European Medicines Agency
Evaluation of Medicines for Human Use

Doc.Ref.:EMEA/47053/2008

ASSESSMENT REPORT FOR ABRAXANE

International Nonproprietary Name:
Paclitaxel

Procedure No. EMEA/H/C/778

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 85 45
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

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1 BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Abraxis BioSciences Ltd. submitted on 25 August 2006 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Abraxane, through the centralised procedure under Article 3 (2) (b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMEA/CHMP on 15 March 2006. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of significant therapeutic innovation.

The legal basis for this application refers to:
Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application

The application submitted is a complete dossier composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Scientific Advice:
The applicant received Scientific Advice from the CHMP on 23 January 2003, a clarification was issued on 14 April 2003. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status:
Abraxane has been given a Marketing Authorisation in USA on 07 January 2005.

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur:	Pieter de Graeff	Co-Rapporteur:	Eva Skovlund

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 25 August 2006.
- The procedure started on 27 September 2006.
- The Rapporteur's Initial Assessment Report was circulated to all CHMP members on 8 December 2006. The Co-Rapporteur's Initial Assessment Report was circulated to all CHMP members on 8 December 2006
- During the meeting on 22-24 January 2007, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 24 January 2007.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 2 April 2007.
- The summary report of the inspection carried out at the following site Abraxis Pharmaceutical Products, Inc. (Grand Island, New York, USA) between on 4-8 June 2007 was issued on 23 August 2007.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 24 May 2007.
- During the CHMP meeting 18-21 June 2007, the CHMP agreed on a List of Outstanding Issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 6 September 2007.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 4 October 2007.

- During the meeting on 15-18 October 2007, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Abraxane on 18 October 2007. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 16 October 2007.
- The CHMP opinions were forwarded, in all official languages of the European Union, to the European Commission, which adopted the corresponding Decision on 11 January 2008.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

Breast cancer is the most frequent cancer in women. The world-wide incidence of breast cancer in the year 2002 was estimated at 1,151,298 cases; mortality in the same year was estimated at 410,712 deaths (GLOBOCAN 2002). The incidence of breast cancer increases with age, doubling about every 10 years until menopause, when the rate of increase slows (McPherson, Steel et al. 2000).

Most patients with breast cancer (about 90%) are diagnosed with operable disease i.e. overt cancer manifestations confined to the breast and the axillary lymph nodes. The extension of the disease to the overlying skin, the underlying chest wall or to more distal nodes is classified as locally advanced disease. Overt metastases to other organs are referred to as metastatic (Stage IV) disease (Goldhirsch A 2004).

Metastatic breast cancer (MBC) remains an incurable disease with a median survival of about 2 years; treatment is therefore essentially palliative (Bernard-Marty, Cardoso et al. 2004; Goldhirsch A 2004). The types of treatment used in MBC can be categorised as endocrine, chemotherapy and biological therapy. Generally, initial treatment in patients with nonaggressive, hormone-sensitive tumours is with endocrine therapy. Tamoxifen and aromatase inhibitors are the most widely used endocrine therapy. In patients with hormone-insensitive or aggressive tumours, chemotherapy is the usual initial treatment (Bernard-Marty, Cardoso et al. 2004; Goldhirsch A 2004). Anthracycline-containing regimes include 5-fluorouracil, doxorubicin and cyclophosphamide (FAC) and 5-fluorouracil, epirubicin and cyclophosphamide (FEC), and the most common non-anthracycline containing regimen is cyclophosphamide, methotrexate and 5- fluorouracil (CMF). With the growing use of anthracycline-containing therapy as adjuvant therapy, the taxanes (paclitaxel and docetaxel) have become established as the standard of care in patients with anthracyclines-resistant MBC (Bernard-Marty, Cardoso et al. 2004; Goldhirsch A 2004; Gralow 2005). Taxanes are also used in patients with MBC with no or minimal prior anthracycline exposure. Following failure of anthracyclines and taxanes, various agents are available, including capecitabine and vinorelbine. As biological therapy he monoclonal antibody, trastuzumab (Herceptin) is available for the treatment of ErbB2 overexpressing breast cancer.

The antineoplastic mechanism of action of paclitaxel as an antimicrotubule agent is well characterized (Schiff, Fant et al. 1979; Schiff and Horwitz 1980). Paclitaxel in a solvent-based cremophor EL formulation has been authorized and marketed in Europe since 1993 (Taxol). As a single agent, solvent-based paclitaxel is indicated for the treatment of metastatic carcinoma of the breast in patients who have failed, or are not candidates for standard, anthracycline containing therapy. In combination solvent-based paclitaxel is indicated for the initial treatment of locally advanced or metastatic breast cancer either with an anthracycline in patients for whom anthracycline therapy is suitable, or with trastuzumab, in patients who over-express HER-2 at a 3+ level as determined by immunohistochemistry and for whom an anthracycline is not suitable.

About the product:

Abraxane is a cremophor-free colloidal suspension of paclitaxel and human serum albumin. Abraxane is a new formulation developed to overcome the water insolubility of the active component paclitaxel and prevent hypersensitivity reactions associated with solvent-containing formulations. Abraxane is presented lyophilized and contains 800 mg albumin per 100 mg paclitaxel prior to reconstitution with 0.9% saline. The size of the paclitaxel nanoparticles is approx.130 nm.

The applicant has submitted an application for a full marketing authorization under Article 8(3) of Directive 2001/83/EC (as amended). The claimed indications and posologies were metastatic breast carcinoma (260 mg/m2 administered intravenously over 30 minutes every 3 weeks) and adjuvant treatment of node-positive breast carcinoma following anthracycline and cyclophosphamide therapy (260 mg/m2 administered intravenously over 30 minutes every 3 weeks for 4 courses). Clinical data to

support the application for the first line therapy MBC was insufficient and the indication has been restricted to treatment of metastatic carcinoma of the breast in patients who have failed, or are not candidates for standard, anthracycline containing therapy. The applicant did not submit any clinical trials to establish the efficacy in breast cancer in the adjuvant setting and this indication has been withdrawn.

2.2 Quality aspects

Introduction

Composition

Abraxane is presented as a sterile lyophilisate for suspension for injection. Before use the product has to be reconstituted with 0.9% sodium chloride solution to obtain a suspension containing 5 mg paclitaxel per ml. Paclitaxel is present in the form of albumin-bound nanoparticles with a mean size of approximately 130 nm.

Other ingredients include human albumin solution, water for injections and nitrogen. Only human albumin is left in the finished product.

The product is packaged type I glass vials closed with a bromobutyl rubber stopper and an aluminium crimp seal. A cardboard box is used to protect the product from light.

Active Substance

Paclitaxel is a known active substance described in the Ph. Eur. and the USP. The chemical name of 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. It is a white or almost white crystalline powder, practically insoluble in water (less than 0.5 mg/ml), soluble in methanol and freely soluble in dichloromethane. Paclitaxel has 11 stereogenic centres and may exist in different crystalline forms. However only one crystal form of paclitaxel is found in the active substance used in the manufacture of the finished product

The chemical structure of paclitaxel has been confirmed using analytical data by elemental analysis, IR, ^{1}H- and ^{13}C-NMR, UV and mass spectrometry. The solid state of paclitaxel has been characterized by means of thermal analysis (differential scanning calorimetry) and X-ray powder diffractometry.

- Manufacture

Paclitaxel is manufactured by extraction from the *Taxus x media* roots followed by successive liquid/liquid extractions, chromatographic column purifications, crystallisation purification steps, granulation and drying. Detailed information about the manufacturing, validation and analytical controls of the active substance has been provided using the ASMF procedure.

The starting material has been adequately characterized and complies with the Ph.Eur. monograph on Pesticides Residues. Appropriate specifications have been adopted for the starting material, solvents, processing aids and intermediates. All relevant impurities have been appropriately discussed. Forced degradation studies have shown the major degradation products. All impurities (including degradation products) have been characterized. The levels of the impurities are supported by the results of toxicological studies and appropriate specifications have been set.

- Specification

The active substance specification includes tests for appearance, identification (IR and HPLC), specific optical rotation, related substances (HPLC), assay (HPLC), water content, residue on ignition, heavy metals, residual solvents, microbial purity and endotoxins.

Batch analysis data from 13 production scale batches and several supporting batches have been provided. In all cases the product complied with the predefined specifications.

- Stability

Stability studies have been performed in accordance with the ICH requirements. Samples from several production scale batches have been stored for 36 months at 25 ºC/60 % RH and for 6 months at 40 ºC/75 % RH. The packaging materials used in the stability studies were the same as those intended for marketing.

The parameters tested were appearance, identification, specific optical rotation, water content, impurities and assay. The stability data provided justify the proposed retest period without special storage conditions.

Medicinal Product

- Pharmaceutical Development

Paclitaxel is a highly lipophilic and essentially insoluble in water substance, but highly soluble in organic solvents. In other currently approved paclitaxel formulations, this problem is addressed by solubilizing paclitaxel in a mixture of organic solvents (e.g.ethanol) and surfactants (e.g. Cremophor®-EL). However, this approach may be associated with a number of side effects. The objective of the pharmaceutical development for Abraxane was to develop a surfactant-free formulation in order to avoid the appearance of possible side effects relating to the excipients used.

In Abraxane the solubility problem of paclitaxel is solved by reducing its size at nano-scale level, thereby greatly increasing the surface area of the particles and improving dissolution.

Human albumin functions as a surface-active polymer providing charge and steric stabilization to the paclitaxel nanoparticles to prevent aggregation. Stabilisation is achieved by the fact that albumin adsorbs onto the surface of the paclitaxel nanoparticles, thus creating a sheet that functions as a surface-active polymer preventing aggregation of paclitaxel particles. The interaction between paclitaxel and human albumin is weak and both substances freely dissociate after reconstitution. Human albumin was chosen since it is a biocompatible excipient and is not associated with toxicity, dosing, or infusion set incompatibility problems. Full quality documentation on the human albumin solution has been provided by the applicant. Information regarding the human plasma starting material is found in the plasma master file (PMF) certificate of the albumin manufacturer, provided in support of this application. The manufacturer's PMF has been issued by the EMEA and is certified to be compliant with EU Community legislation. The human plasma used in the manufacture of the human albumin is collected in the U.S.A. and complies with Ph. Eur. requirements and the US Code of Federal Regulations for source plasma. An agreement is in place between the albumin manufacturer and the applicant in order to maintain the link between Abraxane and post-collection information on the albumin and its starting materials.

The rest of the excipients/processing aids used were chosen for their ability to produce a stable nanoparticle suspension of paclitaxel. Several formulation parameters were tested to optimize the particle size and the stability of the final formulated suspension.

The differences between the initial clinical trial formulation and the final commercial product have been shown not to result in relevant differences in key quality parameters, such as pH, particle size distribution, osmolality and viscosity.

The packaging materials are commonly used in such formulations, while the compatibility with the reconstituted suspension as well as container-closure integrity was demonstrated in stability studies.

For the process development an aseptic filtration process has been chosen, since human albumin denaturates with heat and thus does not allow terminal sterilisation..

- Manufacture of the Product

The manufacturing process is a standard process for these kinds of formulations and consists of the following steps: mixing of oil and water phases, homogenization, evaporation, sterilization by filtration, aseptic filling, in vials, and lyophilisation.
All critical process parameters have been identified and controlled by appropriate in process controls. The validation report from three production scale batches demonstrates that the process is reproducible and provides a finished product that complies with the in-process and finished product specifications.

- Product Specification

The specification for the finished product at release and shelf life includes tests for appearance, identification (HPLC), related substances (HPLC), assay (HPLC), albumin content (HPLC), water content, uniformity of dosage units, reconstitution time, pH, particle size (mean and distribution), osmolality, particulate matter, sterility and endotoxins. All tests included in the specification have been satisfactorily described and validated.

Batch analysis data from 3 primary stability and 3 full scale batches have been presented. All batches met the test limits as defined in the release specification and test methodology valid at the time of batch release.

- Stability of the Product

Stability studies were carried out according to the ICH requirements on three batches of the final commercial formulation. The batches were produced using the same manufacturing process, equipment and container as for the product intended for marketing. Samples were stored in inverted position at 25°C/60% RH for 24 months and at 40°C/75% RH for 6 months.

The parameters tested were: appearance, water content, paclitaxel content, human albumin content, impurities, bacterial endotoxins, sterility, reconstitution time, pH, particle size distribution and particulate matter. The analytical methods were identical to the methods used for release and are stability indicating

Additional stability studies have been performed to demonstrate the stability of the reconstituted product and the reconstituted suspension in intravenous infusion bags. A photostability study was also performed in order to investigate the protective properties of the secondary packaging against the influence of light, as well as the photostability of the reconstituted product in infusion bags.

In all cases the stability results presented were satisfactory and support the proposed shelf life for the commercially packaged product under the conditions specified in the SPC.

Discussion on chemical, pharmaceutical and biological aspects

The quality of Abraxane is adequately established. In general, satisfactory chemical and pharmaceutical documentation has been submitted for marketing authorization. There are no major deviations from EU and ICH requirements.

The active substance is well characterised and documented. It is a poorly soluble substance that has been formulated as nanoparticles in order to overcome the solubility issues and avoid the use of surfactants and solvents and all the problems arising from their use. The nanoparticles are stabilised using human albumin a biocompatible excipient that has received PMF certification from the EMEA. The other excipients are commonly used in these types of formulations and comply with Ph. Eur. requirements. The packaging material is commonly used and well documented. The manufacturing process of the finished product is a standard process that has been adequately described. Stability tests indicate that the product under ICH guidelines conditions is chemically stable for the proposed shelf life. At the time of the Opinion some minor issues remained unresolved and it was agreed to be addressed as post approval obligations. These issues do not affect the benefit / risk of the product.

2.3 Non-clinical aspects

Introduction

Primary and secondary pharmacology studies were not conducted in accordance with GLP but were conducted using standard laboratory practices. The safety pharmacology studies were non-GLP. One pivotal single dose toxicology study and the reproductive toxicology studies were performed according to GLP. Repeated dose toxicity studies were not performed according to GLP.

Pharmacology

The primary pharmacology program is based on studies addressing the antineoplastic mechanism of action of paclitaxel and its delivery to the tumour when formulated as Abraxane.

- Primary pharmacodynamics

The mechanism for tissue distribution of paclitaxel delivered as Abraxane was analysed in several *in vitro* studies (see Table 1):

Table 1: *In vitro* primary pharmacodynamic studies

Study	**Study ID**	**Test system**
Binding of paclitaxel	BIO-EL-1	HSA, microtubules and endothelial cells
Complex formation of paclitaxel and HSA	BIO-EL-2	HSA
Cellular expression of SPARC and caveolin-1	BIO-EL-3	MX-1 breast carcinoma cells
Colocalization of HSA and lysosomal marker	BIO-EL-4	MX-1 breast carcinoma cells
Colocalization of SPARC and albumin	BIO-TF-1	MX-1 xenografts grown in nude mice
SPARC expression	BIO-TF-2	Normal mouse tissues
SPARC expression	BIO-TF-3	Normal human tissues
SPARC expression	BIO-TF-4	Human foetal tissues
Paclitaxel transport across endothelium	BIO-QY-1	Endothelial cell monolayers
Paclitaxel transport across endothelium	BIO-QY-2	Endothelial cell monolayers
Antitumour activity	PR-0001	L1210 murine leukaemia cells

Study BIO-EL-1 shows that Abraxane /Flutax (fluorescent-labelled paclitaxel) (20 µg/ml) exhibited 2.3, 4.0, 9.9 and 2.9 fold higher binding to HSA, microtubules, human umbilical vein endothelial cells (HUVEC) and human M vascular endothelial cells (HMVEC), respectively, than solvent-based paclitaxel/Flutax (20 µg/ml). In addition CEL/ethanol (mixture of 527 mg CrEl and 392.3 mg ethanol) exhibited dose dependent inhibition of Flutax binding to HSA, microtubules, HUVEC and HMVEC. Complete inhibition was observed at a CEL/ethanol concentration of ≥0.01, ≥0.5, ≥0.5 and 0.007%, respectively.

Study BIO-EL-2 showed that when paclitaxel and HSA are mixed they form a complex. The amount of Flutax that binds to HSA is 21% higher when Flutax is mixed with Abraxane than solvent-based paclitaxel, indicating that CrEL/ethanol is an inhibitor for binding of HSA to paclitaxel.

Results from studies BIO-EL-3 and BIO-EL-4 showed that the intracellular accumulation of albumin was mediated by a non-lysosomal mechanism as there was no colocalization between albumin and lysosomes. The internalized albumin was localized to areas of high expression of SPARC (an albumin binding protein on the surface of cells), but not to areas with Caveolin-1 expression. In addition, SPARC was overexpressed on MX-1 breast carcinoma cells but not on normal cells including human mammary epithelial cells (HMEC), human microvascular epithelial cells-lung (HMVEC-L), and HUVEC. A second study, BIO-TF-1 showed that the albumin staining pattern matched that of SPARC, most prominently around necrosis areas. There was no correlation between albumin staining and caveolin staining.

