Progressive Disease	86 (20%)	110 (26%)	
Not Evaluable ot No Post-baseline Assessment	128 (30%)	167 (39%)	
Duration of response #Progression/ # with CR or PR Median duration of response (95% CI)	10/31 (32%) 7.4 (5.552, 8.476)	47/99 (47%) 7.1 (3.745,NA)	
Hazard Ratio (95% CI)	1.07 (0.525, 2.161)		

a.   Based on a Chi-square statistic.

Reviewer's Comments:
- *The duration of response presented by this reviewer was based on the event and censoring definition similar to those definitions used for the primary PFS analysis. Based on the applicant's definition, there were 8/31 (26%) and 39/99 (39%) disease progression events in the ABI-007/gemcitabine and gemcitabine alone arm, respectively. The applicant's calculation did not consider deaths as the disease progression events. The median durations of response based on the applicant's assessment were 8.5 (95% CI=6.5, 11.8) and 7.9 (95% CI=3.8, NA) moths for ABI-007/gemcitabine and gemcitabine alone arm, respectively. This is not a valid comparison as this is not in the as randomized patients but only in responders.*

3.3   Evaluation of Safety

The safety evaluation was not performed in this statistical review. Please refer to the clinical review for more details for the safety assessments.

3.4   Benefit-Risk Assessment

The benefit-risk assessment was not performed in this statistical review.

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4   FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Subgroup analysis results based on gender, race, age group and geographic regions were presented in this section.

4.1   Gender, Race, Age, and Geographic Region

Gender

The hazards ratio estimates based on OS for both male and female subgroups were equal to 0.72 with the upper bound of the 95% CIs being less than 1 which appears to support the favorable treatment effect in the ABI-007/gemcitabine treated arm for both gender subgroups.

Table 15   Reviewer's Summary of Hazard Ratios for OS by Gender

		ABI-007/Gemcitabine **N=431**	Gemcitabine **N=430**
Male	Number of events / total	195/245	218/257
	HR (95% CI) [a]	0.72(0.59,0.88)	
Female	Number of events / total	138/186	141/173
	HR (95% CI) [a]	0.72(0.56,0.93)	

[a]From Cox's Proportional Hazards Model, stratified by geographic region (North America vs. Others), Karnofsky performance score (70 to 80 vs. 90 to 100), and presence of liver metastasis (yes vs. no).

Race

The hazard ratio estimates based on OS from the White and non-White subgroups were both smaller than 1 which demonstrates favorable treatment effect in the ABI-007/gemcitabine arm. The hazard ratio estimate based on the non-White subgroup appears to be smaller than that in the White subgroup (HR=0.67 vs. 0.73, respectively). However, the interpretation of the non-White subgroup should be taken with caution because it is a non-randomized subgroup and only 7% of the patients were in this subgroup which resulted in a wider confidence interval.

Table 16   Reviewer's Summary of Hazard Ratios for OS by Race

		ABI-007/Gemcitabine N=431	Gemcitabine N=430
White	Number of events / total	313/403	337/401
	HR (95% CI) [a]	0.73(0.63,0.86)	
Non-White	Number of events / total	20/28	22/29
	HR (95% CI) [a]	0.67(0.44,1.01)	

[a]From Cox's Proportional Hazards Model, stratified by geographic region (North America vs. Others), Karnofsky performance score (70 to 80 vs. 90 to 100), and presence of liver metastasis (yes vs. no).

Age

The hazard ratio estimates based on OS for both age subgroups were less than 1 which showed a more favorable result observed in the ABI-007/gemcitabine treated arm. Patients who were 65 years or older appear to have a larger hazard ratio estimate. However, because the analysis was based on non-randomized patient subgroups and a smaller sample size in the subgroup, the interpretation of the differential treatment effect in younger and older patient subgroups should be taken with caution.

Table 17   Reviewer's Summary of Hazard Ratios for OS by Age Subgroup

		ABI-007/Gemcitabine N=431	Gemcitabine N=430
<65 years old	Number of events / total	188/254	209/242
	HR (95% CI) [a]	0.64(0.53,0.79)	
≥65 years old	Number of events / total	145/177	150/188
	HR (95% CI) [a]	0.81(0.63,1.03)	

[a] From Cox's Proportional Hazards Model, stratified by geographic region (North America vs. Others), Karnofsky performance score (70 to 80 vs. 90 to 100), and presence of liver metastasis (yes vs. no).

Geographic Region

The hazard ratio estimates for all 4 regions are all less than 1 showing a favorable result observed in the ABI-007/gemcitabine treated arm. The hazard ratio estimate based on Eastern Europe appears to be higher than the hazard ratio estimates from the other regions. However, because the nature of the subgroup analyses and a smaller sample size in the subgroups, the interpretation of the differential treatment effect among regions should be taken with caution.

Table 18   Reviewer's Summary of PFS results by Geographic Regions

		ABI-007/Gemcitabine N=431	Gemcitabine N=430
Australia	Number of events / total	50/61	53/59
	HR (95% CI) [a]	0.67(0.44,1.01)	
Eastern Europe	Number of events / total	62/64	59/62
	HR (95% CI) [a]	0.84(0.58,1.23)	
Western Europe	Number of events / total	14/38	17/38
	HR (95% CI) [a]	0.72(0.35,1.47)	
North America	Number of events / total	207/268	230/271
	HR (95% CI) [a]	0.68(0.56,0.82)	

[a] From Cox's Proportional Hazards Model, stratified by geographic region (North America vs. Others), Karnofsky performance score (70 to 80 vs. 90 to 100), and presence of liver metastasis (yes vs. no).

4.2   Other Special/Subgroup Populations

Forest plots of the hazard ratio estimates based on OS and the corresponding 95% are shown in this section by demographic information and baseline characteristics.

For the forest plots by the demographic information, almost all the hazard ratio estimates were smaller than 1 except in patients who were 75 years old or older. Due to a smaller sample size in this subgroup, the 95% CI was wide and the interpretation should be taken with caution.

Figure 3   Forest Plots based on Hazard Ratio Estimates for OS by Demographic Information

Subgroup		Hazard Ratio and 95% CL	ABI007+Gem(#ev/N):Gem(#ev/N)	HR(95%CI)
Age	< 65		188/254:209/242	0.64(0.53,0.79)
Age	>=65		145/177:150/188	0.81(0.63,1.03)
Age	< 75		301/390:323/381	0.68(0.58,0.80)
Age	>= 75		32/41:36/49	1.08(0.65,1.80)
KPS	70-80		127/161:141/158	0.67(0.52,0.85)
KPS	90-100		206/270:218/272	0.75(0.62,0.91)
Race	Non-White		20/28:22/29	0.63(0.33,1.22)
Race	White		313/403:337/401	0.73(0.63,0.86)
Region	AUSTRALIA		50/61:53/59	0.67(0.44,1.01)
Region	E. EUROPE		62/64:59/62	0.84(0.58,1.23)
Region	N. AMERICA		207/268:230/271	0.68(0.56,0.82)
Region	W. EUROPE		14/38:17/38	0.72(0.35,1.47)
Sex	Female		138/186:141/173	0.72(0.56,0.93)
Sex	Male		195/245:218/257	0.72(0.59,0.88)
Overall			333/431:359/430	0.72(0.62,0.83)

