Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for nanoparticle albumin-bound (nab) Paclitaxel

Proprietary Product Name: Albraxane

Sponsor: Abraxis BioScience Australia Pty Ltd

Date of CER: August 2012

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

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About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Contents

List of abbreviations

Abbreviation	Meaning
ACR	American College of Radiology
AE	Adverse event
ALK	Anaplastic large-cell lymphoma kinase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ANOVA	Analysis of variance
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
AUC	Area under the curve
AUC_{inf}	Area under the curve extrapolated to infinite time
β-hCG	β-subunit of human chorionic gonadotropin
BSA	Body surface area
CBC	Complete blood count
CER	Clinical evaluation report
CI	Confidence interval
CL	Clearance
C_{max}	Maximum plasma concentration of drug
CMH	Cochran-Mantel-Haenszel
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events

Abbreviation	Meaning
DLT	Dose-limiting toxicity
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EML4	Echinoderm microtubule-associated protein-like 4
EORTC	European Organisation for Research and Treatment of Cancer
EOS	End-of-study
EPAR	European Public Assessment Report
EU	European Union
FACT	Functional Assessment of Cancer Therapy
FDA	Food and Drug Administration
G-CSF	Granulocyte colony-stimulating factor
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
Hgb	Haemoglobin
HR	Hazard ratio
HRA/T	Hazard ratio of ABI-007/carboplatin to Taxol/carboplatin
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent-to-treat
IV	Intravenous
IVR	Interactive voice response

Abbreviation	Meaning
KM	Kaplan-Meier
K-ras	Kirsten rat sarcoma
LD	Longest diameter
LLN	Lower limit of normal
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NA	Not applicable
NCI	National Cancer Institute
ND	Not done
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OS	Overall survival
pA	ABI-007/carboplatin response rate
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetics
PR	Partial response
pT	Taxol/carboplatin response rate
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical analysis plan

Abbreviation	Meaning
SD	Standard deviation
SEM	Standard error of the mean
SLD	Sum of the longest diameter
SMQ	Standardized MedDRA query
SPARC	Secreted protein, acidic and rich in cysteine
t1/2	Half-life
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
Vz	Volume of distribution
WBC	White blood cell (count)
WHO	Drug World Health Organization Drug

1. Introduction

This is an application to extend the indications of Abraxane to include the treatment of advanced non-small cell lung cancer (NSCLC). Abraxane is currently indicated for the treatment of metastatic carcinoma of the breast after failure of anthracycline therapy. The application was submitted by Specialised Therapeutics Australia Pty Ltd, on behalf of Abraxis BioScience Australia Pty Ltd (an indirect subsidiary of Celgene Corporation).The proposed extension of indication is:

> *Abraxane, in combination with carboplatin, is indicated for the first-line treatment of non-small cell lung cancer in patients who are not candidates for potentially curative surgery and/or radiation.*

Paclitaxel is obtained from a natural product (*Taxus media*) with antitumour activity. The drug is antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerisation. This action results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions.

2. Clinical rationale

The sponsor's clinical rationale for the submission is based on the need for new therapeutic options for the treatment of NSCLC. The sponsor considers that Abraxane addresses this unmet need because, in combination with carboplatin, the drug provides evidence of increased effectiveness in the treatment of NSCLC compared with Taxol in combination with carboplatin, and significantly reduces taxane related severe peripheral neuropathy and solvent-based paclitaxel drug related hypersensitivity reactions.

Comment: It is accepted that there is an unmet need for new treatment options for NSCLC. In 2007, lung cancer was the fourth most commonly diagnosed cancer in Australia in both males and females, excluding basal and squamous cell carcinoma of the skin (AIHW & Cancer Australia 2011). In that year, a total of 5,948 lung cancers were diagnosed in males and 3,755 in females. The occurrence of lung cancer was strongly related to age, with 84% of new lung cancers in males and 80% in females diagnosed in patients aged 60 years and over. In 2007, 4,715 males and 2,911 females died from lung cancer in Australia making it the leading cause of death in both sexes (21% of all cancer deaths in males, and 17% of all cancer deaths in females). In Australia, between 1982 and 2007 the age-standardized mortality rate from lung cancer for males decreased by 41%, while the mortality rate for females increased by 56%. The prognosis for patients with lung cancer remains poor, and improved little over the 26 years from 1982 to 2007. The 5-year relative survival in 2000-2007 was 11% for males and 15% for males, which compares with 8% for males and 10% for females in 1982-1987.