Results from study BIO-TF-2 showed that SPARC expression was absent in major organs of adult mice (liver, kidney, lung, brain, heart, stomach and spleen). Study BIO-TF-3 confirmed that SPARC expression was absent in colon, rectum, spleen, lung, prostate, heart, tonsil, lymph node, appendix, pancreas, eyeball, ovary and breast and found it present in the squamous epithelium of the oesophagus and spermatagonia and/or sertoli cells of the testis. In addition some of the examined samples of stomach (4/14), liver (3/20), kidney (2/20) and brain (1/14) showed positive staining. An additional study, BIO-TF-4, showed that SPARC expression was absent in the major organs from human foetuses (stomach, colon, rectum, liver, small intestine, spleen, lung, thymus, eyeball, heart, adrenal, kidney, muscle, gall bladder, thyroid, uterus, pancreas, brain and artery-VSMC) except for the squamous epithelium of the oesophagus, Leydig cells of the testis, osteoblast of bone, hofbauer cells of the placenta, vascular smooth muscle cells of the umbilical cord and artery, unidentified scatter cellular component of the bladder, fallopian tube and skin.

In studies BIO-QY-1 and BIO-QY-2 the transport of paclitaxel across human umbilical vein endothelial cell (HUVEC) and human lung microvessel endothelial cell (HMVEC) monolayers was examined. The total paclitaxel transported across the HUVEC and HMVEC monolayer was 2.0-4.2 folds higher for Abraxane than solvent-based paclitaxel. Removing the physiological 5% HSA concentration from the Abraxane mixture significantly reduced the level of paclitaxel trancytosis. Pre-treatment with cyclodextrin (a gp60/caveolae inhibitor) decreased Abraxane paclitaxel transport down to the same level as solvent-based paclitaxel-Flutax (with or without pre-treatment with cyclodextrin)

or Flutax (with or without pre-treatment with cyclodextrin). Abraxane transport was also inhibited (two-fold) with NEM [N-(3,4-dimethoxyphenethyl)-malemide], an alkylating reagent which inhibits caveolae fusion. Total paclitaxel transported was inhibited by 38% when the transport assay was performed in the presence of 100 µg/ml of rabbit polyclonal antibody against SPARC.

Both Abraxane and solvent-based paclitaxel exhibited antiproliferative activity towards L1210 murine leukaemia cells (study PR-0001). The IC50 for Abraxane and solvent-based paclitaxel were 0.014 µg/mL and 0.010 µg/mL, respectively.

In vivo antitumour activity of iv administered Abraxane has been studied in athymic female nude mice transplanted with human tumour xenografts. Small differences in anti-tumour efficacy between paclitaxel formulated as Abraxane or as solvent-based paclitaxel. For HT29 (colon), PC-3 (prostrate), NCI-H522 (lung) and the multi/drug resistant MES-SA-Dx5 sarcoma xenografts solvent-based paclitaxel seems slightly more effective than Abraxane at equimolar dose. For SK-OV-3 (ovary) and MX-1 (mammary) Abraxane seemed somewhat more efficient at equimolar doses.

Antitumour activity against MX-1 human mammary tumour in athymic nude mice was analysed in study SRI-LIF-97-171-9024.2. The efficacy results are summarized in Table 2.

Table 2: Effects of Abraxane VR-3 and VR-4 on MX-1 mammary tumours in mice

Dosage (mg/kg/day)	**Duration (days)**	**CR/Total**			**TFS/TR**			**DCR[a] (days)**			**Non-Specific Deaths**		
		VR3	VR4	Tax	VR3	VR4	Tax	VR3	VR4	Tax	VR3	VR4	Tax
45	5	5/5	5/5	NA	5/0	3/2	NA	>88	>73	NA	0/5	0/5	NA
30	5	5/5	5/5	4/4	5/0	5/0	2/2	>88	>88	>56	0/5	0/5	1/5
20	5	5/5	5/5	4/4	1/4	2/3	1/3	>51	>47	>57	0/5	0/5	1/5
13.4	5	4/5	3/5	4/5	0/5	0/5	1/4	10	8	>29	0/5	0/5	0/5

[a]: DCR: duration of complete regression.

Three studies on rabbits (one *in vitro* and two *in vivo*) and one *in vivo* study on swine were performed to study the effect of Abraxane preventing cell proliferation in other rapidly dividing cell populations using in-stent restenosis as a model. The submitted documentation shows that administration of a single dose of Abraxane with balloon-injured arteries resulted in a lack of endothelial healing and delayed replacement of intimal cells.

- Secondary pharmacodynamics

Studies on secondary pharmacodynamics have not been submitted.

- Safety pharmacology programme

The standard core battery of safety pharmacology tests has not been submitted. Three studies on myelosuppression have been provided (see immunotoxicity studies in the toxicology section).

- Pharmacodynamic drug interactions

Non-clinical drug interaction studies have not been conducted with Abraxane.

Pharmacokinetics

The pharmacokinetics of paclitaxel delivered as Abraxane was studied in the Sprague Dawley rats, New Zealand White rabbits and athymic NCr-nu/nu mice. Absorption, distribution, metabolism and elimination characteristics were assessed following single iv injections, except for the absorption studies on rabbits which where done with intra-arterial injections. An overview of the pharmacokinetic programme is presented in Table 3.

Table 3: Studies conducted to assess pharmacokinetic properties of paclitaxel in animals

Type of study	Study ID	Species	GLP compliant
Absorption, distribution, excretion	P0796003	Rat	Yes
Absorption, distribution, excretion	P1096001	Rat	Yes
Absorption	P0297003	Rat	Yes
Absorption	AFIP-002	Rabbit	Yes
Distribution	A590.1	Mouse	No
Distribution	A590.1.2	Mouse	No
Distribution/metabolism/excretion	P0202002	Rat	Yes
Other	P0303014	Rat	Yes
Other	NP001106	Rat	Yes

Two types of analysis were employed for the determination of paclitaxel in the pharmacokinetic studies, liquid scintillation counting (LSC) of tritium (^{3}H) labelled Abraxane or solvent-based paclitaxel and a validated liquid chromatography with atmospheric pressure ionisation tandem mass spectrometry detection (LC-API/MS/MS). LSC was calibrated to record counts above background noise. The lower limit of quantification for the LC/MS method is 5 ng/mL and the range of reliable responses is 5-1000 ng/mL.

- Absorption-Bioavailability

Studies on absorption for Abraxane were not provided since it is developed for iv infusion. Conventional studies on pharmacokinetic (PK) parameters after iv administration have been examined in rats, and after intra-arterial injection in rabbits.

Three studies in male rats were performed to compare PK parameters of ^{3}H-paclitaxel formulated in Abraxane and solvent-based paclitaxel. Blood samples were collected from 2 minutes to 24 hours after dosing and counted for total radioactivity. Pharmacokinetic results obtained in blood are presented in Table **4**.

Table 4: Single dose PK parameters of ^{3}H-Abraxane in male rats

Treatment	Dose (mg/kg)	Animals/ group	AUC $_{0\text{-}24\ h}$ (µg eq·h /mL)	C_{max} (µg eq/mL)	T_{max} (h)	$T_{1/2\beta}$ (h)	Study
^{3}H-Abraxane	5.1	10	6.1	4.2	0.03	19.0	P1096001
	9.1	5	11.5	7.19	0.03	22.3	P0297003
	26.4	5	43.5	29.5	0.03	16.0	P0297003
	116.7	5	248.9	283.3	0.03	8.48	P0297003
	148.1	5	355.3	414.2	0.03	9.34	P0297003
^{3}H-solvent-based paclitaxel	4.9	10	10.2	13.5	0.03	19.7	P0796003
	10.0	14	35.9	32.3	0.03	14.7	P0796003

Estimated AUC levels in rats increased linearly with dose, but in a more than dose-proportional manner. In humans, the AUC levels appeared to be linear with respect to Abraxane dose for the clinically relevant dose range (80 to 300 mg/m^2). The $T_{1/2}$ varied from 11.7 to 27.4 hours in the human clinical trials. Thus, PK parameters obtained in rats are comparable to the human situation.

A PK study in NZW rabbits (3 males/group) was performed to investigate blood levels of Abraxane in a 2 day period after dosing. Stainless steel stents were deployed in both iliac arteries of two rabbits. Each animal received ^{3}H-Abraxane by intra-arterial administration at doses of 5 or 25 mg/kg. After an initial rapid decline, ^{3}H-Abraxane was slowly eliminated from the blood. Blood concentrations > 0.01 µM were detected for 24-48 hours at an Abraxane dose of 5 mg/kg.

- Distribution

The distributions of ^{3}H-Abraxane (21.7 mg/kg) to tumours following single iv injection were investigated in a 24-hour study on female mice (2-4 mice/time point/group) bearing subcutaneous, implanted MX-1 human mammary tumours (Study A590.1). Results are shown in Table 5:

Table 5: PK parameters in blood, plasma and tumour levels of ^{3}H-Abraxane in mice

Treatment	**Iv dose mg/kg**	**Sample**	**$AUC_{0\text{-}inf}$ (nCi·h/mL)**	**Clearance (mL/h·kg)**	**Vd_{ss} (mL/kg)**	**$T_{½}$ (h)**
^{3}H-Abraxane	21.7	Blood	939	354	6939	17.1
		Plasma	1161	287	5180	16.1
		Tumour	5869	NA	NA	40.2
^{3}H-solvent-based paclitaxel	19.5	Blood	871	382	1409	4.0
		Plasma	1438	231	692	3.3
		Tumour	3716	NA	NA	24.1

The distribution of ^{3}H-Abraxane (20 mg/kg) to different major organs was investigated in a 24-hour study on female (5/group) mice bearing subcutaneous, implanted MX-1 human mammary tumours after iv injection (study A590.1.2) . Results are presented in Table 6:

Table 6: Blood, plasma, tumour, and tissue levels of radioactivity in mice given ^{3}H-Abraxane

	Mean Values (nCi/g)								Mean Value (nCi/mL)	
Time	Heart	Kidney	Lungs	Liver	Muscle	Spleen	Brain	Tumour	Blood	Plasma
5 min	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	68	157	186
15 min	355	568	334	2371	116	259	6.7	69	85	117
30 min	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	110	69	70
60 min	121	236	136	1266	64	155	5.7	132	39	39
3 hrs	56	114	79	655	69	121	7.6	138	17	16
8 hrs	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	76	6.3	7.9
24 hrs	5.6	6.9	8.3	24	4.5	5.4	5.6	60	4.9	6.5

nCi: Nanocurie; N.D.: Not Determined

The distribution of Abraxane was investigated also in healthy rats. Study P02020025 included 5 male and 5 female rats per group following a single iv injection of ^{3}H-Abraxane (5 mg/kg) and compared to ^{3}H-solvent-based paclitaxel (5 mg/kg). For most tissues the exposure levels were slightly higher in animals treated with Abraxane than with solvent-based paclitaxel. In lungs, there was a 3.5-fold higher concentration of solvent-based paclitaxel compared to Abraxane. Males had slightly higher exposure of Abraxane in all measured tissues except for fat. For solvent-based paclitaxel the males had slightly higher exposure than females in tissues except for lung, stomach, small and large intestine, fat and aorta. Study P1096001 studied organ distribution in male rats given a single iv of 5.1 mg/kg Abraxane or 4.9 mg/kg solvent-based paclitaxel. ^{3}H-Abraxane was present in greater quantities than ^{3}H-solvent-based paclitaxel in lung, kidney, pancreas and carcass, but not in brain, heart, liver, GI tract, testes, GI tract contents, spleen, prostate or seminal vesicles. However, the relative differences were minor.

Binding of paclitaxel to plasma proteins is extensive (95%) and inversely related to the Cremophor EL level (Kumar, Walle et al. 1993; van Tellingen, Huizing et al. 1999; Brouwer, Verweij et al. 2000).

Studies on placental transfer have not been submitted.

- Metabolism

The applicant refers to literature for the description of the metabolism of Abraxane. The primary metabolites of paclitaxel are 6α-hydroxypaclitaxel, 3'-p-hydroxypaclitaxel, and 6α, 3'-p-dihydroxypaclitaxel (Sparreboom, Huizing et al. 1995).

One study was performed to assess the metabolism of ^{3}H-Abraxane administered as a single iv dose to Sprague Dawley rats (5/sex/gr.) at a dose of 5 mg/kg (Study P0202002). HPLC analysis showed that, for males and females, ^{3}H-Abraxane derived radioactivity was excreted in urine as paclitaxel metabolite and in faeces as paclitaxel. In comparison, faecal excretion of solvent-based paclitaxel in males was in the form of a metabolite, and in females 62% was excreted as paclitaxel and 38% as metabolites.

- Excretion

The excretion of paclitaxel from Abraxane was evaluated in rats (5/sex/group) receiving ^{3}H-Abraxane (Study P0202002). Results are shown in Table 7.

Table 7: Paclitaxel elimination in rats during the first 48 hours after dosing

Test Article	**Species/sex**	**Dose (mg/kg)**	**% Radioactivity Excreted (mean±S.D.)**	
			Urine	**Faeces**
^{3}H-Abraxane	Rat, male	7.69±0.13	9.51±1.82	82.09±4.42
	Rat, female	7.79±0.13	14.07±1.66	78.70±5.15
^{3}H-solvent-based paclitaxel	Rat, male	5.93±0.11	8.10±2.03	77.76±6.63
	Rat, female	5.98±0.08	12.45±0.74	75.77±6.07

S.D.: Standard Deviation

Studies have not been conducted to determine the extent of excretion in the milk.

- Pharmacokinetic drug interactions

Drug-interaction studies were not submitted.

- Other pharmacokinetic studies

The pharmacokinetic differences between 3 batches of Abraxane produced from three different sources of paclitaxel have been studied (study P0303014). Whole blood paclitaxel levels for the three groups were comparable across the 0-72 hour time curve. There were no significant differences in any of the estimated pharmacokinetic parameters among the three lots tested (AUC, Cmax, Tmax and $T_{1/2}$).

In addition, the pharmacokinetic effect of the ratio of human albumin (HA) to paclitaxel in three formulations was tested. Three groups of 10 animals received a single iv injection of Abraxane at a dose of 50 mg/kg. Blood samples were collected over 72 hours for pharmacokinetic analysis. The whole blood paclitaxel levels for the three groups were comparable across the 0-72 hour time curve. The AUC and Cmax values for the three formulations were similar.

Toxicology

An overview of the toxicology program for Abraxane is presented in Table 8:

Table 8: Toxicology program for Abraxane

Study type/duration	**Study ID**	**GLP**	**Species**	**Sex/Number/Group**	**Dose (paclitaxel; mg/kg/day*)**
Single dose	PR-0003	No	Mice	male/3-4/group	Abraxane (0-30-103-367-548-822) Solvent-based paclitaxel (0-4-6-9-13.4-20.1)
	PR-0002	No	Rats	male/4/group	Abraxane (0-5) Solvent-based paclitaxel (0-5)
	PR-0007	No	Rats	male/3/group	Abraxane (30-90-120-200)
	P0397006	Yes	Rats	males and females/3+3/group	Abraxane (0-5-9-30-90-120) Solvent-based paclitaxel (5-9-30) Saline
	P0897001	Yes	Dogs	males and females/2+2/group	Abraxane (8.4)
	P0997006	Yes	Dogs	males and females/2+2/group	Abraxane (0-8.4)
	LyChron-001	Yes	Swine	males/3/group	Abraxane (0-1-3-6)

Repeat dose/5 days	PR-0004	No	Mice	male/4/group	Abraxane (30-69-103) Solvent-based paclitaxel (4-6-9-13.4-20.1)
	VIV-4	No	Athymic Mice	female/2/group	Abraxane as VR-3 (0-13.4-20-30) Solvent-based paclitaxel (13.4-20-30)
	VIV-6	No	Athymic Mice	female/2/group	Abraxane as VR-3 (0-45-67-100) Abraxane as VR-4 (45-67-100) Solvent-based paclitaxel (45-67-100) Bulk paclitaxel (45-67-100)
Male fertility/12 weeks before mating	4701-002	Yes	Rats	males/30/group	Abraxane (0-0.5-2-7-16-32) Saline (Weekly dosing)
Embryo-fœtal development/GD7-17	4701-001	Yes	Rats	Females/24-25/group	Abraxane (0.5-1-2-4-8) Saline
Impurities	P0603001	Yes	Rats	males and females/8+8/group	Abraxane (50) Abraxane + 7-Epipaclitaxel (50) Saline
	P0904003	Yes	Rats	males and females/4+4/group	Abraxane (50) Abraxane + 7-Epipaclitaxel (50) Saline

*: For male fertility studies the dosing interval was weekly.