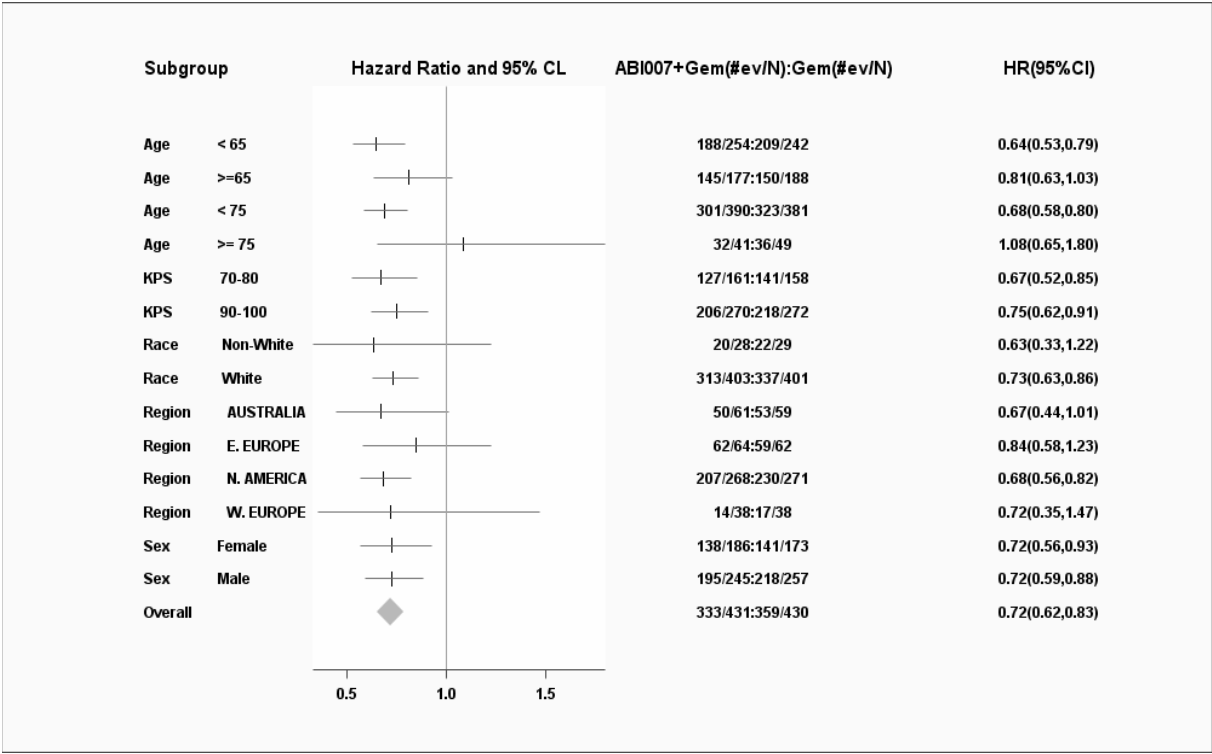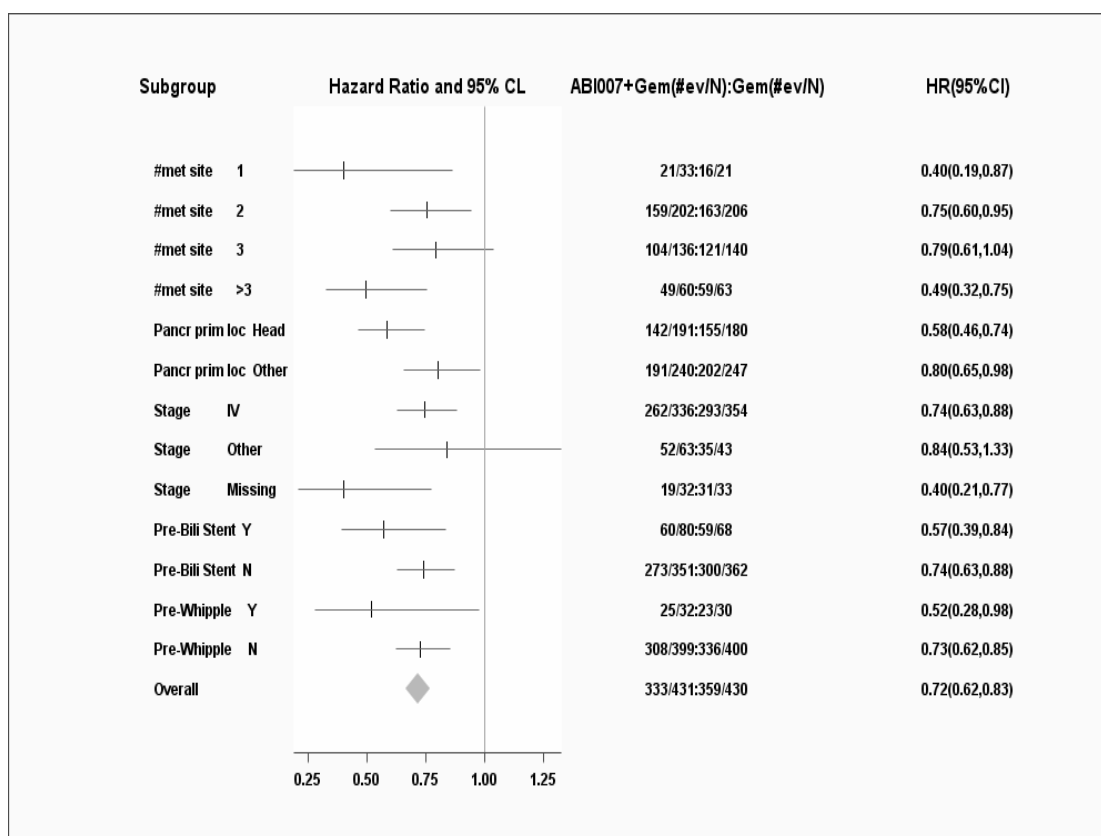The hazard ratio estimates are based on the Cox's Proportional Hazards Model, stratified by geographic region (North America vs. Others), Karnofsky performance score (70 to 80 vs. 90 to 100), and presence of liver metastasis (yes vs. no).

Similarly, the hazard ratio estimates were almost all smaller than 1 (shown in the forest plots below) based on OS by baseline characteristics, except for the hazard ratio estimate observed in the CA19-9 normal subgroup. However, due to a smaller sample size in this subgroup, the 95% CI was wide and one needs to take extra caution in the interpretation in the CA19-9 normal subgroup.

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Figure 4 **Forest Plots based on Hazard Ratio Estimates for OS by Baseline Characteristics – (1)**

The hazard ratio estimates are based on the Cox's Proportional Hazards Model, stratified by geographic region (North America vs. Others), Karnofsky performance score (70 to 80 vs. 90 to 100), and presence of liver metastasis (yes vs. no).