Clinically, primary lung cancer is divided into small-cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), and NSCLC accounts for about 80% of all lung cancers (Boyer MJ, 2003). There are three main subtypes of NSCLC, squamous cell carcinoma (25%), adenocarcinoma (40%) and large cell carcinoma (10%) with the remainder consisting of other subtypes with low frequencies (NCI, 2012). In patients with NSCLC, the possibility of cure depends mainly on their suitability for surgical resection (Carney D and Hansen H, 2000). However, at the time of diagnosis only about 30% of patients with NSCLC are candidates for surgery, while the remaining 70% have inoperable disease (30% with locally advanced inoperable

disease and 40% with inoperable confirmed metastatic disease) (Carney D and Hansen H, 2000). Chemotherapy is the mainstay of treatment for patients with advanced NSCLC (TNM stage IIIB and stage IV) (Goldstraw P *et al*., 2011). The median duration of survival and 5-year survival rates are poor both in patients with NSCLC TNM stage III B (10 months and 7%, respectively), and TNM stage IV (6 months and 2%, respectively) (Goldstraw P *et al*., 2007).

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The submission contained the following clinical information:

- 4 clinical pharmacology studies, including 4 that provided pharmacokinetic data and 1 that provided pharmacodynamic data.
- 1 population pharmacokinetic analysis.
- 1 pivotal efficacy/safety study in patients with NSCLC.
- 3 supportive efficacy/safety studies in patients with NSCLC.
- 4 clinical studies relating to indications other than NSCLC.
- Documentation of Statistical Methods and Interim Analysis Plans for Safety and Efficacy, Statistical Tables and Figures (Safety and Efficacy).
- Post-marketing experience.
- Literature references.

3.2. Paediatric data

The submission did not include paediatric data. The sponsor indicated that there is currently no paediatric development program in place for Abraxane. The sponsor considered that "because non-small cell lung cancer is an adult-related condition that may qualify Abraxane for a disease specific waiver, [it] believes ..[an]..application in the paediatric population is not feasible, and therefore additional evidence of impossibility or impracticality is not necessary". The sponsor has applied to the FDA (USA) for "Waiver of Paediatric Assessment".

Comment: The sponsor's decision not to include paediatric data is acceptable.

3.3. Good clinical practice

The submitted studies were conducted in accordance with the ethical principles of Good Clinical Practice.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

The submission included four completed pharmacokinetic (PK) studies (see Table 1, below). The four studies have been evaluated and are reviewed in Section 4.2 of this clinical evaluation report (CER). In the PK studies, Abraxane is referred to as ABI-007 and this identification code has been maintained in the description of the studies in this CER. The submission also included

comparisons and analyses of the pharmacokinetics of ABI-007 across studies and the results have been reviewed below in Section 4.3.

Two of the PK studies (BIO-VT-5 and 08DA33) were substudies of the pivotal Phase III clinical efficacy and safety study (CA031). Study 08DA33 was of interest as it provided PK interaction data for ABI-007 and carboplatin in Japanese patients. Study BIO-VT-5 was planned as a population-pk analysis in a subgroup of patients from the pivotal efficacy and study but due to the small sample size (n=15) this analysis was not undertaken. Instead, study BIO-VT-5 provided individual and mean ABI-007 plasma PK parameters calculated using standard non-compartmental methods in White patients. However, these non-compartmental PK data were of limited value due to sparse sampling time points following administration of ABI-007. Studies 05DA11 and 05DA13 were single ascending dose PK studies in Japanese patients with advanced solid tumours providing both blood and plasma paclitaxel PK data and formally assessing dose linearity. In addition, both studies 05DA11 and 05DA13 attempted to define a maximum tolerated dose (MTD) for ABI-007 over the dose range studied.