- Single dose toxicity

A single intravenous dose study in male mice determined the LD_{50} values for Abraxane and solvent-based paclitaxel to be 447 and 7.5 mg/kg respectively (study PR-0003) (follow-up 28 days). The LD_{50} for the solvent-based paclitaxel vehicle without paclitaxel was 1325 mg/kg corresponding to a dose of 15.2 mg/kg paclitaxel in solvent-based paclitaxel.

In male rats a single dose (5 mg/kg), 14 days follow-up study (study PR-0002) investigated myelosuppression. White blood cell (WBC) counts were performed on Days 1, 3, 7, 10 and 14. Decreased WBC and body weight occurred in both treatment groups and in the solvent-based paclitaxel vehicle group (no effect on Abraxane vehicle). Recovery period from the nadir was shorter for Abraxane (7 vs. 14 days). Study PR-0007 analysed myelosuppression in male rats (3/group) after single doses of 0, 30, 90, 120 or 200 mg/kg, with a 14 days follow-up. There was a high level of chloroform (2962 ppm) in the formulated drug product. Decreased WBC and body weight was observed at 30 mg/kg dose. At 120 mg/kg dose 2 out of 3 mice died and the third presented diarrhoea, polyuria and kidney lesions. Above this dose all animals died.

A single intravenous dose study (0, 5, 9, 30, 90 or 120 mg/kg of Abraxane and 5, 9, 30 mg/kg of solvent-based paclitaxel) was performed in rats (3 per sex per group) to determine general toxicity. Chloroform levels were 118 ppm in the Abraxane formulation (study P0397006). Abraxane was not lethal at 120 mg/kg, whereas all 12 rats receiving 30 mg/kg solvent-based paclitaxel died by Day 4. Only one rat receiving Abraxane (90 mg/kg) died on day 15. Piloerection and reduced body weight gain was seen animals at doses ≥ 90 of Abraxane. No significant changes in haematology occurred and alterations in electrolyte concentrations were small. The significant histopathology finding for Abraxane was the effect on male reproductive organs at doses of 30, 90 or 120 mg/kg. Acute lethality and central nervous system (CNS) effects associated with doses ≥9 mg/kg of solvent-based paclitaxel were not seen with Abraxane.

Two single dose (175 mg/m^2) dog studies with 14 day recovery (studies P0997006, vehicle controlled and P0897001, uncontrolled) were conducted to determine the toxicity of Abraxane. The study results were inconclusive because of clear evidence of an immune reaction in the dogs to human albumin. The symptoms observed in Abraxane treated dogs were also seen, but to a greater extent, in the control treated animals. Symptoms included depression characterised by quietness and slow responses to stimuli one to four hours after administration, and a syndrome characterised by gastrointestinal symptoms and oedema or vasculitis in the face and extremities of animals in all groups, typically appearing 3-6 days after dosing. In animals receiving the HSA control articles, symptoms were delayed until day 11. Histological changes in all groups were also observed and appeared consistent between the three groups, with the exception of testicular changes (seminiferous tubule degeneration) which were only seen in Abraxane-treated animals.

Study Lychron-001 examined the effects of Abraxane (doses 0, 1, 3, 6 mg/kg) in castrated male pigs (3 per group). Pigs were observed for 14 days, with blood sampling immediately after infusion and on days 5, 10 and 14, and necropsy on day 14. There was 1 death due to aspiration pneumonia at 6 mg/kg. At this dose also diarrhoea, vomiting, depression, loss of appetite and neutrophilia were observed. Decreased BW, slightly elevated body temperature, decreased WBC, decreased neutrophils count and neutropenia were observed at doses ≥ 3 mg/kg. Neutropenia was also seen at 1 mg/kg. Gross necropsy revealed no obvious treatment-related changes, and histopathology did not show any cellular changes attributable to Abraxane.

- Repeat dose toxicity (with toxicokinetics)

One repeat dose pilot study in immune-competent male mice and two dose-range finding studies in athymic female mice have been performed with Abraxane. Only preliminary studies of general toxicity were conducted.

In study PR-004 CD1 mice (4 males per group) were administered daily iv infusions of Abraxane (30, 69 or 103 mg/kg) or solvent-based paclitaxel (4, 6, 9, 13.4 or 20.1 mg/kg) for 5 days. The animals were observed for body weight and mortality for 28 days after treatment. In the Abraxane treated mice no deaths were recorded at 30 mg/kg, one animal died at 69 mg/kg and all animals died at 103 mg/kg. LD50 for Abraxane was calculated to 76.2 mg/kg. In the solvent-based paclitaxel treated mice no animals died at the lowest dose, one and two mice died at 6 and 9 mg/kg, respectively and all animals died at 13.4 mg/kg and 20.1 mg/kg. LD_{50} solvent-based paclitaxel was 8.1 mg/kg.

Athymic female NCr-nu mice (2 per group) were administered iv infusions of either Abraxane at doses of 13.4, 20, or 30 mg/kg paclitaxel per day for 5 days or Abraxane vehicle (Study VIV-4). Solvent-based paclitaxel at the same paclitaxel doses was also included as a control. No signs of toxicity were observed in the three groups, although weight loss was observed in the highest dose of Abraxane (30 mg/kg/day) and solvent-based paclitaxel (30 mg/kg/day) treated animals. The 5-day repeated dose LD50 for all formulations was greater than 30 mg/kg/day.

In study VIV-6 groups of 2 athymic female NCr-nu mice received iv injections of Abraxane, solvent-based paclitaxel, bulk paclitaxel (45, 67, or 100 mg paclitaxel/kg/day) or Abraxane vehicle (600, 893 or 1333 mg/kg/day HSA) for 5 consecutive days. Animals were observed for frank signs of toxicity over a 19-day period. The LD10 for Abraxane formulation and for solvent-based paclitaxel was less than 45 mg/kg/day, with all animals dying in each dose group. The LD10 for Abraxane formulation and bulk paclitaxel were 58 mg/kg/day. All animals died in the high dose group (100 mg/kg/day). No deaths were recorded in mice treated with HSA. No signs of frank toxicity are described.

- Genotoxicity

Studies assessing the genotoxic potential of Abraxane have not been submitted.

- Carcinogenicity

Studies assessing carcinogenicity of Abraxane have not been submitted.

- Reproduction Toxicity

A reproduction toxicity study was performed in male rats receiving twelve weekly iv doses of Abraxane (0.5, 2, 7, 16 or 32 mg/kg/week) (Study 4701-002). Dose-dependent adverse effects on mating performance and male fertility were observed. The NOAEL was 0.5 mg/kg/week. The adverse effects on fertility were only partly reversible during recovery. There was no evidence of foetal alterations, but there were indications of pre- and/or post-implantation loss.

In study 4701-001 pregnant rats were administered daily iv injections of Abraxane (0.5, 1, 2, 4, or 8 mg/kg/day). Maternal toxicity occurred at a NOAEL of 0.5 mg/kg/day, which is below the proposed clinical dose for Abraxane. Developmental toxicity was evident at 1, 2, 4 and 8 mg/kg/week, with a significant reductions in foetal body weight, and no live foetuses at 4 and 8 mg/kg. Post implantation

loss (embryo-foetal mortality) was evident from 1 mg/kg, including significant increases in the number of dams with any resorption, early and late resorption (combined and separate values) and the percentage of dams with all foetuses dead or that underwent resorption.

Studies on prenatal or postnatal development, including maternal function were not performed. Studies on juvenile animals were not performed.

- Toxicokinetic data

No studies were submitted.

- Local tolerance

A local irritation study was performed female New Zealand White (NZW) rabbits (4 per group) demonstrating acceptable local irritation profile for Abraxane using para-venous, intravenous, intra-arterial, and subcutaneous administration.

- Other toxicity studies

Antigenicity

Studies on antigenicity were not submitted.

Immunotoxicity

In study MS-AB-1 male SD rats (6-8 males per group) were administered single iv injections of Abraxane (paclitaxel, 10, 15, 50 mg/kg), solvent-based paclitaxel (paclitaxel, 10 mg/kg), Taxotere (docetaxel, 10 mg/kg), solvent-based paclitaxel vehicle (Cremophor EL/Ethanol, volume matched) or Taxotere vehicle (Polysorbate 80/Ethanol, volume matched). Blood samples were collected daily for 12 days, and were analyzed for complete cell counts and differentials. Results show that 3/6, 7/12, and 3/6 rats treated with Abraxane (50 mg/kg), solvent-based paclitaxel and Taxotere, respectively, died prematurely. Weight loss was observed in all groups except for solvent-based paclitaxel vehicle, and was more severe for solvent-based paclitaxel than for Abraxane doses at 10 mg/kg and 15 mg/kg. Reversible myelosuppression was observed in all treatment groups (except vehicle controls), and was more severe for Taxotere than for Abraxane (all doses). All groups dosed with docetaxel or paclitaxel developed neutropenia, lymphopenia and monocyte suppression, followed by recovery, and the suppressions were significantly more severe for Taxotere (10 mg/kg) than for Abraxane at 10 and 15 mg/kg and solvent-based paclitaxel (10 mg/kg).

Study PR-0002 analysed male SD rats (4 males per group) administered single iv injections of Abraxane (5 mg/kg paclitaxel), solvent-based paclitaxel (5 mg/kg paclitaxel), Abraxane vehicle (albumin, equivalent to 5mg/kg paclitaxel) or solvent-based paclitaxel vehicle (Cremophor EL/Ethanol, equivalent to 5mg/kg paclitaxel). In this study Abraxane produced statistically significant less myelosuppression in rats than solvent-based paclitaxel (white blood cell nadir 24% and 55% of baseline respectively). The recovery periods from the white blood cell suppression were about 7 days and 14 days for the Abraxane and the solvent-based paclitaxel treated animals, respectively. Body weight changes were less pronounced following Abraxane treatment than with solvent-based paclitaxel or solvent-based paclitaxel vehicle. The vehicle for solvent-based paclitaxel produced neutropenia, which was similar in extent (white blood cell nadir approximately 61% of baseline) and recovery period to solvent-based paclitaxel-induced neutropenia, while Abraxane vehicle showed no significant myelosuppression.

In study PR-0007 male SD rats (3 males per group) were administered single iv injections of 30, 90, 120 and 200mg/kg paclitaxel as Abraxane. The batch of medicinal product used in this study had a chloroform level of 2962 μg/g (ppm). The animals were examined for 14 days after dosing, and blood samples were drawn at days 1, 3, 7, 10 and 14. All animals in the 200 mg/kg dose group died on the day of dosing and two of three animals in the 120 mg/kg group died by day 6. There was a dose-related decrease in body weight and white blood cells. Nadir of white blood cells was around day 3-7, and recovery by day 14. The one remaining rat treated with 120 mg/kg over-expressed white blood cells by day 10, and the counts remained elevated in this animal at day 14. Only animals treated with 30 mg/kg Abraxane returned to normal weight before end of the study. All animals treated with 90 or 120 mg/kg of Abraxane showed diarrhoea and polyuria. Animals in the 90 mg/kg group appeared to

recover by day 9 post-treatment. Kidney lesions were observed at necropsy (day 14) for 1 animal dosed at 120 mg/kg and 1 animal dosed at 90 mg/kg.

Dose-related adverse effects on spleen (a cyst or enlargement), thymus (atrophy or enlargement) and lymph nodes (reddening) were seen in groups dosed with 7, 16 and 32 mg/kg/week Abraxane in the fertility and early embryonic development study in male rats (4701-002).

Metabolites
Studies on metabolites were not submitted.

Studies on impurities
Study P0603001 was performed to compare the toxicity of Abraxane with typical (0.09%) and with elevated levels (1.9%) of the primary paclitaxel decomposition product 7-epipaclitaxel.
Doses of 50 mg/kg were administered to groups of 4 male and four female rats. Animals were observed for general signs of toxicity, and sacrificed for necropsy on days 8 and 29. Saline was administered to control animals. There were no deaths or overt manifestations of toxicity. At necropsy, and common with results seen in previous studies, all male animals exhibited decreased testis size and discoloration with necrosis of the germinal epithelium.

In Study P0904003, 12 male and 12 female rats received an intravenous injection of saline or Abraxane containing low or elevated levels of 7-epipaclitaxel. No definitive differences were seen toxicologically in haematology and serum chemistry mean results between Abraxane and Abraxane with elevated 7-epipaclitaxel levels up to 7 days following intravenous administration at 50 mg/kg in rats. It is concluded that an upper limit of NMT 1.0% for 7-epipaclitaxel in the drug product will not increase the toxicity of ABI 007.

Ecotoxicity/environmental risk assessment
A revised Environmental Assessment Report (EAR) is provided based on the drug paclitaxel. The $PEC_{SURFACEWATER}$ value for paclitaxel in ABRAXANE is 0.0001 µg/l, based on peak (maximum) projected consumption at Year 2017 (projected figures provided from Year 2008 to 2017). This value is significantly below (100 times) the 0.01 µg/l Phase I action limit, as stipulated in the Guideline EMEA/CHMP/SWP/4447/00.It is concluded that Abraxane offers a negligible risk to the environment following its prescribed usage in metastatic breast cancer patients and from its storage and disposal.

The applicant has provided ISM Health data to address the potential emission to the environment after use of Abraxane. Abraxane was estimated to take a 35% share in the estimated use of taxanes to treat the indicated health condition. Under this assumption the PEC is 0.1 ng/L. Even for a 100% share in the group of patients treated with taxanes, the PEC would not be surpassed.

Discussion on the non-clinical aspects

The majority of the studies have been performed with rodents (mice and rats), while the use of non-rodents (dogs and swine) was limited because of immune responses against HSA. All studies were performed with the iv route of administration.

The standard core battery of safety pharmacology tests has not been performed. This is considered acceptable, since paclitaxel is a well-known substance with well-defined safety and efficacy. In addition, differences in pharmacokinetics between Abraxane and solvent-based paclitaxel appear relatively small (max 2-fold difference). The two most significant dose limiting toxicities of taxanes, including paclitaxel, are myelosuppression and peripheral neuropathy. Studies on myelosuppression have been provided, demonstrating a reversible, dose related myelosuppression. Studies on peripheral neuropathy have not been provided. Closely assessed during the clinical development, peripheral sensory neuropathy was apparent in the pivotal clinical studies and more frequent with Abraxane than with solvent-based paclitaxel, leading to a warning included in section 4.4 of the SPC.

The measured radioactivity in plasma was significantly higher for solvent-based paclitaxel than for Abraxane the first 3 hours, indicating a faster distribution of paclitaxel delivered as Abraxane than of solvent-based paclitaxel. Levels of radioactivity in most of the evaluated tissues were not higher for

Abraxane than for solvent-based paclitaxel. In tumours however, the levels of radioactivity were higher for Abraxane than for solvent-based paclitaxel at some time points, and it is important that the retention time of radioactivity in tumour was longer than in the other tissues. Interestingly, the *in vitro* studies supports albumin-dependent cellular uptake and transport of Abraxane across endothelial cells by a mechanism involving binding to the gp60 receptor and formation of vesicles within the caveolae and suggests a possible accumulation of Abraxane in tumour cells. The *in vivo* studies in different tumour models show that at maximum tolerated doses (solvent-based paclitaxel is more toxic than Abraxane) the anti tumour effect of Abraxane is equal to or better than the effect of solvent-based paclitaxel.

No studies on genotoxicity or carcinogenicity were performed with Abraxane. The genotoxic properties of paclitaxel have already been evaluated for solvent-based paclitaxel, and no further studies are considered necessary for Abraxane. Paclitaxel was not mutagenic in standard Ames tests (Ma 1996), or in Drosophila wing Somatic Mutation Assay (Cunha, Reguly et al. 2001). On the other hand, paclitaxel can cause increased micronuclei formation in mouse bone marrow (Tinwell and Ashby 1994), and chromosome aberrations in human lymphocytes (Digue, Orsiere et al. 1999). The overall conclusion from a number of genotoxicity studies with paclitaxel is that it affects the chromosomal spindle via microtubule disorganization but does not react directly with DNA. The consequence of this is apoptosis or necrosis (Wang, Wang et al. 2000). A warning has been include in section 5.3 of the SPC.

Abraxane causes embryo/foetal mortality, malformations, reduced foetal weights and delayed ossification at exposure levels. These findings are reflected in section 5.3 of the SPC and Abraxane should not be used during pregnancy as stated in section 4.6 of the SPC. It is not known if paclitaxel is excreted in human milk. Because of potential serious adverse events in breast-feeding infants, Abraxane is contraindicated during lactation (in section 4.3 of the SPC).

In male fertility studies, paclitaxel-related toxicity was seen in male rats. Potential effects on male fertility have been reflected in the SPC section 4.6, with reference to animal findings (section 5.3).