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Figure 5   Forest Plots based on Hazard Ratio Estimates for OS by Baseline Characteristics – (2)
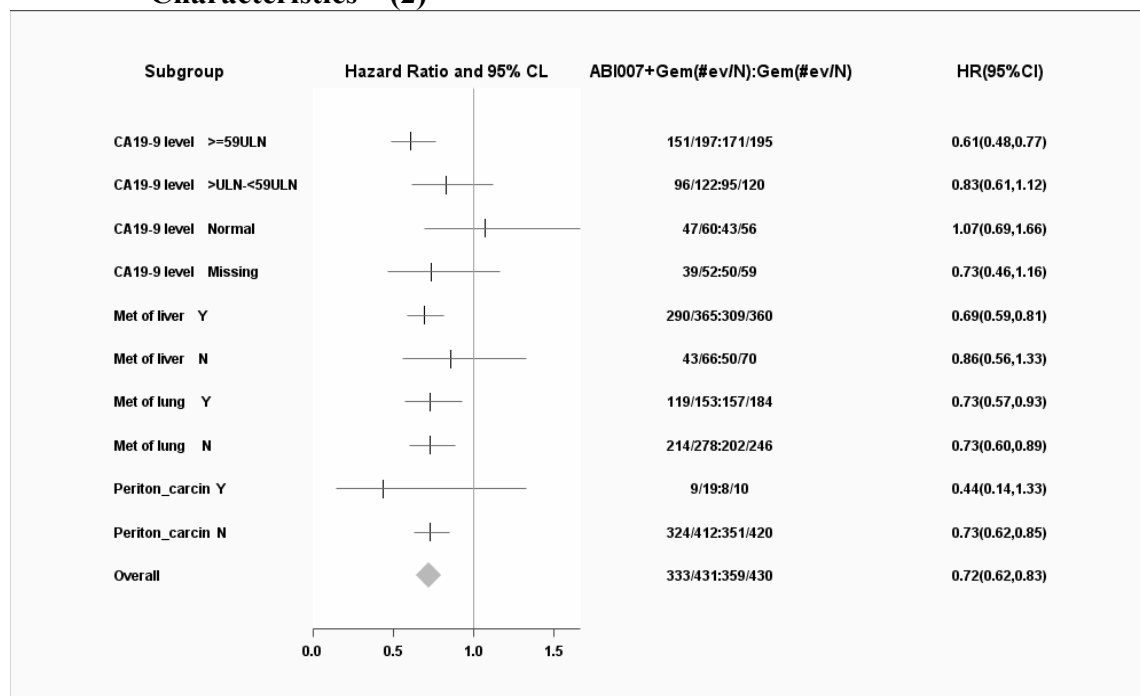
The hazard ratio estimates are based on the Cox's Proportional Hazards Model, stratified by geographic region (North America vs. Others), Karnofsky performance score (70 to 80 vs. 90 to 100), and presence of liver metastasis (yes vs. no).

Subgroup Analysis for Baseline Pain Status

A subgroup analysis by baseline pain status was also performed. The baseline pain status was defined as patients who had any baseline sign or symptom of pain (extracted from the CE [clinical event] data) or patients who took narcotic medication prior to randomization (from ADCM data [Concomitant Medication analysis data]). Two analyses were performed, one includes patients who took narcotic medications only (n=509) and the other includes patients who had baseline sign and symptom of pain or patients who took narcotic medication prior to randomization (n=734). The results showed that ABI-007/gemcitabine treated arm appears to have longer overall survival in patients who experienced baseline pain as compared with those shown in the gemcitabine treated arm.

Table 19   Reviewer's Summary of OS results by Baseline Pain Status

Subgroup	#event/total ABI-007+Gem vs Gem	Hazard Ratio [a]	Median (95% CI) Gem only	Median (95% CI) Abi-007+Gem	Difference (ABI-007+Gem- Gem)
1: patients who had baseline pain signs and symptoms or who took narcotic	295/375:309/359	0.67(0.57,0.78)	6.3(5.5,6.9)	8.2(7.6,9.0)	1.94
2: Patients who took pre-treatment narcotic	194/256:219/253	0.62(0.51,0.76)	5.8(5.2,6.5)	8.2(6.9,9.2)	2.46

[a] Estimated using the stratified Cox proportional hazard model

5   SUMMARY AND CONCLUSIONS

5.1   Statistical Issues and Collective Evidence

Based on study CA046, the results showed significant improvement of the overall survival (HR=0.72, 95% CI=0.62, 0.84; p-value<0.0001). The median OS time was improved from 6.7 months (95% CI=6.0, 7.2) in the gemcitabine arm to 8.5 months (95% CI=7.9, 9.5) in the ABI-007/gemcitabine arm. The hazard ratio estimate was 0.72 (95% CI=0.62, 0.84) in favor of the ABI-007/gemcitabine arm. The favorable results from the ABI-007/gemcitabine arm were robust based on various sensitivity analyses and consistent results were shown throughout various subgroups. The results based on progression free survival also showed statistical significance in favor of the ABI-007/gemcitabine arm (HR=0.69, 95% CI=0.58, 0.82; p-value <0.0001). The median PFS time was 5.5 months (95% CI=4.5, 6.0) and 3.7 months (95% CI=3.6, 4.0) for ABI-007/gemcitabine arm and gemcitabine alone arm, respectively. In addition, the result based on the objective response rate also demonstrates statistical significance in favor of the ABI-007/gemcitabine arm (ORR=23% vs. 7% for ABI-007/Gemcitabine arm and gemcitabine alone arm, respectively; p-value <0.0001). A summary of these primary efficacy results is shown below:

Table 20   Reviewer's Summary of PFS, OS and ORR results

Endpoint		ABI-007/Gemcitabine N=431	Gemcitabine N=430
OS (based on 9/17/2012 cutoff date)	Number (%) of events death	333(77)	359 (83)
	Duration of progression free survival (mon.) Median (95% CI) a	8.5 (7.89,9.53)	6.7 (6.01, 7.23)
	p-value (stratified log-rank test)b	<0.0001	
	Hazard ratio (95% CI; stratified)c	0.72 (0.617, 0.835)	
PFS (based on 9/17/2012 cutoff date)	Number (%) of events Progressive disease	277 (65)	265 (62)
	Duration of progression free survival (mon.) Median (95% CI) a	5.5 (4.47,5.95)	3.7 (3.61, 4.04)
	p-value (stratified log-rank test)b	<0.0001	
	Hazard ratio (95% CI; stratified)c	0.69 (0581, 0.821)	
ORR	Objective response rate 95% CI	99 (23%) (19.1%, 27.2%)	31 (7%) (5.0%, 10.1%)
	Median duration of response(month) a 95% CI	7.4 (5.55, 8.48)	7.1 (3.75, NA)
	p-value (Chi-square test)	<0.0001	

CI=confidence interval;
a Median and percentiles are based on Kaplan-Meier survival estimates.
b Stratified log rank test, stratified by geographic region (North America vs. Others), Karnofsky performance score (70 to 80 vs. 90 to 100), and presence of liver metastasis (yes vs. no).
c Estimated using the Cox proportional hazard model stratified by the stratification factors.

Based on subgroup analyses, the ABI-007/gemcitabine treated arm appears to have longer overall survival across various demographic and baseline disease characteristic subgroups including patients who experienced baseline pain .

The main issue from this study is the concern of the unplanned sample size increase.   However, based on this reviewer's analyses, the more favorable treatment effect in the ABI-007/gemcitabine treated arm does not seem to be affect by different cutoff dates, either based on the original planned number of deaths (=455) or the revised planned number of deaths (=608). The hazard ratios estimates were 0.69 and 0.73 based on number of deaths 455 and 608, respectively. Another issue is on the finding of the differential censoring distribution in the analysis of PFS based on the independent assessment. This review acknowledges that the potential bias for the treatment effect estimates based on IRR assessed PFS may be introduced as a result of the differential censoring. However, the results may appear to be more conservative

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as compared to those results from the scenario of no differential censoring and they also appear to be supported by the investigator assessed PFS results and other sensitivity analyses.

5.2   Conclusions and Recommendations

In summary, based on study CA046, the results demonstrated statistically significant improvement on overall survival, progression free survival and objective response rate for the ABI-007/gemcitabine treated arm in patients with _____ (b) (4) metastatic adenocarcinoma of the pancreas.   The results appear to be robust based on sensitivity analyses including the analyses using different database cutoff dates. The results also appear to be consistent across various subgroups including patients who experienced baseline pain status.

In conclusion, this statistical reviewer confirms the applicant's results submitted. Whether the results demonstrate an overall favorable benefit to risk ratio in supporting an indication of the ABI-007/gemcitabine treatment in patients with _____ (b) (4) metastatic adenocarcinoma of the pancreas will defer to the clinical review team.