Table 1: Four completed PK studies.

Report No. (Study Code)	Description of PK Analysis	ABI-007 Dose	Study Population (Race)	No. of Patients (M/F)	Sponsor
BIO-VT-5 (CA031 sub-study)	Single-dose sparse PK, in combination with carboplatin	100 mg/m^2 Cycle 1 Day 1	NSCLC (White[a])	15 (10/5)	Abraxis BioScience, LLC, a wholly owned subsidiary of Celgene Corporation
08DA33 (J-0103) (CA031 sub-study)	Single and multiple-dose PK Drug-drug interaction between ABI-007 and carboplatin	100 mg/m^2 Cycle 1 Days 1, 8, 15	NSCLC (Japanese)	12 (9/3)	Taiho Pharmaceutical Co., Ltd.[b]
05DA11 (J-0101)	Single ascending dose PK	80-125 mg/m^2 Cycle 1 Day 1	Advanced solid tumor (Japanese)	15 (6/9)	Taiho Pharmaceutical Co., Ltd.[b]
05DA13 (J-0100)	Single ascending dose PK	200-300 mg/m^2 Cycle 1 Day 1	Advanced solid tumor (Japanese)	12 (10/2)	Taiho Pharmaceutical Co., Ltd.[b]

F = female; M = male; No. = number; NSCLC = non-small cell lung cancer; PK = pharmacokinetics.

a. Of the 15 patients, the race categories included 14 White (Non-Hispanic) patients and 1 Black patient and were referred to collectively as White patients for ease of discussion.
b. Taiho Pharmaceutical Co., Ltd. is the Marketing Authorization Holder and Distributor of ABI-007 in Japan.

4.2. Summary of the submitted pharmacokinetic studies (Module 5)

4.2.1. PK interaction substudy, Japanese patients, NSCLC (08DA33)

4.2.1.1. Objectives and methods

Study 08DA33 was a multi-centre, open-label, single-sequence PK interaction substudy of the pivotal Phase III study (CA031) in Japanese patients with NSCLC. The objective of this substudy was to investigate the pharmacokinetics of paclitaxel following administration of ABI-007 in the presence and absence of carboplatin. In addition, the pharmacokinetics of plasma total and free platinum was assessed following administration of carboplatin to patients pre-treated with ABI-007. The study was conducted in Japan between 12 December 2008 and 18 January 2010, and the study report was dated 13 July 2011. The sponsor was Taiho Pharmaceuticals Co Ltd, the local Japanese sponsor of the pivotal Phase III study (CA031).

In study CA013, ABI-007 was administered once weekly on Days 1, 8 and 15 of a 21-day cycle by IV infusion over 30 minutes at a dose of 100 mg/m^2, and carboplatin was administered after ABI-007 on Day 1 of each 21-day cycle by IV infusion over 60 minutes at a dose of AUC = 6

mg.min/mL. Plasma paclitaxel plasma concentration was assessed from blood sampled serially for 72 hours after the start of the ABI-007 infusion on Day 1 (first administration) and Day 15 (third administration) of Cycle 1. On both Day 1 and Day 15, blood samples were taken before dosing with ABI-007 and then after dosing at 0.5, 1, 1.5, 2, 4, 6, 8, 24, 48 and 72 hours. Plasma platinum concentration was assessed from blood samples taken only on Day 1 of Cycle 1 at 0.5, 1, 1.5, 3.5, 5.5, 7.5 and 23.5 hours after administration of carboplatin. The standard range of PK parameters was calculated using non-compartmental methods and appropriate PK computer software.