2.4 Clinical aspects

Introduction

The clinical development program for Abraxane in breast cancer as a single-agent treatment for the treatment of metastatic breast cancer consisted in one pivotal Phase III study (CA012-0) and two supportive Phase II studies (CA002-0LD and CA002-0). Five additional Phase I and II clinical trials in patients with MBC were included in the safety analysis (Studies CA013-0, CA016, CA024, CA025 and CA201). Two studies, DM97-123 and CA101, have been conducted to determine the maximum tolerated dose of Abraxane administered. Phase I and II studies in patients with advanced solid tumours (DM97-123, CA005-0, CA008-0, CA019, CA201, CA037) were submitted to support the pharmacokinetic program. No studies were submitted in the adjuvant setting.

Scientific Advice was issued by the CHMP on 23 January 2003 and clarified on 14 April 2003.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Pharmacokinetics

Four studies are submitted, with pharmacokinetic data from a total of 65 subjects (both males and females, 85-100 % Caucasian) receiving doses of Abraxane from 80 to 375 mg/m^2 (Table 9). In addition, published data regarding paclitaxel and solvent-based formulations for *in vitro* metabolism, plasma protein binding, hepatic metabolism and drug-drug interactions are provided.

Table 9: Pharmacokinetic studies

	Study start Location	**Study objective**	**No of subjects receiving Abraxane in PK study**	**Dose Abraxane**	**Inclusion criteria**
DM97-123	1998 USA	Phase I/II Dose ranging	16	135-375 mg/m^2 q3w	Advanced solid tumours: malignant melanoma, breast cancer
CA005-0	2000 USA	Phase I Dose ranging	23	80-200 mg/m^2 weekly, 3 doses every 4 weeks	Advanced non-haematological malignancies: melanoma, breast
CA008-0	2003 Russia	Phase I PK Comparison with solvent-based paclitaxel	14	260 mg/m^2 q3w	Advanced solid tumours: breast, lung/bronchus, ovary
CA012-0	2001 Russia	PK substudy of phase III Comparison with solvent-based paclitaxel	12	260 mg/m^2 q3w	Metastatic breast cancer

A sensitive high performance liquid chromatographic method with atmospheric pressure ionisation tandem mass spectrometry detection (LC-API/MS/MS) was developed and validated for determination of paclitaxel in human plasma. This method was also validated for different biological material such as human whole blood, urine and faeces. The LC-API/MS/MS method involved a solid phase extraction of the analyte(s) and the internal standard from the biological material, followed by a reverse phase liquid chromatography with tandem mass spectrometry detection, by positive ionisation. A penta-deuterated derivative (d5) of paclitaxel was used as internal standard.

Most studies used non-compartmental pharmacokinetic analyses**.** PK analysis of the paclitaxel blood or plasma concentration-time data was conducted using the non-compartmental Model 202 (constant infusion) of WinNonlin, Version 4.1. Actual sample collection times were used in the paclitaxel PK analysis. PK analysis of 6α-hydroxypaclitaxel and 3'-p-hydroxypaclitaxel blood concentration-time data was conducted using the non-compartmental Model 200 (extravascular input) of WinNonlin. Descriptive statistics were provided. In post hoc analysis studying age effect, the general linear modelling (GLM) procedure in SAS version 8.1 was used to perform the analysis of variance (ANOVA) using the log of AUC_{inf}d and log of clearance. Significance level or alpha was set at 0.05.

The mean paclitaxel pharmacokinetic parameters from studies with Abraxane doses relevant for the applied posology are given in Table 10.

Table 10: Mean pharmacokinetic parameters

	Dose Abraxane mg/m^2	**No subjects**	**C_{max} ng/ml (range)**	**Vd l/m^2 (range)**	**AUC_{inf} ng·hr/ml (range)**	**T ½ hr (range)**	**CLt l/hr/m^2 (range)**
DM97-123	200	3	7757 (6110-10900)	401 (186-656)	8998 (7073-10536)	13.2 (4.6-21.3)	22.9 (19.0-28.4)
	300	5	13520 (11800-14200)	387 (267-524)	16736 (11530-21749)	14.4 (13.1-18.1)	18.7 (13.8-26)
CA 005-0	200	2	13400 (12700-14100)	483 (396-570)	11363 (10042-12683)	18.62 (17.4-19.84)	17.9 (15.8-19.9)
CA 008-0	260	14	22969 (4060-86700)	230.7* (53.2-493)*	14789 (5982-28680)	21.6 (16.5-29.6)	21.13 (8.72-43.4)
CA 012-0	260	12	18741 (8787-24938)	632 195.5* (348-1831)	17940 (11205-23900)	27.4 (19.8-54.7)	15.2 (10.9-23.2)

*Vdss

- Absorption

No absolute bioavailability studies have been carried out on Abraxane, since the product is administered intravenously.

Bioequivalence was tested for clinical batches with different ratios of human albumin to paclitaxel. One final modification was made for commercial manufacturing process: the pH adjustment of the human albumin solution (20%) and final formulated suspension was omitted (product code 103450). This last modification did not change the product characteristics as determined by particle size distribution, release testing and stability. The use of different albumin: paclitaxel ratios within Study CA005-0 did not affect the dose-normalised AUC_{inf}. Furthermore, a comparison of the AUC_{inf} vs. dose across all studies and all clinically relevant doses shows that the change in the albumin: paclitaxel ratio does not affect the pharmacokinetics of paclitaxel.

Study CA008-0 investigated Abraxane and solvent-based formulations of paclitaxel, 260 mg/m^2 q3w and 175 mg/m^2 q3w, respectively. Abraxane was administered IV over a period of 30 min, while solvent-based paclitaxel was administered over 3 hr. Mean pharmacokinetic parameters are given in Table 11. Whole blood concentration versus time curves for Abraxane and solvent-based paclitaxel (data not shown) indicate that the initial decrease in concentration (15 minutes after infusion) appears to be more rapid for Abraxane than for solvent-based paclitaxel, reflecting the increased CL and Vz for Abraxane. At the terminal elimination phase, the declines in paclitaxel concentration for the two preparations appear to be parallel.

Table 11: Mean pharmacokinetic parameters from study CA008-0.

Parameter	ABI-007 260 mg/m^2 (n = 14)	Taxol 175 mg/m^2 (n = 12)	*P* Value
CL (L/h·m^2)	21.13	14.76	0.048
V_z (L/m^2)	663.8	433.4	0.040
AUC_{inf} (ng/h·mL)	14788.6	12602.7	0.524
C_{max} (ng/mL)	22968.6	3543.3	< 0.001
C_{maxda} (ng/mL)	88.69	20.14	< 0.001
$T_{1/2}$ (h)	21.6	20.5	0.479

CL = Total blood clearance; V_z = apparent volume of distribution related to the terminal phase elimination rate constant; AUC_{inf} = area under the concentration-time curve from time zero to infinity; C_{max} = maximum blood concentration; C_{maxda} = dose-adjusted C_{max}; $T_{1/2}$ = terminal phase half-life.

- Distribution

No tissue distribution studies of paclitaxel after Abraxane administration have been performed in humans.

Protein binding studies have not been performed for Abraxane. From published data from as solvent-based paclitaxel (Kumar, Walle et al. 1993; Brouwer, Verweij et al. 2000), it is estimated that the protein binding of paclitaxel following Abraxane administration is about 90% (value in the absence of Cremophor). Solvent-based paclitaxel was bound about 95%. Human serum albumin and α_1-acid glycoprotein were found to contribute equally to the binding, with a minor contribution from lipoproteins (Kumar, Walle et al. 1993).

- Elimination

Paclitaxel pharmacokinetics in blood displayed a biphasic (study DM97-123) or multiphase (studies CA005-0, CA008-0, CA012-0) disposition profile. The elimination is mainly non-renal, and mainly as metabolites. Mean total body clearance was 15-21 l/hr/m^2. Urinary and faecal excretion of paclitaxel and two metabolites (6α-hydroxypaclitaxel and 3'-p-hydroxypaclitaxel) are shown in Table 12.

Table 12: Excretion of paclitaxel and metabolites in study CA012-0

Compound	Mean %Dose (%CV) Range	
	Urine	Faeces [a]
Paclitaxel	3.92 (39) 1.27 – 5.75	2.77 (74) 0.50 – 5.89
6α-Hydroxypaclitaxel	0.15 (108) 0.03 – 0.59	18.04 (65) 5.06 – 37.65
3'-p-Hydroxypaclitaxel	0.04 (79) 0.01 – 0.11	1.08 (80) 0.25 – 2.41
Total (range)	4.10 (1.34-5.85)	21.88 (5.97-44.78)

[a] Several patients in this study were constipated over the 5 day study period. For the 2/12 patients who produced 5 measurable faecal samples over 5 days, the total recovery of paclitaxel and metabolites was 45-44 %.

Pharmacokinetic parameters of the metabolites 6α-hydroxypaclitaxel and 3'-p-hydroxypaclitaxel are presented in Table 13 (Study CA012-0):

Table 13: Summary of PK parameters for 6α-Hydroxypaclitaxel and 3´-p-hydroxypaclitaxel

Metabolite	C_{max} (ng/ml)	T_{max} (h)	AUC (h*ng/ml)	Parent/Metabolite AUC_{inf} Ratio
6α-Hydroxypaclitaxel				
Mean	591	1.11	2528	21.6
C.V. (%)	(82)	(89)	(145)	(81)
Range	(161-1534)	(0.50-4.00)	(257-13025)	(1.6-58.0)
3′-p-Hydroxypaclitaxel				
Mean	220	0.86	1075	58.9
C.V. (%)	(74)	(47)	(125)	(92)
Range	(45-610)	(0.50-2.00)	(82-4009)	(6.0-182.3)

Using human hepatocytes, (Nallani, Goodwin et al. 2004) examined the effects of paclitaxel on the activity and expression of hepatic CYP3A4. Paclitaxel at clinically relevant concentrations potently induced CYP3A4 activity and expression in hepatocytes treated for 48-96 h. The effect of paclitaxel on CYP2C8 activity or expression has not been studied.

- Dose proportionality and time dependencies

Mean pharmacokinetic parameters derived from plasma/ blood data of paclitaxel administered as Abraxane for the different doses are given in Table 14 **(**Study DM97-123**).** The correlation between mean AUC_{inf} and dose level appears to be linear across the three lower dose levels, and nonlinearity becomes evident at 375 mg/m^2. Clearance and half-life were relatively similar across different dose levels. Linear regression analysis of AUC_{inf} versus dose showed a linear relationship between AUC_{inf} and dose, although the correlation was not strong (R2=0.5352).

Table 14: Pharmacokinetic parameters of Abraxane at different doses

Dose (mg/m^2)	Infusion Duration (min)	n	Mean (%CV)					
			C_{max} (ng/ml)	AUC_{inf} (ng•h/ml)	AUC_{inf}/Dose (ng•h/ml)	$T_{1/2}$ (hr)	CLt (l/h/m^2)	Vz (l/m^2)
135 [a]	180	3	1392 (30)	5427 (35)	40.2	15.7 (27)	27.2 (34)	598 (33)
135 [a]	30	1	6100	5844	43.3	14.5	23.2	485
200 [b]	25 - 30	3	7757 (35)	8998 (20)	45.0	13.2 (63)	22.9 (21)	407 (58)
300 [c]	27 - 30	5	13,520 (7)	16,736 (22)	55.8	14.4 (15)	18.7 (24)	387 (26)
375 [c]	30 - 45	4	19,35 (15)	32,525 (36)	86.7	11.7 (29)	12.9 (41)	235 (64)

[a] PK parameters generated from plasma samples
[b] PK parameters generated from plasma (n=1) and whole blood (n=2)
[c] PK parameters generated from whole blood samples

- Special populations

Excretion in the urine has been shown to be minimal and specific studies in renal impaired patients were not performed. In one study with solvent-based paclitaxel (Gelderblom, Verweij et al. 2001), a high and reproducible AUC and longer $T_{1/2}$ was observed in a female patient with severe renal impairment, compared to patients with normal renal function. The observed increase in systemic exposure in this patient was attributed to decreased renal metabolism and/or urinary excretion of unchanged drug or polar metabolites.

Data from studies DM97-123, CA005-0, CA012-0 and CA008 were combined in a post-hoc analysis to determine whether age had any influence on the PK of paclitaxel following Abraxane administration (see Table 15). The subjects' ages in the studies ranged from 33 to 85 years of age. The mean $AUC_{\infty}d$ and the mean CL of the ≥ 65 year-old age group was not statistically different from the < 65 year-old age group in these studies. $AUC_{\infty}d$ and CL were thus independent of age as categorised in this analysis.

Table 15: Effect of age on ABI-OO7 main pharmacokinetic parameters.

Age	Age mean (range)	N	$AUC_{\infty}d$	CL
Group 0 = < 65 yrs	48 (33-62)	45	57.17 (23.62)	20.44 (8.14)
Group 1 = ≥ 65 yrs	71 (65-85)	19	50.27 (18.29)	22.78 (9.06)
P value			0.82	0.82

The effects of gender, race, or body weight on the pharmacokinetics of Abraxane have not been studied. PK studies in children have not been performed. Specific warnings have been included in section 4.2 of the SPC including a special warning on section 4.4 for hepatic impaired patients.

- Pharmacokinetic interaction studies

Possible interactions of Abraxane with other products have not been investigated. A review of published studies of drug-drug interactions of paclitaxel, mostly given as solvent-based paclitaxel, has been provided (see Tables 16 and 17):

Table 16: *In vitro* interaction studies with paclitaxel

Drug/product	Effect	Enzyme source	References
Cimetidine	No effect on 6α-hydroxy-PAC	Human liver microsomes	Jamis-Dow et al 1995
Diphenhydramine			
Carboplatin	No inhibition of 6α-hydroxy-PAC	Human liver microsomes	Bun et al 2003
Cisplatin			
Etoposide			
5-Fluorouracil			
Vinorelbine			
Doxorubicin	Inhibition of 6α-hydroxy-PAC		
Clozapine			
Quercetin			
Quinidine	Inhibition of 6α-hydroxy-PAC	Human liver microsomes	Jamis-Dow et al 1995
Dexamethasone			
Cremophor EL			
Ketokonazole			
Ketoconazole	Inhibition of 6α-hydroxy-PAC and 3'-p-hydroxy-PAC	Human liver microsomes	Bun et al 2003
Miconazole			
Amiodarone	Inhibition 3'-p-hydroxy-PAC		
Dexamethasone			
Erythromycin			
Verapamil			
Cremophor EL	No inhibition of 6α-hydroxy-PAC	Human liver slices	Jamis-Dow et al 1995
Phenolic antioxidants: fisetin, quercetin, morin, resveratrol	Inhibition of 6α-hydroxy-PAC more than inhibition of 3'-p-hydroxy-PAC	Human liver microsomes	Vaclavikova et al 2003

Table 17: *In vivo* interactions with paclitaxel

Drug	PK effect	Toxicity, clinical effect	References
Doxorubicin	Reduced clearance, increased level of doxorubicin Reduce the biliary excretion of doxorubicin by inhibiting P-glycoprotein	Increased toxicity, depends on the order of administration.	Baxter 2006
Epirubicin	Increased concentrations of epirubicin metabolites Reduce the biliary excretion of epirubicin by inhibiting P-glycoprotein		Baxter 2006
Aprepitant	Aprepitant inhibits CYP3A4		Baxter 2006
Ifosfamide		Additive or synergistic, or antagonistic effect, depending on the order of administration.	Baxter 2006

Cyclophosphamide		Toxicity depends on the order of administration.	Baxter 2006
Capecitabine	No effects		Baxter 2006
Gemcitabine	No effect	Increased gemcitabine triphosphate levels, potentially improving efficacy	Baxter 2006
Amifostine	No effect	Reduced toxicity of taxanes?	Baxter 2006
Carboplatin		Toxicity depends on the order of administration. Reduced thrombocytopenia associated with carboplatin	Baxter 2006
Cisplatin		Toxicity depends on the order of administration.	Baxter 2006
Phenytoin Carbamazepine Phenobarbital	Increased metabolism and clearance of paclitaxel	Increased maximal tolerated dose of paclitaxel	Baxter 2006
Ketoconazole	No effect		Baxter 2006
Antivirals	Competition for the CYP3A enzyme system	Increased toxicity of paclitaxel	Bundlow & Aboulafia 2004

- Pharmacokinetics using human biomaterials

Studies were not submitted.

Pharmacodynamics

No pharmacodynamic or pharmacokinetic-pharmacodynamic relationship studies in patients treated withAbraxane have been submitted.

- Mechanism of action

No studies have been submitted.

- Primary and secondary pharmacology

No studies have been submitted.

- Discussion on clinical pharmacology

Abraxane is an albumin-bound nanoparticle formulation of paclitaxel, which may have substantially different pharmacological properties compared to other formulations of paclitaxel.