5.3   Labeling Recommendations

This statistical review supported the inclusion of results from the overall survival, progression free survival and objective response rate for the indication of _____ (b) (4) metastatic adenocarcinoma of the pancreas based on the ABI-007/gemcitabine treatment.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21660Orig1s037

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

Submission Date: March 21, 2013

NDA Number:	NDA 21661 Suppl 37 (SDN 519 eCTD 257)
Product Name:	Abraxane (nab-paclitaxel)
Route of Administration:	Intravenous
Proposed Indication:	Pancreatic Cancer
Submission Type:	Efficacy Supplement
Sponsor:	Celegene
Reviewer:	Stacy S. Shord, Pharm.D.
Team Lead:	Hong Zhao, Ph.D.

Introduction

On March 21, 2013, Celegene submitted a supplemental NDA to provide safety and efficacy data for Abraxane for the first-line treatment of patients with   (b) (4) metastatic adenocarcinoma of the pancreas in combination with gemcitabine. The proposed dose is 125 mg/m^2 as an intravenous infusion over 30-40 minutes in combination with gemcitabine at a dose of 1,000 mg/m^2 as an intravenous infusion over 30-40 min beginning immediately after the completion of Abraxane administration on days 1, 8, and 15 of each 28-day treatment cycle. The submission includes data from Study CA046 (registration trial) and Study CA040 (dose escalation and expansion trial). Biomarker and PET reports were provided for Study CA040. Pharmacokinetic samples were not collected as part of either study.

On July 23, 2013, the clinical review team requested Clinical Pharmacology review the proposed changes to Section 7 of the labeling.

Background

Abraxane is an albumin-bound form of paclitaxel with a mean particle size of approximately 130 nanometers. Paclitaxel exists in the particles in a non-crystalline, amorphous state. It is a microtubule inhibitor that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. Paclitaxel induces abnormal arrays or "bundles" of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

Abraxane has been approved for:

- The treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy at a dose of 260 mg/m^2 intravenously over 30 minutes every 3 weeks; prior therapy should have included an anthracycline unless clinically contraindicated (approved January 7, 2005);

- First-line treatment of locally advanced or metastatic non-small cell lung cancer at a dose of 100 mg/m^2 intravenously over 30 minutes on Days 1, 8, and 15 of each 21-day cycle, in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy (October 11, 2012).

Labeling

The following text lists the proposed labeling as submitted by Celegene. The tracked changes identify proposed changes by clinical pharmacology regarding hepatic impairment and drug interactions.

------- **DOSAGE AND ADMINISTRATION** -----

- Metastatic Breast Cancer: Recommended dosage of ABRAXANE is 260 mg/m^2 intravenously over 30 minutes every 3 weeks. (2.1)
- Non-Small Cell Lung Cancer: Recommended dosage of ABRAXANE is 100 mg/m^2 intravenously over 30 minutes on Days 1, 8, and 15 of each 21-day cycle;   (b) (4) . (2.2)
- Adenocarcinoma of the Pancreas: Recommended dosage of ABRAXANE is 125 mg/m^2 intravenously over 30-40 minutes on Days 1, 8 and 15 of each 28-day cycle;   (b) (4) (b) (4) (2.3)
- No adjustment is necessary for patients with mild hepatic impairment. Withhold ABRAXANE if AST > 10 x ULN or bilirubin > 5 x ULN. Reduce starting dose in patients with moderate to severe hepatic impairment. (2 3)
- Dose Reductions: Dose reductions or discontinuation may be needed based on severe hematologic, neurologic, cutaneous, or gastrointestinal toxicities. (2 5)
- Use caution when handling cytotoxic drugs. Closely monitor the infusion site for extravasation and infiltration. No premedication is required prior to administration. (2.6)

-------------- **DRUG INTERACTIONS** -------------

- Use caution when concomitantly administering ABRAXANE with inhibitors or inducers of either CYP2C8 or CYP3A4. (7)

2 DOSAGE AND ADMINISTRATION

2.4 Dosage in Patients with Hepatic Impairment

No dose adjustment is necessary for patients with mild hepatic impairment. Patients with moderate and severe hepatic impairment treated with ABRAXANE may be at increased risk of toxicities known to paclitaxel. Withhold ABRAXANE if AST >10 x ULN or bilirubin > 5 x ULN. Recommendations for dosage adjustment for the first course of therapy are shown in Table 1.

For metastatic breast cancer, the dose of ABRAXANE can be increased from 130 mg/m^2 up to 200 mg/m^2 in patients with severe hepatic impairment in subsequent cycles based on individual tolerance.

(b) (4)

Monitor patients closely *[see Warnings and Precautions (5.6), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)]*.

Table 1: Recommendations for Starting Dose in Patients with Hepatic Impairment

	SGOT (AST) Levels		Bilirubin Levels	ABRAXANE Dose[a]		
				MBC	NSCLC[c]	Pancreatic[c] Adenocarcinoma
Mild	< 10 x ULN	AND	> ULN to ≤ 1 25 x ULN	260 mg/m^2	100 mg/m^2	125 mg/m^2
Moderate	< 10 x ULN	AND	1.26 to 2 x ULN	200 mg/m^2	75 mg/m^2	Not Recommended
Severe	< 10 x ULN	AND	2.01 to 5 x ULN	130 mg/m^2 [b]	50 mg/m^2	Not Recommended
	> 10 x ULN	OR	> 5 x ULN	(b) (4)	(b) (4)	Not Recommended

MBC = Metastatic Breast Cancer; NSCLC = Non-Small Cell Lung Cancer.
[a] Dosage recommendations are for the first course of therapy. The need for further dose adjustments in subsequent courses should be based on individual tolerance.
[b] A dose increase to 200 mg/m^2 in subsequent courses should be considered based on individual tolerance.

(b) (4)

7   DRUG INTERACTIONS

The metabolism of paclitaxel is catalyzed by CYP2C8 and CYP3A4. In the absence of formal clinical drug interaction studies, caution should be exercised when administering ABRAXANE concomitantly with medicines known to inhibit (e.g., ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir) or induce (e.g., rifampicin, carbamazepine, phenytoin, efavirenz, and nevirapine) either CYP2C8 or CYP3A4.

8   USE IN SPECIFIC POPULATIONS

(b) (4)

8.6   Patients with Hepatic Impairment

Because the exposure and toxicity of paclitaxel can be increased in patients with hepatic impairment, the administration of ABRAXANE should be performed with caution in patients with hepatic impairment *[see Dosage and Administration (2.4), Warnings and Precautions (5 6), and Clinical Pharmacology (12.3)]*. **12   CLINICAL PHARMACOLOGY**

Pharmacokinetic Interactions between ABRAXANE and Carboplatin

Administration of carboplatin immediately after the completion of ABRAXANE infusion to patients with non-small cell lung cancer did not cause clinically meaningful changes in paclitaxel exposure. The observed mean AUC_{inf} of free carboplatin was approximately 23% higher than the targeted value (6 min*mg/mL), but its mean half-life and clearance were consistent with those reported in the absence of paclitaxel.

Pharmacokinetic Interactions between ABRAXANE and Gemcitabine

A pharmacokinetic interaction between gemcitabine and ABRAXANE has not been studied.