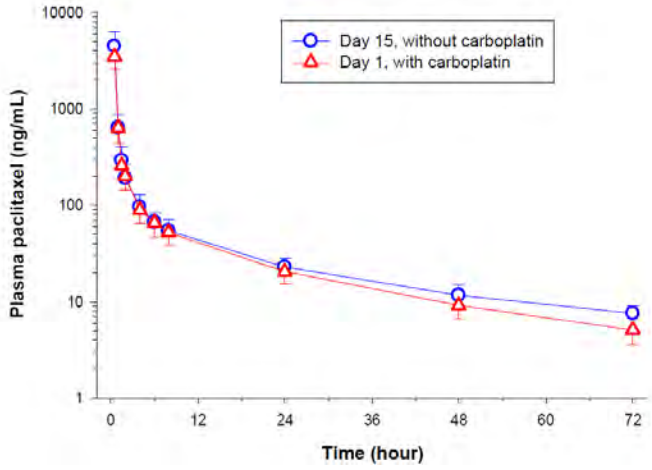
Paclitaxel plasma concentration was quantified using validated liquid chromatography tandem mass spectrometry (LC/MS/MS) with a lower limit of quantification (LLOQ) of 1 ng/mL, and a quantification range of 1 to 500ng/mL. Platinum concentration in plasma and protein-free ultrafiltered plasma was quantified using inductively coupled plasma mass spectrometry (ICP-MS) with a LLOQ of 1ng/mL, and a quantification range 1 to 5000ng/mL.

4.2.1.2. Results

The 12 subjects were Japanese patients (9 males, 3 females) with NSCLC. The basic demographic characteristics of the subjects were: mean age 63 years (range: 37, 72); mean height 159.6 cm (range: 146.7, 168.4); mean body weight 58.9 kg (range: 49.2, 71.7); mean BSA 1.61 m^2 (range: 1.41, 1.83); and mean CrCL 90 mL/min (range: 71, 136).

The mean (SD) plasma concentration – time profiles of paclitaxel following ABI-007 administered with carboplatin (Cycle 1, Day 1) and without carboplatin (Cycle 1, Day 15) were comparable and are summarized below in Figure 1.

Figure 1: Study 08DA33 – Paclitaxel plasma concentration - time curves with and without carboplatin; semi-log scale.



Paclitaxel plasma PK parameters were similar in Cycle 1 on Day 1 (with carboplatin) and on Day 15 (without carboplatin), and are summarized below in Table 2, below).

Table 2: Study 08DA33 – Paclitaxel PK parameters with carboplatin on Day 1 (n=12) and without carboplatin on Day 15 (n=9 to 10).

Pharmacokinetic parameter	Unit	1st administration (Day 1)					3rd administration (Day 15)				
		Mean	SD	CV	Range		Mean	SD	CV	Range	
t_{max}	hr	0.5	0.0	0.0	0.5	0.5	0.5	0.0	0.0	0.5	0.5
C_{max}	ng/mL	3460	905	26.2	2330	4740	4443	1827	41.1	1110	8020
λz	1/hr	0.0290	0.0035	12.0	0.0237	0.0337	0.0237	0.0026	11.1	0.0201	0.0288
$t_{1/2}$	hr	24.2	3.02	12.5	20.6	29.3	29.5	3.18	10.8	24.1	34.6
AUC_{0-t}	ng·hr/mL	3893	897	23.0	2414	5117	4565	1346	29.5	2915	6913
AUC_{inf}	ng·hr/mL	4073	929	22.8	2534	5332	5060	1325	26.2	3306	7278
CL	L/hr/m^2	25.9	6.61	25.5	18.8	39.5	21.0	5.51	26.2	13.7	30.2
Vdss	L/m^2	324	108	33.3	179	501	330	173	52.4	160	750
Vz	L/m^2	913	292	32.0	608	1457	897	269	30.0	627	1320

SD: Standard deviation; CV: Coefficient of variation (%)

Exposure to paclitaxel following ABI-007 with carboplatin was 15% (AUC_{inf}) to 16% (C_{max}) lower than following ABI-007 alone (see Table 3, below).

Table 3: Study 08DA33 – Paclitaxel PK parameters Day 1 and Day 15 comparison.