In vitro studies addressing the metabolism of Abraxane have been not been submitted. The applicant refers to published studies. No metabolism was detected with kidney microsomes (Cresteil, Monsarrat et al. 1994), but with liver microsomes two metabolites were found, 6α-hydroxypaclitaxel and 3'-p-hydroxypaclitaxel (Cresteil, Monsarrat et al. 1994; Harris, Katki et al. 1994; Jamis-Dow, Klecker et al. 1995). These were also shown to be the major metabolites recovered in patients (Monsarrat, Alvinerie et al. 1993; Harris, Rahman et al. 1994). A third metabolite, 6α, 3'-p-dihydroxypaclitaxel was also described to be the second most important metabolite in feces (Sparreboom, Huizing et al. 1995). The enzymes responsible for the metabolism of paclitaxel to these metabolites in human have been identified as the cytochrome P450 enzymes CYP2C8 and CYP3A4 (Rahman, Korzekwa et al. 1994; Bun, Ciccolini et al. 2003). Both 6α-hydroxypaclitaxel and 3'-p-hydroxypaclitaxel was reported to be less active the paclitaxel (Sparreboom, Huizing et al. 1995).

Abraxane has not been studied in patients with hepatic or renal dysfunction. Only isolated studies are published on paclitaxel PK after solvent-based paclitaxel administration in patients with hepatic impairment. Some of these are summarized by (Panday, Huizing et al. 1997), and it was shown that hepatic impairment has a great influence on the systemic exposure of paclitaxel and metabolites. Decreased paclitaxel clearance in patients with impaired hepatic function (liver metastases, hepatitis viral C infection and chronic active hepatitis) was noted with an increased incidence of myelosuppression and mucocytosis.

PK/PD differences between Abraxane and solvent-based paclitaxel could be explained by the presence of Cremophor in the solvent-based paclitaxel formulation and by the increased dose of paclitaxel in the Abraxane treatment regimen. Paclitaxel may be retained in Cremophor micelles in the serum resulting in a slower tissue distribution and a higher AUC. On the other hand Abraxane shows a faster tissue distribution that may explain the lower neutropenia and myelosuppression observed. In the same way, peripheral neuropathy was related to cumulative paclitaxel dose and because of the higher dose of paclitaxel was given for Abraxane compared to solvent-based paclitaxel an increase in peripheral neuropathy was observed (see Clinical Safety). The resolution of peripheral neuropathy observed with Abraxane remains to be further investigated. The applicant has committed to provide additional safety data on the topic from ongoing studies and PSURs.

No specific study has been submitted to explore the effect of renal or liver function on Abraxane pharmacokinetics. As renal clearance was estimated to be only about 4% of the total clearance, the effect of impaired renal function should be minimal. A specific study on the effect of liver impairment on Abraxane pharmacokinetics will be performed as a follow-up measure to explore the need for dose adjustment in patients with impaired liver function.

Possible interactions of paclitaxel with other products have not been formally investigated by the applicant. However, considerable information is available in the scientific literature and was reviewed. In vivo studies have demonstrated that metabolism of paclitaxel by CYP2C8 is the most important pathway in humans with a minor contribution of CYP3A4. Therefore, caution should be exercised when administering paclitaxel concomitantly with medicines known to inhibit (e.g. erythromycin, fluoxetine, gemfibrozil) or induce (e.g. rifampicin, carbamazepine, phenytoin, phenobarbital, efavirenz, nevirapine) either CYP2C8 or 3A4. A warning with the full interaction data known for solvent-based paclitaxel has been included in section 4.5 of the SPC until this information is available for Abraxane.

Clinical efficacy

The clinical study programme for the assessment of efficacy of Abraxane given every three weeks in patients with MBC comprises a total of three studies, one pivotal Phase III study (Study CA0120-0) and two supportive Phase II studies (studies CA002-0 and CA002-0LD) (see Table 18).

Table 18: Completed studies for dose, dosage regimen, efficacy and safety in patients with MBC

Study Number	Design
CA002-0LD	Open label, multi-centre, Phase II study of Abraxane administered at 175mg/m^2 q3w in pts with MBC.
CA002-0	Open label, multi-centre, Phase II study of Abraxane administered at 300mg/m^2 q3w in pts with MBC.
CA012-0	Controlled randomised, Phase III, multi-centre, open-label study of Abraxane at 260mg/m^2 over 30 minutes q3w and solvent-based paclitaxel at 175 mg/m^2 over 3 hours q3w in pts with MBC.

- Dose response studies

Two studies, DM97-123 (USA) and CA101 (China), with a total of 41 subjects (54% Asian, 44% Caucasian, 2% Hispanic, 39% male, 61% female) have been conducted to determine the maximum tolerated dose of Abraxane administered using the proposed posology (q3w).

In study DM97-123, a total of 19 subjects received in the first cycle 135 (4 subjects), 200 (3 subjects), 300 (6 subjects), or 375 mg/m^2 (6 subjects). Individual patients received from 1 to 13 cycles. The patient population was 95% Caucasian and 5% Hispanic, largely female patients (84% female; 16% male). Dose-limiting toxicities observed at 375 mg/m^2 were keratitis, blurred vision, sensory neuropathy, stomatitis, and Grade 4 neutropenia. These events were generally Grade 2 or 3, were reported after Cycle 1 dosing and were generally transient.

In study CA101, an open-label, single-centre, dose-escalation, Phase I trial, all 22 patients were Asian (Chinese), 59% male and 41% female. Abraxane was administered IV q3w, 135 (3 subjects), 175 (4 subjects), 225 (3 subjects), 260 (3 subjects), 300 (6 subjects), and 350 mg/m^2 (3 subjects). All of the

patients except 1 in the 175 mg/m^2 dose group received ≥ 2 treatment cycles. Dose-limiting toxicities at 350 mg/m^2 were grade 4 neutropenia and grade 3 double vision, which occurred in 1 patient each.

In both studies, the MTD was defined as the study drug dose that elicited > Grade 2 non-myelosuppressive toxicity or > Grade 3 myelotoxicity in at least 2 of 6 patients. A minimum of 6 patients were to be treated at the MTD in each study. The MTD for both studies was 300 mg/m^2 given IV over 30 minutes every 3 weeks.

- Main study

Study CA012-0

A controlled, randomised, multicentre, open-label, Phase III, non-inferiority study to evaluate the safety/tolerability and antitumour effect of intravenously (IV) administered Abraxane compared to that of solvent-based paclitaxel in patients with metastatic breast cancer.

METHODS

Study Participants

A patient was considered eligible for inclusion in this study, if all of the following criteria were met.

- patient was female, non-pregnant and not lactating, and ≥ 18 years of age
- patient had a histological or cytological confirmed measurable metastatic breast cancer and was a candidate for paclitaxel therapy in accordance with standard of care
- if patient had received solvent-based paclitaxel or docetaxel as adjuvant therapy; she had not relapsed with breast cancer within 1 year of completing adjuvant solvent-based paclitaxel or docetaxel
- patient had no other malignancy within the past 5 years, except non-melanoma skin cancer, cervical intraepithelial neoplasia (CIN), or in-situ cervical cancer (CIS)
- patient was a suitable candidate for single-agent paclitaxel treatment
- patient had an expected survival of > 12 weeks

A patient was considered non eligible for inclusion in this study, if any of the following criteria were met:

- patient had clinical evidence of active brain metastases, including leptomeningeal involvement requiring steroid or radiation therapy
- patient's only evidence of metastasis was lytic or blastic bone metastases or pleural effusion or ascites
- patient had a clinically serious concurrent illness (as determined by the Principal Investigator)
- patient had an ECOG (Zubrod) performance status of > 2
- patient was unlikely, in the Investigator's opinion, to be able to complete the study through the Week 15 visit
- patient had received treatment with any of the following:

– Hormonal therapy within 2 weeks prior to first dose
– Chemotherapy (except for palliative bisphosphonate therapy for bone pain which could be administered as clinically indicated) within 4 weeks prior to first dose
– Investigational drug or immunotherapy within 4 weeks prior to first dose
– Concurrent radiation therapy (except for palliative radiotherapy for bone pain which could be administered as clinically indicated)

- patient had received paclitaxel or docetaxel because of metastatic carcinoma
- patient had pre-existing peripheral neuropathy of National Cancer Institute (NCI) Common Toxicity Criteria (CTC) Grade ≥ 1

Treatments

Patients received either Abraxane at 260 mg/m^2 administered IV over 30 minutes repeated every 3 weeks without steroid pre-medication and without granulocyte colony-stimulating factor (G-CSF) prophylaxis, or solvent-based paclitaxel at 175 mg/m^2 administered IV over 3 hours repeated every 3 weeks with standard pre-medication as per the package insert for solvent-based paclitaxel authorized in the country in which the study was being conducted. Cross-over to Abraxane after progression for

patients in the solvent-based paclitaxel arm was not offered as part of the protocol, nor were patients in the Abraxane arm offered additional Abraxane after progression.

Study drug was administered at Weeks 0, 3, 6, 9, etc. Patients without progressive disease (PD) after 6 cycles could continue their assigned treatment at the Investigator's discretion, provided none of the following withdrawal criteria had been met:

- PD after a minimum of 2 cycles of Abraxane or solvent-based paclitaxel, or after initial response followed by increasing tumour size
- development of a toxicity which is unacceptable, in the opinion of the Investigator, as defined by the NCI CTC
- if, following the second dose reduction of Abraxane to 180 mg/m^{2,} there was a recurrence of Grade 4 neutropenia or any other haematologic toxicity that was Grade 3 or 4, or any Grade 3 or 4 non-myelosuppressive adverse event (AE) (excluding alopecia), unless at the discretion of the Investigator there was evidence of continuing benefit to the patient
- initiation of further anticancer therapy

Dose reductions were permitted for patients with either haematologic or non-haematologic toxicities. A maximum of 2 dose reductions were allowed from the initial 260 mg/m^2 dose. The first dose reduction was by 40 mg/m^2 o 220 mg/m^2, and the second dose reduction was by 40 mg/m^2 to 180 mg/m^2. If a Grade 3 or 4 AE (excluding alopecia) recurred after a dose reduction to 180 mg/m^2, the patient was discontinued from the study unless the Investigator determined there was a continuing benefit to the patient.

Objectives

The primary objectives were:

– to compare the anti-tumour activity of Abraxane with that of solvent-based paclitaxel in patients with MBC
– to evaluate the safety/tolerability of Abraxane compared to that of solvent-based paclitaxel

The secondary objectives were:

– to evaluate time to disease progression (TTP) and survival
– to evaluate changes from baseline in quality of life (QOL)
– to determine the PK of Abraxane

Outcomes/endpoints

The primary efficacy endpoint for this study was the percentage of patients who achieved confirmed **complete or partial target lesion response** as defined by Response Evaluation Criteria in Solid Tumours (RECIST) guidelines. Tumours were assessed at Weeks 5, 9 and 15 and thereafter every six weeks. Confirmation of CR and PR required response duration $\geq$ 4 weeks.

Secondary efficacy endpoints for this study included the following:

- percentage of patients who achieved complete or partial overall response
- time to disease progression (TTP)
- patient survival
- percentage of patients who achieved each target lesion response/overall response of complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD)
- time to first complete or partial target lesion response/overall response
- duration of complete or partial target lesion response/overall response
- number of cycles of therapy to maximum target lesion response/overall response
- duration of CR, PR, or SD for target lesion response/overall response
- QOL evaluated by changes from baseline in scores on the Eastern Cooperative Oncology Group (ECOG) (Zubrod) performance status scale, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30, and weight

Two primary datasets were used: a) the clinical investigators' assessments of response (Investigator Response Assessment Dataset) and b) an independent, blinded assessment of response based on radiological assessments made by a central radiology facility that was not otherwise associated with

the study (IRL Response Assessment Dataset). A reconciliation algorithm was established to create a third, derived dataset (the Reconciled Response Assessment Dataset), which conservatively reconciled any differences between the other 2 datasets.

Sample size
The study was powered to provide at least 80% power with a 1-sided Type I error (α) of 0.025 (2-sided $\alpha = 0.05$) to assure that Abraxane was at least 75% as active as solvent-based paclitaxel, assuming a baseline response rate of 30% for solvent-based paclitaxel. Enrolment was planned for approximately 460 patients to provide approximately 210 evaluable patients per treatment arm.

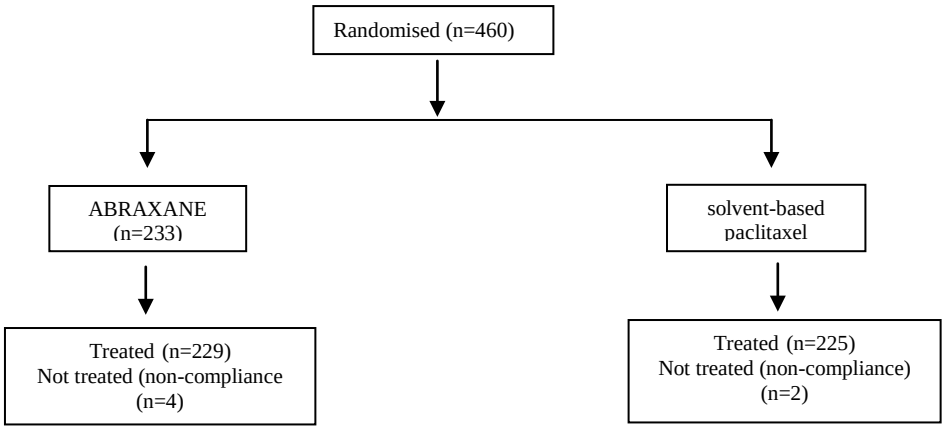
Randomisation
Within each country, randomisation (1:1 to the treatment groups) was stratified based on prior anthracycline use (yes/no) using a block size of 2.

Blinding (masking)
This was an open-label study.

Statistical methods
The primary efficacy analysis incorporated a multiple nested test procedure which is a closed test procedure:
Step 1: Non-inferiority test of Abraxane versus solvent-based paclitaxel for the ITT population
The lower bond of the 95% confidence interval for the difference is < 0.75.
The analysis was stratified for the 1st line therapy versus > 1 st line therapy
Step 2: Superiority of Abraxane compared to solvent-based paclitaxel, ITT population
Step 3: Superiority of Abraxane compared to solvent-based paclitaxel, in the 1st line patients.

RESULTS

Participant flow



Recruitment

A total of 460 patients enrolled into the study and were randomized to treatment with ABI- 007 (233 patients) or with solvent-based paclitaxel (227 patients). Patients were enrolled at 28 sites in Russia/Ukraine (353 patients; 77% of patients), 20 sites in the UK (67; 15%), and 22 sites in the US/Canada (40; 9%).

The first patient was enrolled at the 01 November 2001 and the data cut-off was 07 April 2003 when the 460th patient had the Cycle 4/Week 9 response assessment.

Conduct of the study
The protocol for this study, originally dated 19 June 2001, was amended 3 times after the randomization of the first patient. Amendments 1-2 were in effect prior to the data cut-off date and Amendment 3 went into effect after the data cut-off date. The first amendment allowed continued treatment after 6 cycles at the Investigator's discretion to be consistent with standard for breast cancer

patient care in some participating countries. Additionally, patients who initiated further anticancer therapy were to be discontinued from the study. Several of the other amendments are made to improve clarity and consistency, and also to improve safety.

In the Abraxane and solvent-based paclitaxel groups, 10 and 2 patients, respectively, had important predefined protocol deviations. Of these, 4 patients in the Abraxane group and 2 in the solvent-based paclitaxel group were randomized but did not meet the eligibility criteria and were discontinued from the study before receiving any study medications; these patients were not included in the ITT Population. Data for the remaining 9 patients with predefined protocol deviations were considered evaluable for all efficacy and safety analyses, except for the per-protocol analysis of the primary efficacy endpoint.

Three patients in the Abraxane group received aromatase inhibitors (letrozole, exemestane, and anastrozole, respectively) between the first and last doses of study drug (overlapping the study regimen for 4 months, 1 week, and 2 weeks, respectively).

Baseline data

All patients were female, 97% were Caucasian, and 83% were postmenopausal. Mean (S.D.) age was 53.2 (10.10) years (range: 26 to 83 years); 86% of patients were < 65 years of age. Mean (S.D.) height was 161.7 (6.06) cm (range: 145 to 182 cm), and mean (S.D.) baseline weight was 70.0 (13.26) kg (range: 40 to 125 kg). No important differences between the treatment groups were noted in demographic parameters. Baseline disease characteristics are provided in Tables 19, 20, and 21:

Table 19: Initial diagnosis of breast cancer (ITT Population)

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

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

Table 20: History of prior therapies at baseline (ITT population)

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

Table 21: History of prior metastatic treatments at baseline (ITT population)

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

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 only, 40% in the metastatic setting only, 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.