Signatures

Stacy S Shord, Pharm.D.
Reviewer
Division of Clinical Pharmacology V

Hong Zhao, Ph.D.
Team Leader
Division of Clinical Pharmacology V

Cc: DOP2: RPM – **M Libeg**; MO – **A Nair**; MTL – **S Lemery**
        DCPV: DDD - **B Booth**;   DD - N**A Rahman**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21660Orig1s037

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	July 2, 2013
To:	Patricia Keegan, MD Director **Division of Oncology Products 2 (DOP2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
	Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Nathan Caulk, MS, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
	Marybeth Toscano, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name) Dosage Form and Route:	ABRAXANE for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) (albumin-bound)
Application Type/Number:	NDA 21-660
Supplement Number:	S-037
Applicant:	Celgene Corporation

1   INTRODUCTION

On March 21, 2013, Celgene Corporation submitted for the Agency's review an Efficacy Supplement (S-037) to their approved New Drug Application (NDA) 21-660 for ABRAXANE (paclitaxel protein-bound particles for injectable suspension) (albumin-bound). The purpose of this submission is to provide for a new indication for the first-line treatment of patients with _____ (b) (4) metastatic adenocarcinoma of the pancreas, in combination with gemcitabine.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology Products 2 (DOP2) on May 17, 2013 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for ABRAXANE (paclitaxel protein-bound particles for injectable suspension) (albumin-bound).

2   MATERIAL REVIEWED

- Draft ABRAXANE (paclitaxel protein-bound particles for injectable suspension) (albumin-bound) PPI received on March 21, 2013, and received by DMPP and OPDP on March 21, 2013.

- Draft ABRAXANE (paclitaxel protein-bound particles for injectable suspension) (albumin-bound) Prescribing Information (PI) received on March 21, 2013, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 20, 2013.

3   REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible

- ensured that the PPI is consistent with the Prescribing Information (PI)

- removed unnecessary or redundant information

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.

- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

Reference ID: 3334667

MEMORANDUM
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)

****Pre-decisional Agency Information****

Memorandum

Date:	July 2, 2013
To:	Meredith Liberg, Regulatory Project Manager Division of Oncology Products 2 (DOP2) Office of Hematology Oncology Products (OHOP)
From:	Marybeth Toscano, PharmD, Regulatory Review Officer Office of Prescription Drug Promotion (OPDP)
Subject:	OPDP comments on draft product labeling for Abraxane for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) (albumin-bound) NDA 21660, S37

In response to your consult request dated May 17, 2013, OPDP has reviewed the proposed product labeling (PI) for Abraxane efficacy supplement S37. Specifically, OPDP has reviewed the Highlights and Sections 1, 2, 5, 6, 7, 8.5, 12, 14.3, and 17.

If you have any questions about OPDP's comments on the PI, please contact Marybeth Toscano at 6-2617 or at Marybeth.Toscano@fda.hhs.gov.

Section	Statement from draft	Comment
• **8 USE IN SPECIAL POPULATIONS-** **6.3 Clinical Trials Experience in Adenocarcinoma of the Pancreas**	(b) (4)	This statement may be used misleadingly in promotion.

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

/s/

MARYBETH TOSCANO
07/02/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21660Orig1s037

<u>ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS</u>

IND 115027

MEETING PRELIMINARY COMMENTS

Abraxis Bioscience LLC, a wholly-owned subsidiary of Celgene Corporation
c/o Abraxis Bioscience, LLC, Corporation
Attention: Deborah Tady, Pharm.D., RPh, MBA, RAC
Director, Global Regulatory Affairs-Oncology Solid Tumors
9225 Indian Creek Pkwy., Suite 900
Overland Park, KS 66210

Dear Dr. Tady:

Please refer to your **Investigational New Drug Application (IND)** submitted under section
505(i) of the Federal Food, Drug, and Cosmetic Act for "Abraxane."

We also refer to your October 9, 2012, correspondence requesting a Type B pre-sNDA meeting
to discuss with the FDA the data to be used as the primary basis of efficacy and safety for the
new indication for Abraxane in combination with gemcitabine for the first-line treatment of
patients with advanced adenocarcinoma of the pancreas.

Our preliminary responses to your meeting questions are enclosed.

If you have any questions, call me, at (301) 796-4236.

Sincerely,

{See appended electronic signature page}

Mona Patel, Pharm.D.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
DOP2's End-of-Phase 2 General Advice for Planned Marketing Applications
Additional DOP2 CDISC Guidance

PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: pre-sNDA
Meeting Date and Time: January 15, 2013 12-1pm
Meeting Location: WO, Bldg., 22 Room 1311
Application Number: IND 115027
Product Name: Abraxane
Indication: advanced adenocarcinoma of the pancreas
Sponsor/Applicant Name: Abraxis Bioscience LLC

FDA Attendees:
Patricia Keegan, M.D., Director, DOP2/OHOP/CDER
Mona Patel, Pharm.D., Regulatory Project Manager, DOP2/OHOP/CDER
Steven Lemery, M.D., M.H.S., Medical Officer, Team Leader, DOP2/OHOP/CDER
Shan Pradhan, M.D., Medical Officer, DOP2/OHOP/CDER
Abhilasha Nair, M.D., Medical Officer, DOP2/OHOP/CDER
Hong Zhao, Ph.D., Clinical Pharmacology Team Leader, OTS/OCP/CDER
Hua Lillian Zhang, Ph.D., Clinical Pharmacologist, OTS/OCP/CDER
Whitney Helms, Ph.D., Supervisory Toxicologist, DHOT/OHOP/CDER
Margaret Brower, Ph.D., Toxicologist, DHOT/OHOP/CDER
Kun He, Ph.D., Supervisory Statistician, OTS/OB/DBV
Janet Xiaoping Jiang, Ph.D., Statistical Reviewer, OTS/OB/DBV
Liang Zhou, Ph.D., Supervisory Chemist, OMPT/CDER/OPS/ONDQA/DNDQAI

Abraxis Bioscience Attendees:

Brian Lu, MD	Director, Clinical Research & Development
Xiaolong Luo, PhD	Senior Research Fellow, Biostatistics
Richard Pilot, MD	Senior Director, Drug Safety and Risk Management
Markus Renschler, MD	Vice President, Clinical Research & Development
Alfredo Romano, MD	Senior Director, Clinical Research & Development
Gad Soffer, PhD, MBA	Executive Director, Project Leadership
Joycelyn Seymour, BA, RAC	Manager, Regulatory Affairs
Deborah Tady, PharmD, MBA	Senior Director, Regulatory Affairs
Renu Vaish, MS	Executive Director, Regulatory Affairs
Xinyu Wei, PhD	Associate Director, Biostatistics

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for January 15, 2013, between Abraxis Bioscience LLC and the Division of Oncology Products 2. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you

determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the premeeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting.

1.0 MEETING OBJECTIVES

- Provide an overview of the Abraxane development program for adenocarcinoma of the pancreas and the top-line results from the pivotal phase 3 multicenter, international, randomized, open-label, controlled, first-line treatment study of Abraxane plus gemcitabine versus gemcitabine monotherapy (study CA046).

- Identify any potential problems or regulatory issues that will need to be addressed in the planned sNDA to facilitate the filing and enable review of the sNDA.

2.0   BACKGROUND

On October 9, 2012, Abraxis Bioscience, LLC, requested a Type B, pre-sNDA meeting to discuss the data obtained from Protocol CA046 to be used as the primary basis of an sNDA for Abraxane, when administered in combination with gemcitabine, for the first-line treatment of patients with _____ (b) (4) metastatic adenocarcinoma of the pancreas. Abraxis Bioscience, LLC, previously submitted a Type C meeting request and meeting package to the IND on August 24, 2012 to review the approach for the summarization and presentation of data in a sNDA; FDA denied the request on September 7, 2012, advising Abraxis Bioscience, LLC, to submit a new meeting request after performing the primary analysis for Study CA046 and determining that there is at least preliminary evidence of effectiveness to support a request for the proposed new indication.