Pharmacokinetic parameter	Unit	n	Day 1 (+CBDCA)	Day 15 (Control)	Day 1/Day 15 (Mean)	90% confidence interval		p-value
C_{max}	(ng/mL)	10	3366	4009	0.84	0.64	1.10	0.2616
AUC_{0-t}	(ng·hr/mL)	10	3866	4388	0.88	0.79	0.98	0.0649
AUC_{inf}	(ng·hr/mL)	9	4195	4907	0.85	0.76	0.95	0.0310

After logarithmic conversion of each pharmacokinetic parameter, a paired t-test was conducted. Each pharmacokinetic parameter is shown as the geometric mean. The p-value is shown for the null hypothesis in which the population mean is the same for the 1st administration (concomitant use of CBDCA) and the 3rd administration (ABI-007 alone)

The plasma and ultrafiltered plasma platinum concentrations after administration of carboplatin on Day 1, Cycle 1, are summarized below in Table 4. The AUC_{inf} calculated from the platinum concentration in ultrafiltered plasma had a mean of 3.89 ± 0.3 mg.min/mL, and the AUC_{inf} in terms of carboplatin was 7.41 ± 0.68 mg.min/mL. The AUC_{inf} for carboplatin was approximately 24% higher than the target of 6 mg.min/mL.

Table 4: Study 08DA33 – PK parameters of platinum (plasma and ultrafiltered plasma) after administration of carboplatin.

Pharmacokinetic parameter	Unit	Pt in plasma					Pt in ultrafiltered plasma				
		Mean	SD	CV	Range		Mean	SD	CV	Range	
t_{max}	hr	0.98	0.08	8.0	0.73	1	1.02	0.06	5.7	1	1.20
C_{max}	ng/mL	21707	3030	14.0	17350	27640	23903	3901	16.3	18470	32160
λz	1/hr	0.0586	0.0065	11.1	0.0445	0.0729	0.175	0.009	5.3	0.164	0.193
$t_{1/2}$	hr	12.0	1.42	11.8	9.51	15.6	3.97	0.21	5.2	3.60	4.23
AUC_{0-t}	mg·min/mL	4.70	0.50	10.6	4.04	5.62	3.86	0.35	9.1	3.26	4.47
AUC_{inf}	mg·min/mL	5.61	0.65	11.5	4.81	6.74	3.89	0.36	9.2	3.28	4.53
CL	mL/min	62.7	9.77	15.6	47.1	80.5	93.4	16.2	17.4	66.7	123.4
Vdss	L	42.0	6.55	15.6	33.6	54.8	15.4	1.95	12.6	12.8	18.7
Vz	L	64.8	11.6	17.9	46.0	83.1	32.0	5.3	16.7	24.2	44.1

SD: Standard deviation; CV: Coefficient of variation (%)

Comment: The paclitaxel plasma concentration – time curves were similar following ABI-007 administered with carboplatin on Day 1 (Cycle 1) and without carboplatin on Day 15 (Cycle 1). The time interval of about 14 days between treatments should have been more than adequate to ensure elimination of carboplatin following

administration on Day 1 as the later phase half-life of platinum following carboplatin is around 24 hours (see carboplatin PI). Exposure to paclitaxel following ABI-007 with and without carboplatin was not bioequivalent as assessed by the C_{max}, AUC_{0-t} and AUC_{inf} as the 90% CIs for the relative mean ratios were not enclosed completely within the standard bioequivalence interval of 0.8 to 1.25. Exposure to paclitaxel was 15% (AUC_{inf}) to 16% (C_{max}) lower when ABI-007 was administered with carboplatin compared with when ABI-007 was administered alone. However, carboplatin could not have influenced the C_{max} of paclitaxel on Day 1 as this parameter was assessed from blood samples taken prior to initiation of the carboplatin infusion. The higher paclitaxel plasma C_{max} on Day 15 compared with Day 1 might have been due, at least in part, to accumulation of paclitaxel prior to the Day 15 dose as paclitaxel was detectable in the plasma in approximately 50% of patients before administration of the third dose on Day 15.