Numbers analysed

Patient disposition was shown for the all randomized population (AR). Efficacy and safety analyses were performed for the ITT and safety populations, respectively; both of these populations were defined as randomized patients who received at least 1 dose of study drug. The primary efficacy analysis was also performed for the Per Protocol (PP) and AR populations. The PP population excluded 25 patients from the ITT population: 9 patients (Abraxane: 8; solvent-based paclitaxel: 1) with protocol deviations and 16 (ABI- 007: 10; solvent-based paclitaxel: 6) who received only 1 dose of study drug. Thus the PP population consisted of 429 patients, 211 in the Abraxane group and 218 in the solvent-based paclitaxel group. Patient populations for analysis are summarized in Table 22.

Table 22: Patient population for analysis

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

Outcomes and estimation

TARGET LESION RESPONSE RATE (PRIMARY EFFICACY ANALYSIS)

Test of inferiority

The main efficacy results for the test of non-inferiority of study BR.21 are summarized in Table 23.

Table 23: Target lesion response rates and test of non-inferiority (ITT population)

Category	Abraxane (n = 229)	solvent-based paclitaxel (n = 225)	Ratio [a] (P Value)[c]
Investigator Response Assessment Dataset			
Patients in dataset, n	229	225	1.876 (<0.001*)
Patients with **target** lesion response, n	72	37	
*inv*TLRR, %	31.4	16.4	
95% Confidence interval [b]	25.43−37.45	11.60−21.29	1.322−2.661
IRL Response Assessment Dataset			
Patients in dataset, n	176	171	2.650 (0.001*)
Patients with **target** lesion response, n	37	13	
*irl*TLRR, %	21.0	7.6	
95% Confidence interval [b]	15.00−27.04	3.63−11.57	1.461−4.807
Reconciled Response Assessment Dataset			
Patients in dataset, n	229	225	2.110 *(<0.001*)*
Patients with **target** lesion response, n	55	25	
*rec*TLRR, %	24.0	11.1	
95% Confidence interval [b]	18.48−29.55	7.00−15.22	1.368−3.254

Ratio = (Abraxane response rate) / (solvent-based paclitaxel response rate). Ratio and 95.305% CI were adjusted for first-line versus > first-line therapy.
95% Binomial confidence interval of response rate.
P value from Cochran-Mantel-Haenszel test stratified by first-line versus > first-line therapy;

3. Test of superiority in patients receiving 1st-line therapy

Because the primary endpoint passed the tests for non-inferiority and superiority in the overall population, the test for superiority in patients receiving 1st-line therapy was conducted (see Table 24).

Table 24: Target lesion response rates and test of superiority in patients receiving 1st-line therapy (ITT population)

Category	Abraxane (n = 229)	solvent-based paclitaxel (n = 225)	Ratio[a] (P Value)[b]
Investigator Response Assessment Dataset			
Patients in dataset, n	97	89	1.516 *(0.053)* 0.986−2.332
Patients with target lesion response, n	38	23	
*inv*TLRR, %	39.2	25.8	
95% Confidence interval[c]	29.46−48.89	16.75−34.94	
IRL Response Assessment Dataset[d]			
Patients in dataset, n	74	64	2.486 *(0.009*)* 1.196−5.168
Patients with target lesion response, n	23	8	
*irl*TLRR, %	31.1	12.5	
95% Confidence interval[c]	20.54−41.63	4.40−20.60	
Reconciled Response Assessment Dataset			
Patients in dataset, n	97	89	1.892 *(0.013*)* 1.121−3.193
Patients with target lesion response, n	33	16	
*rec*TLRR, %	34.0	18.0	
95% Confidence interval[c]	24.59−43.45	10.00−25.96	

a).Ratio = (Abraxane response rate) / (solvent-based paclitaxel response rate). b).95% Binomial confidence interval of response rate.
c).P value from chi-square test; c.* P < 0.05.

SECONDARY ENDPOINTS

OVERALL RESPONSE RATE (ORR)

The investigator's overall response rate (*inv*ORR) for all patients was 33.2% in the Abraxane group and 18.7% in the solvent-based paclitaxel group (95% CI 27.09, 39.29 vs. 13.58, 23.76, p = 0.001). Of the 76 patients in the Abraxane group with confirmed overall responses, 74 achieved a PR and 2 achieved a CR; of the 42 in the solvent-based paclitaxel group, 39 achieved a PR and 3 achieved a CR. An independent radiological laboratory (IRL) conducted blinded assessments of tumour images. The IRL evaluated only tumours that could be assessed radiological and therefore could not make

assessments on 25 patients, of which 15 had only clinically detected lesions and 10 had poor or no scans. These patients were therefore excluded from the IRL dataset, which consisted of 215 patients in the Abraxane group and 214 in the solvent-based paclitaxel group. Overall response rates using the IRL dataset *(irl*ORR*)* were 21.4% in the Abraxane group and 10.3% solvent-based paclitaxel group (p = 0.002; ratio = 2.037 CI: 1.276-3.252).

Statistical testing of treatment group differences in the response rates was performed. Testing was done using the CMH (Cochran-Mantel-Haenszel statistical analysis) test stratified by 1st line vs. >1st line therapy or the chi-square test, as appropriate. The *inv*ORR analysis in patients receiving 1st-line therapy is shown in table 25.

Table 25. *inv*ORR by Line of Therapy (ITT Population)

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

[a] Ratio = (ABI-007 response rate) / (Taxol response rate).
[b] 95% binomial confidence interval of response rate.
[c] P-value from chi-square test; * P < 0.05.
Source Data: Summary Table 15.9.0, 15.9.0.1, and Listing 13.0

Regarding prior anthracycline therapy, the *inv*ORRs were statistically significantly higher in the Abraxane group than the solvent-based paclitaxel group in patients with prior anthracycline therapy (adjuvant or metastatic) (34.1% vs. 18.3%, P = 0.002) and in patients with prior metastatic anthracycline therapy (27.0% vs. 13.8%, P = 0.010).

TIME TO PROGRESSION (TTP)

Time to disease progression, analyzed using the Investigator's Response Assessment, was statistically significantly longer in the Abraxane group than in the solvent-based paclitaxel group (21.9 vs. 16.1 weeks, P = 0.030). This result was confirmed by the analysis of TTP using the Reconciled Response Assessment Dataset (16.6 vs. 15.4 weeks, p = 0.016).

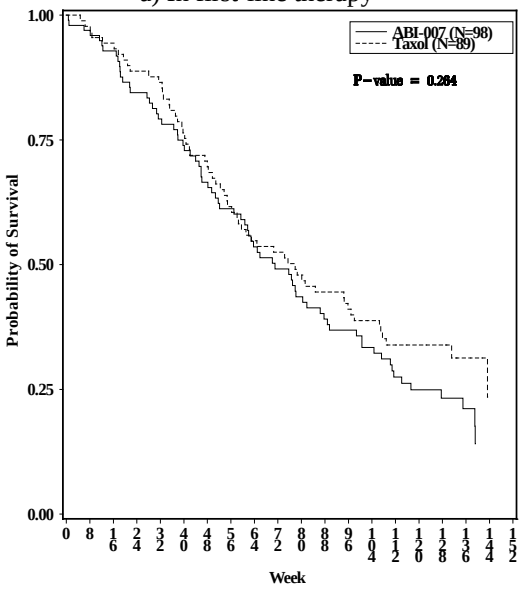
Time to disease progression was analyzed by line of therapy using the Investigator Response Assessment. TTP was higher for the Abraxane group, both for patients receiving 1st-line therapy (28.4 vs. 21.1 weeks, P = 0.056) and for patients receiving > 1st line therapy (19.4 vs. 16.1 weeks, P = 0.199).

SURVIVAL

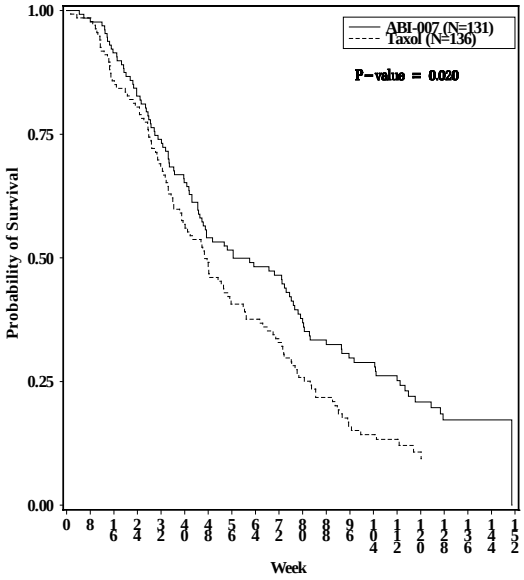
Median time to death was not statistically different for the Abraxane and solvent-based paclitaxel groups (65.0 vs. 55.3 weeks; HR = 0.899; p = 0.322), nor for first line patients, but it appeared significant for patients receiving second or greater line therapy (56.4 vs. 46.7 weeks, HR = 0.726, CI 95% 45.1, 76.9 vs. 39.0, 55.3, p= 0.020). For patients who received study drug as first line treatment there was a trend toward shorter survival in the Abraxane arm compared to the solvent-based paclitaxel arm (71.0 vs. 77.9 weeks, HR=1.215, p=0.264). At the time of this analysis overall at least 80% of patients had died or were lost to follow-up. See figure 26a and 26b:

Figure 26: Survival in Patients Receiving Second or Greater Line Therapy (ITT population)

a) In first-line therapy



b) In second or greater line therapy

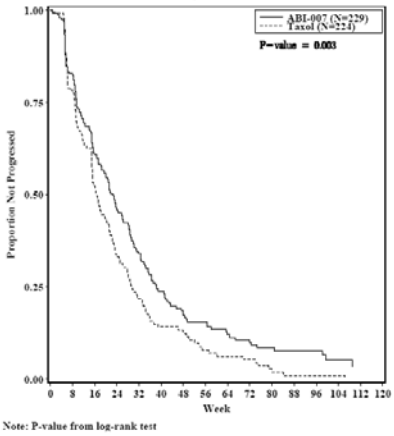


PROGRESSION FREE SURVIVAL (PFS)

Median Progression-Free Survival (PFS) was significantly longer with Abraxane than with solvent-based paclitaxel for all patients (22.7 vs. 16.6 weeks; HR = 0.734; P = 0.003, log-rank) (See Figure 27).

PFS appeared longer for patients who received first-line therapy (23.7 vs. 19.7 weeks; HR = 0.788; P = 0.173), although this difference was not statistically significant. PFS also was significantly longer with Abraxane than with solvent-based paclitaxel for patients who received study drug as second- or greater-line therapy (20.6 vs. 16.1 weeks; HR = 0.714; P = 0.010).

Figure 27. Progression-Free Survival (ITT Population)



QUALITY OF LIFE ASSESSMENT

Using the EORTC QLQ-C30 questionnaire, version 3, virtually no statistically significant differences between the treatment groups were noted in baseline values and mean change from baseline to each visit for scale scores. For patients with confirmed target lesion response, no statistically significant differences between the treatment groups were noted, with a noted exception of “Pain Symptom” at baseline (Abraxane: 3.8 [1.73] vs. solvent-based paclitaxel: 2.7 [0.98], P = 0.004). Absolute values for the total score and the scale “Global Health Status/QOL” did not show notable trends or statistically significant differences between the treatment groups.

Ancillary analyses

- Analysis performed across trials (pooled analyses and meta-analysis)

N/A

- Clinical studies in special populations

No data are available to evaluate safety in patients with renal, hepatic impairment, paediatric patients and pregnant women.

- Supportive studies

CA002-0LD

Of the forty-three patients enrolled, 31 (72%) completed ≥ 6 cycles. Most of the patients discontinued due to disease progression (67%) and lost to follow up (25%). Confirmed target lesion response rates (TLRRs) were 39.5% (95% CI 24.9%, 54.2%) for all 43 patients (5% CRs, 35% PRs, 28% SD and 26% PD), 42.9% for the 21 anthracycline-naïve patients, 36.4 % for the 22 patients previously treated with anthracyclines and 44.8% for the 29 first-line patients. Response was noted both for patients with visceral dominant site lesions (45.2%) and for patients with nonvisceral dominant site lesions (25.0%).

CA002-0

Of the sixty-three patients enrolled, 37 (59%) completed ≥ 6 cycles. Most of the patients discontinued due to disease progression (69%) and other Grade 3 or 4 toxicity (19%, neuropathy). Confirmed TLRRs were 47.6% (95% CI: 35.3%, 60.0%) for all 63 patients (3% CRs, 44% PRs, 17% SD and 30% PD), 57.7% for the 26 anthracycline-naïve patients, 40.5% for the 37 patients previously treated with anthracyclines and 64.1% for the 39 first-line patients. Response was noted both for patients with visceral dominant site lesions (39.5%) and for patients with nonvisceral dominant site lesions (68.4%).

- Discussion on clinical efficacy

Overall, the results suggest that Abraxane as >1st-line therapy has a statistically significantly better anti-tumour effect in patients with MBC than solvent-based paclitaxel.

In patients who received Abraxane as first-line therapy, a difference was observed in the primary endpoint of response rate but not in terms of secondary endpoints such as TTP and PFS, and shorter survival was observed in the Abraxane arm compared to the solvent-based paclitaxel arm (71.0 vs. 77.9 weeks, HR = 1.215, p = 0.264). The efficacy of Abraxane as 1st-line treatment of patients with MBC has not been demonstrated and this application was withdrawn after the D120 List of Questions.

There are no clinical data available regarding the activity of Abraxane as adjuvant treatment of patients with breast cancer. This indication was withdrawn after the D120 List of Questions.

Clinical safety

The total number of patients exposed to Abraxane at any dose and any dose regime in any study sponsored by the applicant was 1,223. All patients were treated intravenously. About half of the exposed patients had MBC and 30 had early stage breast cancer. Most of the remaining patients exposed to Abraxane had other solid tumours, particularly non-small-cell lung cancer and melanoma, except for 106 patients with ischaemic heart disease who were treated with Abraxane following placement of a coronary stent.

A total of 445 breast cancer patients treated with Abraxane were included in a primary integrated safety database. This database comprised of patients with MBC who were treated with Abraxane at doses ranging from 135 to 375 mg/m2 of 30 minutes infusion every 3 weeks. In the integrated safety database encompassed, besides CA012-0, studies DM97-123, CA008-0, CA CA018, CA101 as well as CA002-0LD and CA002-0.

- Patient exposure

Dosing and duration of the treatment in cycles is summarised for the different studies in Table 28.

Table 28: Cumulative dose, average dose intensity, and cycles administered in phase I (CA008-0), phase II and III studies of every-3-weeks regimen

	Phase II: CA018	**Phase II: CA002-0LD**	**Phase III: CA012-0 (controlled study)**		**Phase II: CA002-0**	**Phase I : CA008**	
	Abraxane 260 mg/m^2 (n = 43)	**Abraxane 175 mg/m^2 (n = 43)**	**solvent-based paclitaxel 175 mg/m^2 (n = 225)**	**Abraxane 260 mg/m^2 (n = 229)**	**Abraxane 300 mg/m^2 (n = 63)**	**solvent-based paclitaxel 175 mg/m^2 (n = 13)**	**Abraxane 260 mg/m^2 (n = 14)**
Cumulative Dose During Study (mg/m^2)							
Mean	1514	1021.5	909.0	1459.3	1431.9	892.1	1615.7
S.D.	671.83	319.35	494.88	787.85	709.72	586.01	613.4
Median	1560	1050.0	875.0	1560.0	1725.0	700	1690
min, max	260, 2340	175, 1750	175, 3150	260, 4680	300, 3000	175, 2275	520, 23.40
Average Dose Intensity (mg/m^2/week)							
Mean	85.16	57.58	57.02	85.13	93.50	55.31	85.52
S.D.	3.048	1.765	3.008	3.118	10.732	5.33	2.22
Median	86.67	58.33	58.07	86.43	99.24	58.03	86.67
min, max	76.2, 88.1	49.9, 59.5	31.7, 70.2	69.8, 92.0	53.3, 102.6	40.8, 59.8	79.1, 86.7
Cumulative Dose During Study (mg)							
Mean	2709.6	1610.0	1578.8	2567.6	2293.4	1589.3	2943.3
S.D.	1169.38	568.74	887.20	1420.64	1182.66	1156.06	1154.02
Median	2808.0	1625.2	1644.0	2540.0	2471.0	1160	3098.5
min, max	424,4680	307, 2925	10, 5760	390, 8424	463, 5078	284, 4410	920, 4428
Cycles administered							
Mean per patient	5.9	5.8	5.2	5.6	5.1	5.2	6.2
S.D.	2.58	1.82	2.85	3.04	2.62	3.31	2.36
Median	6	6.0	5.0	6.0	6.0	4.0	6.5
Min, Max	1,9	1, 10	1, 18	1, 18	1, 13	1, 13	2, 9

In this primary integrated safety database 301 (66.2 %) received the recommended dose for the target indication (260 mg/m2); 84 patients (18.9 %) were assigned higher doses (maximum: 375 mg/m2); and 60 patients (13.5 %) were assigned lower doses (minimum: 135 mg/m2).