On October 16, 2012, FDA provided preliminary guidance for an sNDA submission through written responses to the questions posed in the briefing package submitted by Abraxis Bioscience, LLC, on August 24, 2012. FDA provided recommendations regarding the format of content and location of the Integrated Summary of Safety and the Integrated Summary of Efficacy. FDA also addressed questions regarding the format of datasets and the provision of patient safety narratives and case report forms in the sNDA.

On November 14, 2012, Abraxis Bioscience, LLC, submitted revised proposals in response to the FDA October 16, 2012, submission on the integration and presentation of the safety data

from study CA046 and study CA040, patient safety narratives, and on the format of the clinical datasets for a proposed sNDA. FDA provided additional guidance through written responses to the November 14, 2012, submission on January 3, 2013. In the response, FDA provided recommendations regarding additional variables to include in datasets; requests for inclusion of patient narratives for patients who discontinued study drugs for reasons categorized as other, lost to follow-up, physician decision, or subject decision in the sNDA; and requested confirmation that all safety data will be submitted in the sNDA for patients receiving the combination of gemcitabine plus Abraxane in Abraxis-sponsored trials regardless of indication for treatment.

Additional interactions between FDA and Abraxis Bioscience, LLC, regarding the proposed indication include:

- A September 9, 2008, Type A meeting during which the design of Study CA046 was discussed. During the meeting FDA stated that overall survival was an acceptable primary efficacy endpoint and that the use of gemcitabine alone compared to gemcitabine plus Abraxane in a superiority study may be acceptable, but that advisory committee discussion may be considered depending on results.

- An August 4, 2011, Type C meeting regarding the Study CA046 interim analysis results. Abraxis Bioscience, LLC, wanted to discuss plans for potentially submitting the Study CA046 interim analysis results as the basis for an sNDA and possible accelerated approval; During the meeting, Abraxis Bioscience, LLC, agreed that Study CA046 would continue as originally planned, based on the Agency's advice that overall survival should remain the primary endpoint of the study.

Abraxane was granted orphan–drug designation for the treatment of pancreatic cancer in the US on September 3, 2009.

The planned sNDA is targeted for submission in April 2013. The primary basis for the sNDA will consist of results from Study CA046 and supportive data from study CA040. Abraxis Bioscience, LLC, plans to seek full approval for the proposed indication.

Study CA046 was an open-label, randomized, multicenter trial of Abraxane in combination with gemcitabine versus gemcitabine monotherapy in patients with metastatic adenocarcinoma of the pancreas. The primary endpoint was overall survival (OS). Secondary endpoints were progression free survival (PFS) and objective tumor response (ORR). Patients had histologically or cytologically confirmed adenocarcinoma of the pancreas with initial diagnosis of metastatic disease within 6 weeks of randomization.

Patients were randomized (1:1) to one of the following treatment arms

- Abraxane 125 mg/m^2 followed by gemcitabine 1000 mg/m^2 administered on Days 1, 8, 15, 29, 36, and 43 of a 56-day cycle in Cycle 1 only, and subsequently administered on Days 1, 8, and 15 of a 28-day cycle

- gemcitabine 1000 mg/m^2 administered on Days 1, 8, 15, 22, 29, 36, and 43 of a 56-day cycle in Cycle 1, and subsequently administered on Days 1, 8, and 15 of a 28-day cycle.

Randomization was stratified by geographic region (North America, Western Europe, Eastern Europe, Australia), performance status (70-80, 90-100), and presence of liver metastases (yes, no). For the primary endpoint of overall survival (OS), 608 events from 842 patients would provide 90% power to detect a HR of 0.769 with a two-sided alpha of 0.049. Progression free survival and ORR were evaluated based on blinded, central, independent radiologic review using RECIST v1.0. Radiologic assessments were performed every 8 weeks.

A total of 861 patients were enrolled, 431 in the Abraxane/gemcitabine arm and 430 in the gemcitabine arm. Abraxis Bioscience, LLC, reports a median survival of 8.5 months in the Abraxane/gemcitabine arm (at 333 deaths) compared to 6.7 months in the gemcitabine arm (at 359 deaths); HR 0.72; 95% CI 0.617, 0.835; p<0.0001 (stratified log-rank test). Abraxis Bioscience, LLC, reports a median PFS of 5.5 months in the Abraxane/gemcitabine arm compared with 3.7 months in the gemcitabine arm; HR 0.69; 95% CI 0.581, 0.821; p<0.0001. Abraxis Bioscience, LLC, reports an improvement in ORR from 7% in the gemcitabine alone arm to 23% in the Abraxane/gemcitabine arm; RR ratio 3.19; 95% CI 2.178, 4.662; p<0.0001, chi-square test.

3.0   DISCUSSION

Clinical

1. ***Question 1:*** The top-line efficacy and safety data from study CA046 are provided in this briefing document for the Type B Pre-sNDA meeting. Does the Agency agree that the totality of efficacy and safety data from study CA046 are likely to provide the basis, pending complete review of the dossier, for approval of labeling for Abraxane in combination with gemcitabine for the first-line treatment of patients with adenocarcinoma of the pancreas? (see Section 5.2.2)

    FDA Response to Question 1: The clinical data from Study CA046 are adequate to support an sNDA submission for the proposed indication; determinations regarding approvability and labeling will be made once the supplement is submitted and reviewed.

    In addition to the Study CA046 and Study CA040 results, the sNDA should also include all other safety data available to Abraxis Bioscience, LLC, for the Abraxane-gemcitabine combination, as previously conveyed in FDA's letter dated January 3, 2013.

2. ***Question 2:*** As Abraxis Bioscience, LLC, prepares to complete the compilation of this sNDA for the use of Abraxane in combination with gemcitabine for the treatment of patients with adenocarcinoma of the pancreas, does the Agency have additional advice that will enable and facilitate the priority review and full approval of this application? (see Section 5.3)

> ***FDA Response to Question 2:*** FDA has no additional advice beyond that previously conveyed in FDA's October 16, 2012, and January 3, 2013, letters regarding the planned sNDA, DOP2's General Advice for Planned Marketing Applications (included with the October 16, 2012 letter), and the DOP2 CDISC Guidance (included with the October 16, 2012 letter).

Additional Comments

3.   In the sNDA please include summary results of any exploratory analyses of efficacy according to SPARC expression from Study CA046. Please also include patient level data and information regarding biospecimens and methods used to assess SPARC expression.

PREA PEDIATRIC STUDY PLAN

The Food and Drug Administration Safety and Innovation Act of 2012 changes the timeline for submission of a PREA Pediatric Study Plan and includes a timeline for the implementation of these changes. You should review this law and assess if your application will be affected by these changes. If you have any questions, please email the Pediatric Team at Pedsdrugs@fda.hhs.gov.

PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm 084159.htm. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

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

/s/

MONA G PATEL

01/11/2013

FOOD AND DRUG ADMINISTRATION

_____

Meeting Date and Time:	August 4, 2011 11 am to 12 noon
Meeting Type:	Type C Meeting
Meeting Category:	Pre-IND
Meeting Location:	Teleconference
Application Number:	NDA 021660
Product Name:	Abraxane
Received Briefing Package	June 30, 2011
Sponsor Name:	Celgene Corporation
Meeting Requestor:	Aleece C. Nolasco
Meeting Chair:	Virginia Maher, MD
Meeting Recorder:	Yolanda G. Adkins, R.N., MSHA

Meeting Attendees:

FDA Attendees

Robert L. Justice, M.D., M.S., Director, DDOP

Anthony Murgo, M.D., Associate Director, OODP

V. Ellen Maher, M.D., Clinical Team Leader, DDOP

Nancy Scher, M.D., Medical Officer, DDOP

Qi Liu, Ph.D., Clinical Pharmacology Team Leader, DCP5

Safaa Burns, Ph.D., Clinical Pharmacology Reviewer, DCP5

Yolanda G. Adkins, R.N., MSHA, Regulatory Project Manager, DDOP

External Attendees

Deborah (Debbie) Tady, PharmD	Director, Regulatory Affairs
Florence (Flo) Houn, MD	Vice President, Regulatory Affairs
Joycelyn (Joy) Seymour	Manager, Regulatory Affairs
(b) (4)	Consultant, Celgene Regulatory Affairs
Renu Vaish, MS	Executive Director, Regulatory Affairs
Bob Delap, MD	Vice President, Global Clinical Research
Jose Iglesias, MD	Vice President, Clinical Development
Markus Renschler, MD	Vice President, Clinical Development
Benton Brown, MD	Senior Director, Drug Safety
Nguyen Dat, PhD	Vice President, Biostatistics
Paul Bhar, MS	Senior Director, Biostatistics
Richard McNally, PhD	Principal Statistician, Biostatistics
Gondi Kumar, PhD	Executive Director, DMPK
Nianhang Chen, PhD	Principal Scientist, Translational Medicine – Clinical Pharmacology
Ying Ye, PhD	Associate Director, Clinical R&D

1.0   BACKGROUND

ABRAXANE for Injectable Suspension is an albumin-bound form of paclitaxel. It was approved by FDA in 2005 for treatment of breast cancer after the failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated. The approved dose of ABRAXANE is 260 mg/m^2 intravenously (IV) over 30 minutes every 3 weeks. Celgene wishes to discuss with FDA a plan to conduct an interim analysis (on an acceptable surrogate endpoint) in the ongoing, open-label phase 3 trial CA046 (ABRAXANE 125 mg/ m^2 IV weekly 3 weeks out of 4 + gemcitabine vs. gemcitabine alone) in metastatic adenocarcinoma of the pancreas. The primary endpoint is OS.

2.0   DISCUSSION

1. As the Agency continues to gain experience and evolves its policies regarding the use of surrogate endpoints for accelerated approval under 21 CFR Subpart H, Celgene would like to discuss whether there is a pathway for accelerated approval of ABRAXANE in the treatment of patients with metastatic adenocarcinoma of the pancreas.

For the ongoing phase 3 randomized controlled study CA046 of ABRAXANE in combination with gemcitabine vs gemcitabine monotherapy, does the Agency consider there to be a reasonable path for conducting an interim analysis based on an acceptable endpoint and, provided the results met prespecified criteria, to submit this study as the basis for an sNDA for review and possible accelerated approval?

FDA Response:

No. Overall survival should remain the primary endpoint. CA046 should continue as originally planned. The secondary endpoints (ORR, PFS) have not been shown to be "reasonably likely" to predict clinical benefit (OS) in this disease setting.

Applicant Response:

Clear response to the question posed in the Type C Briefing Book; study CA046 will continue as planned.

Additional Clinical Pharmacology Comments:

1. **You need to evaluate the drug-drug interaction potential between Abraxane and gemcitabine. This can be accomplished by including the assessment of the pharmacokinetics of Abraxane and gemcitabine when given in combination in a subset of patients in your ongoing or planned trials, such as the proposed Phase 3 Study CA046.**

   <u>**Applicant Response**</u>:

   Paclitaxel clearance is primarily determined by cytochrome P450 2C8 and 3A4 mediated metabolism, while gemcitabine is inactivated by cytidine deaminase (Sugiyama et al., Clinical Pharmacokinetics, 2010, 49:8, 549-558; Plunkett et al., Anticancer Drugs, 6:S7-S13, 1995 (Suppl 6), Gemzar® prescribing information). Thus they do not share common metabolic systems and there is no evidence to suggest that they affect each other's metabolism resulting in pharmacokinetic drug-drug interactions. This has been demonstrated both preclinically in rat (Study ABI-PK-01005) as well as clinically (Gemzar Prescribing Information).

   - Celgene (formerly Abraxis BioScience) conducted study ABI-PK-01005 to evaluate the pharmacokinetics (PK) of Abraxane® and gemcitabine (Gemzar®) when administered IV concurrently versus as single agents in Sprague Dawley rats. The goal was to assess whether there was any

significant change in the PK profiles of Abraxane and gemcitabine when dosed concurrently. Each rat received an intravenous bolus dose of the assigned compound at a target paclitaxel dose level of 21 mg/kg and gemcitabine dose level of 167 mg/kg. Blood samples were collected at the following post-dose intervals: 0.0167, 0.083, 0.25, 0.5, 1, 4, 8, 12, 24, and 48 hours. Actual blood collection times were recorded. Whole blood samples were submitted to Abraxis BioScience Analytical Chemistry Department for LC/MS/MS analysis of concentrations of paclitaxel, gemcitabine and its metabolite, 2',2'-difluoro-2' deoxyuridine (dFdU). Following final blood collection, rats were euthanized by carbon dioxide inhalation; no necropsy was performed. PK parameters from treatment group dosed with Abraxane concurrently with gemcitabine were compared with each compound dosed as a single agent. There were no statistically significant differences in plasma paclitaxel and gemcitabine C_{max} and AUC_{last} between Abraxane + gemcitabine concurrent administration and single-agent treatment groups, suggesting that concurrent administration of Abraxane and gemcitabine has no significant impact on the pharmacokinetic profiles of either drug. For the inactive gemcitabine metabolite dFdU, Abraxane + gemcitabine concurrent treatment resulted in significant increases in plasma C_{max} (2.06 fold) and AUC_{last} (2.11 fold) for the metabolite compared with gemcitabine alone. The reasons for this observation are not known. However, since the inactive dFdU is derived from the parent gemcitabine, whose pharmacokinetics was unaffected, the increased levels of the inactive dFdU have no overall pharmacological relevance. See attached report for study ABI-PK-01005.

- DDI between paclitaxel and gemcitabine was not observed in clinical studies. Additional support which addresses the DDI recommendation is available from information provided in the Gemzar® prescribing information Section 12.3 Pharmacokinetics which states "Analysis of data from metastatic breast cancer patients shows that, on average, Gemzar has little or no effect on the pharmacokinetics (clearance and half-life) of paclitaxel and paclitaxel has little or no effect on the pharmacokinetics of Gemzar." See Gemzar prescribing information
  http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020509s069lbl.pdf

Discussion

The Agency agrees.

2. We also recommend that you add sparse plasma sample collection for both Abraxane and gemcitabine during your Phase 3 Study CA046 and explore the exposure-response relationships for both effectiveness and toxicity. Refer to Guidances for Industry found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf and http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf for more information.

<u>**Applicant Response**</u>:

- The phase 3 clinical study CA046 is well advanced and has already enrolled 70% of the planned sample size (i.e., 596 patients of the planned 842 patients have been enrolled with 1:1 randomization). We estimate that sparse PK data from approximately 100 patients would be needed in order to draw reasonable conclusions from a population PK/PD analysis. By the time we could amend the protocol and informed consent, and complete IRB approval, we estimate there would be fewer than 60 patients remaining to enroll for the Abraxane+gemcitabine treatment group who would be eligible to participate in collection of sparse PK samples. Of those less than 60 patients, based on recent experience with the NSCLC study) we estimate best case scenario would be for 50% to consent to sparse PK sample collection which would provide, at best, a sample size of approximately 30 patients. As such, Celgene does not believe it is feasible to add sparse PK to the CA046 study.