- Adverse events

The most commonly reported AEs from this study are summarised in Table 29:

Table 29: Incidence of Treatment-Emergent Adverse Events by NCI CTC Term in the Phase III study, CA012-0, occurring in ≥ 10% of patients in either group of the Treated Population

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

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

CV = cardiovascular

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

AEs frequently reported in CA012-0 but with different frequencies in group Abraxane vs. solvent-based paclitaxel are shown in Table 30.

Table 30: Common adverse events with notably different incidences between treatment groups (Study CA012-0)

Adverse event (NCI CTC term)	**Number (%) patients**		**p-value** Fisher's exact
	Abraxane (N = 229)	**solvent-based paclitaxel (N = 225)**	
Neurology: Neuropathy-sensory	163 (71)	125 (56)	0.001
Treatment-related only	163 (71)	124 (55)	–
Treatment-related Grade 3	24 (10)	5 (2)	–
Treatment-related Grade 4	0	0	–
Blood/Bone Marrow: Neutrophils	78 (34)	110 (49)	0.002
Treatment-related only	77 (34)	110 (49)	–
Treatment-related Grade 3	45 (20)	56 (25)	–
Treatment-related Grade 4	24 (10)	48 (21)	–
Gastrointestinal: Nausea	69 (30)	48 (21)	0.041
Treatment-related only	67 (29)	46 (20)	–
Treatment-related Grade 3	6 (3)	1 (< 1)	–
Treatment-related Grade 4	0	0	–
Gastrointestinal: Diarrhoea	60 (26)	33 (15)	0.002
Treatment-related only	57 (25)	29 (13)	–
Treatment-related Grade 3	1 (< 1)	2 (< 1)	–
Treatment-related Grade 4	0	0	–
Gastrointestinal: Vomiting	42 (18)	22 (10)	0.010
Treatment-related only	37 (16)	19 (8)	–
Treatment-related Grade 3	4 (2)	2 (< 1)	–
Treatment-related Grade 4	1 (< 1)	0	–
Dermatology/Skin: Flushing	6 (3)	32 (14)	< 0.001
Treatment-related only	6 (3)	30 (13)	–
Treatment-related Grade 3	0	0	–
Treatment-related Grade 4	0	0	–

The incidence of peripheral neuropathy was greater with Abraxane than solvent-based paclitaxel in Study CA012-0. No grade 4 sensory neuropathy was reported. Of the 24 patients that developed a grade 3 sensory neuropathy due to Abraxane, the median time to improvement (to grade 1 or 2) was 22 days vs. 79 days for the 5 grade 3 patients on solvent-based paclitaxel (p = 0.028 log-rank test). Analysis of the effect of the cumulative paclitaxel dose on the severity of peripheral neuropathy in Study CA012-0 showed the expected relationship between cumulative dose and severity.

- Serious adverse event/deaths/other significant events

The toxicity/AE most frequently reported as a serious adverse event (SAE) was neutropenia (see Table 31); all SAEs of neutropenia were considered to be treatment-related. Otherwise, no other SAE showed a notable difference in incidence between the treatment groups.

Table 31: Most commonly reported (≥2 % in either group) serious adverse events in the pivotal study

NCI CTC Term	**ABI -007 (N=229)**		**solvent-based paclitaxel (N=225)**		**p-value[1]**
Patients with atleast one Toxicity	63	(28%)	78	(35%)	0.105
Blood/Bone Marrow: Neutrophils	24	(10%)	48	(21%)	0.002*
Cancer Related	8	(3%)	9	(4%)	0.810
Hepatic: GGT	9	(4%)	6	(3%)	0.601
Infection/Febrile Neutropenia: Infection with unknown ANC	4	(2%)	6	(3%)	0.541
Infection/Febrile Neutropenia: Febrile Neutropenia	4	(2%)	3	(1%)	>0.999
Musculoskeletal: Other-fracture	5	(2%)	1	(<1%)	0.216

[1] P-values are from Fisher's exact test. [Module 2; Summary]

In the pivotal study, 6 patients in the Abraxane group and 8 in the solvent-based paclitaxel group died while on study (see Table 32). In all cases, death was caused by progression of the patients' breast cancer, although for some patients, the more immediate cause was listed (eg, multiorgan failure, brain metastases, brain edema). One death (due to multi-organ failure) in the solvent-based paclitaxel group was considered possibly related to study drug; all of the other deaths were considered not related to study drug.

Table 32: Summary of deaths on study by NCI CTC term (safety population)

	Number (%) of Patients		
	ABI-007 (N = 229)	**Taxol (N = 225)**	**Total (N = 454)**
All Deaths on Study	6 (3%)	8 (4%)	14 (3%)
NCI CTC Term			
Cancer Related	3 (1%)	5 (2%)	8 (2%)
Hepatic: Liver dysfunction/failure	2 (<1%)	0	2 (<1%)
Not classified	1 (<1%)	1 (<1%)	2 (<1%)
CV (General): Cardiac-ischemia/infarction	0	1 (<1%)	1 (<1%)
Neurology: Other	0	1 (<1%)	1 (<1%)

- Laboratory findings

In the Phase III study, mean counts of lymphocytes, monocytes, eosinophils, and basophils, and mean values for mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC), showed no notable differences between the treatment groups. The only laboratory value that was notably different between the 2 arms was serum glucose, which was greater in the solvent-based paclitaxel arm. This finding was associated with a higher incidence of hyperglycaemia as an adverse event in the solvent-based paclitaxel arm (3 patients [1%] vs. 15 patients [7%], p = 0.003). In the phase I and II studies, there were no notable changes in these parameters. In the phase I and II studies, no notable trends were observed for changes from baseline in clinical chemistry parameters.

A summary of hematological toxicities observed for Abraxane is provided in Table 33:

Table 33: Important haematology parameters per NCI CTC toxicity grade – Phase I (CA008), II and III studies.

Parameter	Study: Treatment [b]	NCI CTC Toxicity Grade 1	2	3	4
ANC	Phase II: CA002-0: Abraxane, 300 mg/m^2, (n = 62)	14 (23%)	10 (16%)	17 (27%)	15 (24%)
	Phase III: (CA012-0): Abraxane, 260 mg/m^2, (n = 226)	**48 (21%)**	**56 (25%)**	**57 (25%)**	**20 (9%)**
	Taxol, 175 mg/m^2, (n = 222)	**22 (10%)**	**43 (19%)**	**70 (32%)**	**48 (22%)**
	Phase II: CA002-0LD : Abraxane, 175 mg/m^2, (n = 42)	5 (12%)	10 (24%)	4 (10%)	2 (5%)
	Phase II: CA018: Abraxane, 260 mg/m^2, (n = 43)	9 (21)	8 (19)	4 (9)	0
	Phase I: CA008: Abraxane, 260 mg/m^2, (n = 14)	2 (14%)	3 (21%)	4 (29%)	3 (21%)
	Taxol, 175 mg/m^2, (n = 13)	1 (8%)	2 (15%)	4 (31%)	5 (38%)
WBC	Phase II: CA002-0: Abraxane, 300 mg/m^2, (n = 63)	16 (25%)	26 (41%)	12 (19%)	3 (5%)
	Phase III: (CA012-0): Abraxane, 260 mg/m^2, (n = 226)	**66 (29%)**	**81 (36%)**	**15 (7%)**	**0**
	Taxol, 175 mg/m^2, (n = 222)	**51 (23%)**	**100 (45%)**	**23 (10%)**	**2 (<1%)**
	Phase II: (CA002-0LD): Abraxane, 175 mg/m^2, (n = 43)	10 (23%)	9 (21%)	4 (9%)	0
	Phase II: (CA018): Abraxane 260 mg/m^2, (n = 43)	7 (16)	3 (7)	0	0
	Phase I: (CA008): Abraxane, 260 mg/m^2, (n = 14)	4 (29%)	8 (57%)	1 (7%)	0
	Taxol, 175 mg/m^2, (n = 13)	3 (23%)	7 (54%)	2 (15%)	0
Platelets	Phase II: (CA002-0): Abraxane, 300 mg/m^2, (n = 63)	4 (6%)	0	3 (5%)	0
	Phase III: (CA012-0): Abraxane, 260 mg/m^2, (n = 226)	**25 (11%)**	**1 (<1%)**	**1 (<1%)**	**0**
	Taxol, 175 mg/m^2, (n = 222)	**29 (13%)**	**2 (<1%)**	**2 (<1%)**	0
	Phase II: (CA002-0LD): Abraxane, 175 mg/m^2, (n = 43)	2 (5%)	0	2 (5%)	0
	Phase II: (CA018): Abraxane 260 mg/m^2, (n = 43)	6 (14)	6 (14)	0	0
	Phase I: (CA008): Abraxane, 260 mg/m^2, (n = 14)	3 (21%)	0	0	0
	Taxol, 175 mg/m^2, (n = 13)	3 (23%)	0	0	0
Haemoglobin	Phase II:(CA002-0): Abraxane, 300 mg/m^2, (n = 63)	30 (48%)	24 (38%)	3 (5%)	1 (2%)
	Phase III (CA012-0): Abraxane, 260 mg/m^2, (n = 226)	**76 (34%)**	**26 (12%)**	**2 (<1%)**	**1 (<1%)**
	Taxol, 175 mg/m^2, (n = 222)	**75 (34%)**	**20 (9%)**	**0**	**1 (<1%)**
	Phase II: (CA002-0LD): Abraxane, 175 mg/m^2, (n = 43)	21 (49%)	17 (40%)	3 (7%)	0
	Phase II: (CA018): Abraxane 260 mg/m^2, (n = 43)	24 (56)	8 (19)	0	0
	Phase I: (CA008): Abraxane, 260 mg/m^2, (n = 14)	7 (50%)	4 (29%)	0	0
	Taxol, 175 mg/m^2, (n = 13)	5 (38%)	4 (31%)	0	0

a)Comparison between treatment arms of CA012-0. P-values from the Cochran-Mantel-Haenszel test. * P-values < 0.05.
b)Based on available laboratory data.
ANC – Grade 1: ≥ 1.5 to <2.0 x 10^9/L; Grade 2: ≥ 1.0 to <1.5 x 10^9/L; Grade 3: ≥ 0.5 to <1.0 x 10^9/L; and Grade 4: < 0.5 x 10^9/L
WBC – Grade 1: < LLN to 3.0 x 10^9/L; Grade 2: ≥ 2.0 to <3.0 x 10^9/L; Grade 3: ≥ 1.0 to < 2.0 x 10^9/L; Grade 4: <1.0 x 10^9/L
Haemoglobin – Grade 1: < LLN to 10.0 g/dL; Grade 2: 8.0 to < 10.0 g/dL; Grade 3: 6.5 to < 8.0 g/dL; Grade 4: < 6.5 g/dL
Platelets – Grade 1: < LLN to 75.0 x 10^9/L; Grade 2: ≥ 50.0 to < 75.0 x 10^9/L; Grade 3: ≥ 10.0 to < 50.0 x 10^9/L; Grade 4 < 10.0 x 10^9/L

- Safety in special populations

In the pivotal study, toxicities/AEs were compared for patients who had normal liver function tests (bilirubin, AST, ALT) at baseline (Abraxane: 129; solvent-based paclitaxel: 113) with patients who had at least 1 parameter outside the normal range (Abraxane: 95; solvent-based paclitaxel: 108). Similar analyses were done for renal function; however, only 26 patients (Abraxane: 14; solvent-based paclitaxel: 12) had serum creatinine that was not in the normal range at baseline. There were no notable differences for either analysis.

- Safety related to drug-drug interactions and other interactions

Possible interactions of Abraxane with concomitantly administered medications have not been investigated.

- Discontinuation due to adverse events

The proportion of patients on Abraxane that discontinued prematurely from study CA012-0 due to treatment-related adverse events was greater than with solvent-based paclitaxel (7% vs. 4%, respectively, not statistically significant). Sensory neuropathy mostly accounted for this difference. In 13 cases with sensory neuropathy related to Abraxane requiring dose reduction, 10 eventually became grade 3 events and three became grade 2 events.

- Post marketing experience

Cranial nerve palsies, vocal cord paresis, and rare reports of severe hypersensitivity reactions have been reported during post-marketing surveillance of Abraxane. In some patients previously exposed to capecitabine, reports of palmar-plantar erythrodysaesthesiae have been reported as part of the continuing surveillance of Abraxane. Because these events have been reported voluntarily during clinical practice, true estimates of frequency cannot be made and a causal relationship to the events has not been established.

- Discussion on clinical safety

In the randomized Phase III clinical study CA012-0 the degree of neutropenia (all or only Grade 4) was greater with solvent-based paclitaxel than with Abraxane, even though the dose of paclitaxel was 50% higher for Abraxane. The reduced myelosuppression for Abraxane is also consistent with the more rapid clearance of paclitaxel from the plasma for this formulation compared to solvent-based paclitaxel (Study CA008 and ((Sparreboom, Huizing et al. 1995)). The relationship between the PK variables of Abraxane and ANC Nadir values was evaluated using a regression model in which log-transformed ANC Nadir values were used to account for the non-linear (e.g. sigmoid) relationship between absolute neutrophil count (ANC Nadir) and PK variable. There is a significant relationship between absolute ANC Nadir value and the PK parameters of AUCinf and the Duration of Time that paclitaxel concentration remain at or above threshold concentrations of either 84 ng/ml or 42 ng/ml (p-values are <0.001, 0.031, and 0.017, respectively).

There is also a significant relationship between Percentage Decrease in ANC Nadir from Baseline and the PK parameters of AUCinf and the Duration of Time that paclitaxel concentration remains at or above a threshold concentration of 42 ng/ml (p-values are 0.004 and 0.030, respectively). For solvent-based paclitaxel, on the contrary, AUCs would not correlate with ANC nadirs, because it has a delayed tissue distribution due to retention in cremophor micelles and results in higher AUC values. However, since the effects of Cremophor on solvent-based paclitaxel PK are primarily in the ‘early’ distribution phase, as demonstrated by the similar terminal phases for Abraxane and solvent-based paclitaxel, the ‘late measure’ of time above a drug level threshold applies for both drugs.

In the literature, neutropenia has also been correlated with the duration of paclitaxel exposure in the blood (i.e. time above a threshold drug concentration) (Kearns, Gianni et al. 1995). The bone marrow progenitor cells express the MDR1 gene product (pgp). While Cremophor does not penetrate the tissues well enough to inhibit pgp expression in tumour cells, bone marrow exposure to Cremophor in combination with paclitaxel could enhance the marrow toxic effects of paclitaxel by increasing the haemotopoietic intracellular paclitaxel concentrations due to inhibition of the efflux (pgp) pump ((Woodcock, Jefferson et al. 1990; Sparreboom, Verweij et al. 1998).

A dose related increase in frequency of Grade 3 peripheral neuropathy for Abraxanecompared to solvent-based paclitaxel was also observed study CA012-0. The PD relationship of dose to frequency and grade of peripheral neuropathy was evaluated in Phase III clinical Study CA012-0 and demonstrated that the cumulative paclitaxel dose predicted peripheral neuropathy as graded by the physician for both Abraxane and solvent-based paclitaxel. The curves for Abraxane and solvent-based paclitaxel were essentially identical except for the fact that patients receiving Abraxane had a higher cumulative paclitaxel exposure. These data are also consistent with the equal tissue distributions that were demonstrated in the animal models. In addition the Abraxane related neuropathy resolves more quickly than with solvent-based paclitaxel. Cremophor and ethanol, which are contained in solvent-

based paclitaxel but not in Abraxane, have been demonstrated in a rat model to produce axonal degeneration that can be histologically demonstrated in the absence of paclitaxel (Authier, Gillet et al. 2001). In this model, a single injection of Cremophor induced a delayed peripheral neuropathy that persisted longer than that caused by repeated injections of paclitaxel only.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan.

Table Summary of the risk management plan

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Myelosuppression	Routine Pharmacovigilance	SPC section 4.4 contains the following with reference to myelosuppression: Hepatic Impairment: Patients with hepatic impairment may be at increased risk of toxicity, particularly from myelosuppression, and such patients should be closely monitored for development of profound myelosuppression.
Neurotoxicity	Routine Pharmacovigilance Follow-up of patients in future clinical studies until resolution to baseline of symptoms of peripheral neuropathy Studies CA024, CA030, and CA045 to provide initial longer-term follow-up of patients developing who developed peripheral neuropathy during treatment	The SPC for Abraxane, Section 5.1 includes the statement below to advise that the relationship between cumulative dose of paclitaxel and cumulative neurotoxicity beyond 6 cycles has not been studies. '229 patients treated with Abraxane in the randomized, controlled clinical trial were evaluated for safety. Neurotoxictiy to paclitaxel was evaluated through improvement by one grade for patients experiencing grade 3 peripheral neuropathy at any time during therapy. The natural course of peripheral neuropathy due to cumulative toxicity of Abraxane through to resolution to baseline after > 6 courses of treatment was not evaluated and remains unknown.' The frequency of peripheral neuropathy is provided in Section 4.8 of the package insert. Final study reports for CA0241, CA0302, and CA0453 will be completed in QIII 2008, QI 2008, and QIV 2008, respectively.

1 A randomized phase II study of weekly or every 3 weeks ABRAXANE versus every 3 weeks Taxotere as first line therapy of stage IV (metastatic) breast cancer

2 An open-label, pilot study of dose dense adiramycin plus cyclophosphamide (AC) followed by ABRAXANE as adjuvant therapy for patients with breast cancer

3 An open-label, randomized, comparative pilot study of dose-dense adriamycin plus cytoxan (AC) followed by either AbraxaneAbraxane or Taxol with Bevacizumab as adjuvant therapy for patients with breast cancer

Gastrointestinal events	Routine Pharmacovigilance Reports will be closely monitored in ongoing clinical trials and in post-marketing surveillance, and will be the subject of special review in future PSURs. The role in the gastrointestinal events played by the presence or absence of pre-treatment will be discussed.	The frequency of gastrointestinal events is labelled in Section 4.8 of the SPC.
Myalgia and arthralgia	Routine Pharmacovigilance. Reports will be closely monitored in ongoing clinical trials and in post-marketing surveillance, and will be the subject of special review in future PSURs.	The frequency of mylagia and arthralgia is labelled in Section 4.8 of the SPC.
Hypersensitivity Reactions	Routine Pharmacovigilance Reports will be closely monitored in ongoing clinical trials and in post-marketing surveillance, and will be the subject of special review in future PSURs.	The frequency of hypersensitivity is labelled in section 4.8 of the SPC
Cranial Nerve Palsies	Routine Pharmacovigilance. Reports will be closely monitored in ongoing clinical trials and in post-marketing surveillance, and will be the subject of special review in future PSURs.	The frequency of cranial nerve palsies is labelled in section 4.8 of the SPC..
Patients with hepatic impairment	Routine Pharmacovigilance. Establish the clinical safety and pharmacokinetics in patients with hepatic impairment. Establish dose reductions appropriate for patients with mild to moderate hepatic impairment. Clinical study report for study CA037 will be completed in QII 2008.	The SPC for Abraxane, Section 4.2 includes the following statement: 'Insufficient data are currently available to recommend dose modifications in patients with mild to moderate hepatic impairment (see sections 4.4. and 5.2). Patients with severe hepatic impairment should not be treated with paclitaxel.'
Infusion site reactions	Routine Pharmacovigilance Ongoing assessment of events of infusion site reactions is an appropriate form of assessment. Reports will be closely monitored in ongoing clinical trials and in post-marketing surveillance, and will be discussed independently in future PSURs.	The frequency of injection site reactions is labelled in section 4.8 of the SPC.
Cardiotoxicity	Routine Pharmacovigilance	Section 4.4 of the SPC contains the following statement regarding cardiotoxicity 'While cardiotoxicity unequivocally related to Abraxane has not been demonstrated, cardiac events are not uncommon in the indicated population, especially in patients who have previously received anthracyclines or have

		underlying cardiac or pulmonary disease. Thus patients receiving Abraxane should be vigilantly monitored by physicians for the occurrence of cardiac events.'
Off-label use	Routine Pharmacovigilance	In Section 4.1 of the SPC a reference to section 4.4 is included
Concomitant therapy and interactions requiring dose adjustments	Routine Pharmacovigilance Conduct a safety and pharmacokinetics study to evaluate the potential for drug interactions between Abraxane and anthracyclines The clinical study will be completed by March 2010	Section 4.5 of the SPC includes the following information regarding drug interactions: 'No interaction studies have been performed.' Sufficient information is available on the interactions with the solvent-based formulation of paclitaxel however to include the following precautionary statements in section 4.5. 'The metabolism of paclitaxel is catalysed, in part, by cytochrome P450 isoenzymes CYP2C8 and CYP3A4 (see section 5.2). Therefore, caution should be exercised when administering paclitaxel concomitantly with medicines known to inhibit (e.g. erythromycin, fluoxetine, imidazole antifungals) or induce (e.g. rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine) either CYP2C8 or CYP3A4. Abraxane is indicated for mono-therapy. Abraxane should not be used in combination with other anticancer agents.

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of the product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. There are no unresolved quality issues, which have a negative impact on the Benefit Risk balance of the product.

Non-clinical pharmacology and toxicology

Paclitaxel is an antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilises microtubules by preventing depolymerisation. This stability results in the inhibition of the normal dynamic reorganisation of the microtubule network that is essential for vital interphase and mitotic cellular functions. In addition, paclitaxel induces abnormal arrays or "bundles" of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

Abraxane contains human serum albumin-paclitaxel nanoparticles. Albumin is known to mediate endothelial transcytosis of plasma constituents and *in vitro* studies demonstrated that the presence of albumin enhances transport of paclitaxel across endothelial cells. It is hypothesised that this enhanced transendothelial transport is mediated by the gp-60 albumin receptor, and that there is accumulation of paclitaxel in the area of tumour due to the albumin-binding protein SPARC (secreted protein acidic rich in cysteine).

The carcinogenic potential of paclitaxel has not been studied. However, based on the published literature, paclitaxel is a potentially carcinogenic and genotoxic agent at clinical doses, based upon its pharmacodynamic mechanism of action. Paclitaxel has been shown to be clastogenic *in vitro* (chromosome aberrations in human lymphocytes) and *in vivo* (micronucleus test in mice). Paclitaxel has been shown to be genotoxic *in vivo* (micronucleus test in mice), but it did not induce mutagenicity in the Ames test or the Chinese hamster ovary/hypoxanthine-guanine phosphoribosyl transferase (CHO/HGPRT) gene mutation assay.

Paclitaxel at doses below the human therapeutic dose was associated with low fertility and foetal toxicity in rats. Animal studies showed non-reversible, toxic effects on the male reproductive organs at clinically relevant exposure levels.

Efficacy

Data from 454 patients treated in a randomised Phase III comparative study and from 106 patients accrued in two single-arm open-label studies are available to support the use of Abraxane in metastatic breast cancer.

The pivotal trial was conducted in patients with metastatic breast cancer, who were treated every 3 weeks with single-agent paclitaxel, either as solvent-based paclitaxel 175 mg/m^2 given as a 3-hour infusion with premedication to prevent hypersensitivity (N = 225), or as Abraxane 260 mg/m^2 given as a 30 minute infusion without premedication (N = 229). 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 only, 40% in the metastatic setting only, 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.

Results from the pivotal trial showed that the overall response rate was 33.2% in the Abraxane treated group versus 18.7% in the solvent-based paclitaxel group. The use of Abraxane resulted in a statistically significant prolongation of TTP and PFS in all patients and in patients receiving the study drug as >1st-line therapy. However, in patients receiving 1st-line therapy TTP and PFS were not statistically significantly different from the solvent-based paclitaxel group. There was a prolongation of survival of approximately 10 weeks in all patients and in patients who received study drug as > 1st-line therapy in favour of the Abraxane arm. In contrast, for patients who received the study drug as 1st-line therapy there was a trend toward shorter survival in the Abraxane arm compared to the solvent-based paclitaxel arm.

In the single-arm open-label studies Abraxane was administered to metastatic breast cancer patients as a 30-minute infusion at a dose of 175 mg/m2 to in the first study (43 patients) and at a dose of 300 mg/m2 as a 30 minute infusion in the second study (63 patients). Patients were treated without steroid premedication or planned G-CSF support. Cycles were administered at 3 week intervals. The response rates were 39.5% and 47.6% for the two studies, respectively. The median time to disease progression was 5.3 months for the 175 mg/m2 dose study and 6.1 months in the 300 mg/m2 dose study.

Studies in the adjuvant setting for the treatment of patients with node-positive breast carcinoma have not been submitted.

Safety

The most common adverse events related to 229 patients with metastatic breast cancer who were treated with 260 mg/m^2 Abraxane once every three weeks in the pivotal phase III clinical study were qualitatively not different from the known AEs related to currently registered paclitaxel formulations. Neutropenia was the most notable important haematological toxicity (reported in 79% of patients), and was rapidly reversible and dose dependent; leukopenia was reported in 71% of patients. Grade 4 neutropenia (< 0.5 x 10^9/l) occurred in 9% of patients treated with Abraxane. Febrile neutropenia

occurred in four patients on Abraxane. Anaemia (Hb < 10 g/dl) was observed in 46% of patients on Abraxane, and was severe (Hb < 8 g/dl) in three cases. Lymphopenia was observed in 45% of the patients. In general, the frequency and severity of neurotoxicity was dose-dependent in patients receiving Abraxane. Peripheral neuropathy (mostly Grade 1 or 2 sensory neuropathy) was observed in 68% of patients on Abraxane with 10% being Grade 3, and no cases of Grade 4. Nausea occurred in 29% of the patients and diarrhoea in 25% of the patients. Alopecia was observed in 90% of the patients treated with Abraxane. Arthralgia occurred in 32% of patients on Abraxane and was severe in 6% of cases. Myalgia occurred in 24% of patients on Abraxane and was severe in 7% of cases. The symptoms were usually transient, typically occurred three days after Abraxane administration and resolved within a week. General disorders and administration site disorders as asthenia and fatigue were reported in 40% of the patients.

No studies on safety of Abraxane in the adjuvant treatment of breast cancer have been submitted.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

- User consultation

The applicant performed a readability testing ("user consultation") and a satisfactory report has been provided.

Risk-benefit assessment

The benefit/risk profile of Abraxane in the treatment of metastatic carcinoma of the breast in patients who have failed, or are not candidates for standard, anthracycline containing therapy is considered positive. Abraxane does not require pre-medication and a higher tumour response rate was observed in a randomised Phase III study in comparison to solvent-based paclitaxel. In addition, secondary endpoints such TTP, PFS and OS appeared to be prolonged in patients receiving second- or further-line therapy with Abraxane compared with patients treated with solvent-based paclitaxel. The safety profile was similar between ABI007 and solvent-based paclitaxel except for a higher incidence of sensory neuropathy associated with ABI007.

In patients receiving 1st-line therapy there was a trend toward shorter survival in the Abraxane arm compared to the solvent-based paclitaxel arm. The 1st-line therapy indication has been withdrawn by the applicant.

Studies in the adjuvant setting for the treatment of patients with breast carcinoma have not been submitted and the adjuvant indication has been withdrawn by the applicant.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns.
- no additional risk minimisation activities were required beyond those included in the product information.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Abraxane monotherapy for the treatment of metastatic breast cancer in patients who have failed first-line treatment for metastatic disease and for whom standard, anthracycline containing therapy is not indicated, was favourable and therefore recommended the granting of the marketing authorisation.

REFERENCES

Authier, N., J. P. Gillet, et al. (2001). "Assessment of neurotoxicity following repeated cremophor/ethanol injections in rats." Neurotox Res **3**(3): 301-6.

Bernard-Marty, C., F. Cardoso, et al. (2004). "Facts and controversies in systemic treatment of metastatic breast cancer." Oncologist **9**(6): 617-32.

Brouwer, E., J. Verweij, et al. (2000). "Measurement of fraction unbound paclitaxel in human plasma." Drug Metab Dispos **28**(10): 1141-5.

Bun, S. S., J. Ciccolini, et al. (2003). "Drug interactions of paclitaxel metabolism in human liver microsomes." J Chemother **15**(3): 266-74.

Cresteil, T., B. Monsarrat, et al. (1994). "Taxol metabolism by human liver microsomes: identification of cytochrome P450 isozymes involved in its biotransformation." Cancer Res **54**(2): 386-92.

Cunha, K. S., M. L. Reguly, et al. (2001). "Taxanes: the genetic toxicity of paclitaxel and docetaxel in somatic cells of Drosophila melanogaster." Mutagenesis **16**(1): 79-84.

Digue, L., T. Orsiere, et al. (1999). "Evaluation of the genotoxic activity of paclitaxel by the in vitro micronucleus test in combination with fluorescent in situ hybridization of a DNA centromeric probe and the alkaline single cell gel electrophoresis technique (comet assay) in human T-lymphocytes." Environ Mol Mutagen **34**(4): 269-78.

Gelderblom, H., J. Verweij, et al. (2001). "Cremophor EL: the drawbacks and advantages of vehicle selection for drug formulation." Eur J Cancer **37**(13): 1590-8.

GLOBOCAN (2002). "International Agency for Research on Cancer." (http.//www-dep.earc.fr).

Goldhirsch A, C. M., Ed. (2004). Textbook of Medical Oncology Breast Cancer. London, Taylor & Francis.

Gralow, J. R. (2005). "Optimizing the treatment of metastatic breast cancer." Breast Cancer Res Treat **89 Suppl 1**: S9-S15.

Harris, J. W., A. Katki, et al. (1994). "Isolation, structural determination, and biological activity of 6 alpha-hydroxytaxol, the principal human metabolite of taxol." J Med Chem **37**(5): 706-9.

Harris, J. W., A. Rahman, et al. (1994). "Metabolism of taxol by human hepatic microsomes and liver slices: participation of cytochrome P450 3A4 and an unknown P450 enzyme." Cancer Res **54**(15): 4026-35.

Jamis-Dow, C. A., R. W. Klecker, et al. (1995). "Metabolism of taxol by human and rat liver in vitro: a screen for drug interactions and interspecies differences." Cancer Chemother Pharmacol **36**(2): 107-14.

Kearns, C. M., L. Gianni, et al. (1995). "Paclitaxel pharmacokinetics and pharmacodynamics." Semin Oncol **22**(3 Suppl 6): 16-23.

Kumar, G. N., U. K. Walle, et al. (1993). "Binding of taxol to human plasma, albumin and alpha 1-acid glycoprotein." Res Commun Chem Pathol Pharmacol **80**(3): 337-44.

Ma, H. Z., Wang Z.Q., Liao, M.Y. (1996). "Genetic Toxicity of Taxol." Chinese J. Pharmacol. Toxicol. **10**(3): 173-177.

McPherson, K., C. M. Steel, et al. (2000). "ABC of breast diseases. Breast cancer-epidemiology, risk factors, and genetics." BMJ **321**(7261): 624-8.

Monsarrat, B., P. Alvinerie, et al. (1993). "Hepatic metabolism and biliary excretion of Taxol in rats and humans." J Natl Cancer Inst Monogr(15): 39-46.

Nallani, S. C., B. Goodwin, et al. (2004). "Differences in the induction of cytochrome P450 3A4 by taxane anticancer drugs, docetaxel and paclitaxel, assessed employing primary human hepatocytes." Cancer Chemother Pharmacol **54**(3): 219-29.

Panday, V. R., M. T. Huizing, et al. (1997). "Hepatic metabolism of paclitaxel and its impact in patients with altered hepatic function." Semin Oncol **24**(4 Suppl 11): S11-34-S11-38.

Rahman, A., K. R. Korzekwa, et al. (1994). "Selective biotransformation of taxol to 6 alpha-hydroxytaxol by human cytochrome P450 2C8." Cancer Res **54**(21): 5543-6.

Schiff, P. B., J. Fant, et al. (1979). "Promotion of microtubule assembly in vitro by taxol." Nature **277**(5698): 665-7.

Schiff, P. B. and S. B. Horwitz (1980). "Taxol stabilizes microtubules in mouse fibroblast cells." Proc Natl Acad Sci U S A **77**(3): 1561-5.

Sparreboom, A., M. T. Huizing, et al. (1995). "Isolation, purification, and biological activity of mono- and dihydroxylated paclitaxel metabolites from human feces." Cancer Chemother Pharmacol **36**(4): 299-304.

Sparreboom, A., J. Verweij, et al. (1998). "Disposition of Cremophor EL in humans limits the potential for modulation of the multidrug resistance phenotype in vivo." Clin Cancer Res **4**(8): 1937-42.

Tinwell, H. and J. Ashby (1994). "Genetic toxicity and potential carcinogenicity of taxol." Carcinogenesis **15**(8): 1499-501.

van Tellingen, O., M. T. Huizing, et al. (1999). "Cremophor EL causes (pseudo-) non-linear pharmacokinetics of paclitaxel in patients." Br J Cancer **81**(2): 330-5.

Wang, T. H., H. S. Wang, et al. (2000). "Paclitaxel-induced cell death: where the cell cycle and apoptosis come together." Cancer **88**(11): 2619-28.

Woodcock, D. M., S. Jefferson, et al. (1990). "Reversal of the multidrug resistance phenotype with cremophor EL, a common vehicle for water-insoluble vitamins and drugs." Cancer Res **50**(14): 4199-203.