- In addition, Celgene (formerly Abraxis BioScience) has conducted a retrospective exposure-response analysis over a wide range of Abraxane doses (80-375 mg/m^2) in patients with solid tumors. The correlative analysis utilized the PK parameters (AUC and time above the effective concentrations of 0.05 and 1 uM) derived from full PK data, safety data (ANC nadir and incidence of grade 3/4 neuropathy), and efficacy data (overall response and progression free survival) obtained in a total of 92 patients previously enrolled in six Abraxane clinical studies. In this analysis, the only correlation observed was between paclitaxel exposure and neutropenia. It was not possible to perform correlative analysis between the drug exposure and neuropathy due to the low incidence of grade 3/4 neuropathy. An exhaustive attempt made at correlating paclitaxel exposure to efficacy yielded no correlation between the two measures. The analysis also demonstrated that the type of tumor had no impact on the PK of paclitaxel. Finally, the analysis noted a high inter-individual variability in paclitaxel AUC (5982 to 28680 hr*ng/mL) in patients receiving the same Abraxane dose (260 mg/m^2), which would hamper the ability to perform reliable population PK analysis with a small sparse PK dataset since the variability would be higher under sparse PK sampling

conditions (see attached Study CA031 Request for Waiver for PK Sparse Sampling, 20 Oct 2009).

Because both nonclinical and clinical data have concluded there is no PK DDI between paclitaxel and gemcitabine, the analysis results presented for patients receiving Abraxane monotherapy may be applicable to patients receiving Abraxane in combination with gemcitabine. Celgene does not believe that an exposure-response analysis based on one Abraxane dose level (125 mg/m^2) and a limited number of subjects with sparse PK sampling in study CA046 would be able to generate meaningful information.

<u>Discussion</u>

The Agency agrees.

{See appended electronic signature page}

{See appended electronic signature page}

Virginia Maher, M.D.
Clinical Team Leader

Yolanda G. Adkins, R.N., MSHA RPM
Regulatory Project Manager

MEETING DATE: September 9, 2008   **TIME:** 3:00 PM   **LOCATION:** WO Rm 1309

IND: 55, 974   **Meeting Request Date:** July 25, 2008 (S#671)
Briefing Document Receipt Date: July 29, 2008 (S#671)

DRUG: Abraxane® (Paclitaxel protein-bound particles for injectable suspension)

SPONSOR/APPLICANT: Abraxis BioScience

TYPE of MEETING: Type-A meeting request

FDA PARTICIPANTS:

Ramzi Dagher, M.D., Deputy Division Director, DDOP (chair)
Patricia Cortazar, M.D., Medical Team leader, DDOP
Jennie Chang, PharmD., Medical Reviewer, DDOP
Raji Sridhara, Ph.D., Statistics Team Leader, OB/DBV
Xiaoping (Janet) Jiang, Ph.D., Statistical Reviewer, OB/DBV
Carl Huntley, R.Ph., MBA, Regulatory Project Manager

INDUSTRY PARTICIPANTS:

Mitchall G. Clark, B. Pharm, MRPharmS, Sr. Vice President, Global Regulatory Affairs
José Iglesias MD, Chief Med Officer and Vice President, Global Clinical Development
Daniel Von Hoff MD, Principal Investigator, Study CA040
Dr. Ron Korn MD, PhD, Independent Radiology Reviewer
Sanjukta Bhaduri, MBBS, MFPM, Sr. Director, Regulatory Affairs
Paul Bhar MS, Director, Biostatistics
Neil Desai, PhD, Vice President, Research and Development

BACKGROUND: (from meeting request)

Abraxis proposes to submit an sNDA in patients with metastatic adenocarcinoma of the pancreas,

(b) (4)

Indication:
Abraxane in combination with gemcitabine is indicated in the first-line chemotherapy treatment
of patients with metastatic adenocarcinoma of the pancreas.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

MEETING QUESTIONS

<u>Study CA046: First-line treatment of metastatic pancreatic cancer</u>

A) The study endpoints and objectives are described in Attachment 6: CA046 Protocol
Synopsis. The primary efficacy endpoint of this study is overall survival and the
secondary efficacy endpoints are objective tumor response and progression-free survival.
Please confirm that the study objectives and endpoints are appropriate to assess the
efficacy of Abraxane and gemcitabine in the 1st line treatment of metastatic
adenocarcinoma of the pancreas.

FDA Response:
The proposed study endpoints are acceptable to assess the efficacy of Abraxane in the 1st line
treatment of metastatic adenocarcinoma of the pancreas. However, we have concerns with the
proposed control arm of gemcitabine alone. As you are aware, FDA recently approved the
combination of gemcitabine + erlotinib for 1st line treatment of metastatic pancreatic cancer.
The acceptability of an sNDA based on this study will be a review issue.

Discussion:
The Sponsor clarified that this study will be done internationally with sites in regions where
erlotinib may not be available. The FDA stated that the use of gemcitabine alone compared
to gemcitabine plus Abraxane in a superiority study may be acceptable. Depending on the
results an advisory committee discussion may be considered.

B) Abraxane at a dose of 125 mg/m^2 + gemcitabine at a dose of 1000 mg/m^2 weekly x 3 q 4
weeks i.v. will be used in combination as the active treatment for this Phase 3 study. The
gemcitabine US Package Insert states that gemcitabine should be administered at a dose of
1000 mg/m2 over 30 minutes once weekly for up to 7 weeks, followed by a week of rest in
the first cycle, followed by a schedule of weekly x 3 every 4 weeks in subsequent cycles.
Gemcitabine administered at a dose of 1000 mg/m2 weekly x 3 q 4 weeks is commonly
recommended in this population based on published NCCN Treatment Guidelines.
Furthermore, in the Phase IB study CA040, gemcitabine is being administered in combination
with Abraxane, according to this administration schedule. In the absence of data for
Abraxane and gemcitabine given weekly for 7 weeks, Abraxis proposes to administer
gemcitabine, as the comparator drug in this study, at a dose of 1000 mg/m2 weekly x 3 q 4
weeks (i.e. similar to the active arm administration schedule).
Please concur that the proposed administration schedules for both the active and the
comparator treatments are appropriate to support the approval of this dosing regimen in this
patient population.

FDA Response:
Please support your proposal to use the Gemcitabine weekly x3 in a 4 week schedule with published studies.

Discussion:
The Sponsor clarified that the gemcitabine dose and schedule to be used will be as per the package insert (weekly x7 induction, then weekly x3 every 4). The FDA stated that this was acceptable.

C) The sample size calculations and the statistical methods applied to this study are described in Attachment 1. Please confirm that the sample size calculations and the statistical methods are appropriate to support the approval of Abraxane combined with gemcitabine in the treatment of metastatic adenocarcinoma of the pancreas.

FDA Response:
Yes. The sample size calculations and the statistical methods are acceptable. If you plan to claim efficacy based on secondary endpoints after OS analysis has demonstrated significant improvement, then priority of testing of secondary endpoints should be pre-specified in the protocol and statistical analysis plan, controlling overall family-wise type I error rate at one-sided 0.025 level for the secondary endpoints.

Discussion: None

D) Described in this protocol synopsis are the safety endpoints and methods of safety analysis for this study. Please confirm that the sponsor's approach to assessment of safety in these patients is appropriate.

FDA Response:
The safety endpoints appear to be appropriate.

Discussion: None

(b) (4)

Discussion: None

The meeting was adjourned at 3:30 PM

_____ Concurrence Chair: _____
Project Manager   Ramzi Dagher, MD
Carl Huntley, R.Ph., MBA   Deputy Division Director

Linked Applications	Sponsor Name	Drug Name
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IND 55974	ABRAXIS BIOSCIENCE INC	CAPXOL (PACLITAXEL) INJ

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

/s/

RAMZI N DAGHER
09/12/2008