The observed mean AUC_{inf} for free carboplatin in the plasma was 7.41 min.mg/mL, which was approximately 24% higher than the targeted mean value of 6 min.mg/mL. The sponsor notes that the mean half-life and clearance values for total carboplatin in plasma and free carboplatin in ultrafiltered plasma following co-administration of ABI-007 and carboplatin were consistent with those for carboplatin alone reported in the literature (Obasaju et al, 1996), leading the sponsor conclude that there were no pharmacokinetic drug-drug interactions between ABI-007 and carboplatin. Perusal of the data from Obasaju et al, 1996 from patients with malignant tumours (n=11) shows that the total mean±SD clearance of carboplatin was 64.6±27.9 mL/min in the absence of Taxol and 64.6±27.9 mL/min in the presence of Taxol, and the corresponding values for the clearance of free carboplatin was 107±34.5 mL/min and 112.8±36.3 mL/min. In Obasaju *et al*, 1996, the AUC_{24h} for free carboplatin in the absence of Taxol was 3.4 mg.min/mL and 3.22 mg.min/mL in the presence of Taxol, and both values were consistent with the projected target AUC of 3.75 mg.min/mL. The results from Obasaju *et al*., 1996 have been summarized.

The sponsor speculates that the difference in free carboplatin clearance observed between the two studies was probably due to the difference in the methodology used to estimate the carboplatin dose. In both Obasaju et al., 1996 and study 08DA33 carboplatin dose was based on the Calvert formula (i.e., dose [mg] = [Target AUC] x GFR + 25), with the GFR being derived from the Cockcroft and Gault formula (1976) in Obasaju et al, 1996 and the creatinine clearance being substituted for the GFR in study 08DA33. While it is possible that the reason for the difference in the results between the two studies might relate to methodological differences used to calculate the dose, it is considered that the observed results from study ODA33 do not exclude the possibility that there is a true PK drug-drug interaction between AB1-007 and carboplatin in Japanese patients. The racial background of the 11 patients included in Obasaju et al., 1996 were not provided in the study report.

4.2.2. Phase I, single-dose study, Japanese patients, solid tumours (05DA11)

Study 05DA11 was a Phase I, single-centre, open-label, parallel-group, dose-escalation study investigating the pharmacokinetics of ABI-007 administered once weekly in Japanese patients (n=15) with solid tumours. The study was undertaken in Japan from 14 July 2006 to 31 August 2007, and was translated from Japanese to English on 31 May 2011. The study was undertaken according to relevant Japanese regulatory Guidelines.

There were four planned ABI-007 ascending dose levels of 80 mg/m^2 (n=3), 100 mg/m^2 (n=6), 125 mg/m^2 (n=6) and 150 mg/m^2 (no patients) administered IV over 30 minutes once weekly. The 125 mg/m^2 dose was judged to be the maximum tolerated dose (MTD), and no patients

were exposed to the highest dose of 150 mg/m2. The pharmacokinetics of paclitaxel was determined after the first ABI-007 dose (Day 1). Blood sampling was undertaken before administration, and then after administration at 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 10, 24, 48 and 72 hours. ABI-007 was measured in both blood and plasma using validated LC-MS/MS (LLOQ = 5 ng/mL [blood] and 1 ng/mL [plasma]).

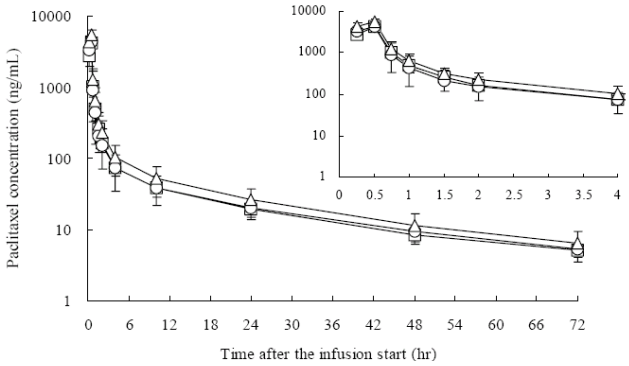
All patients in the study were Japanese and the basic demographic characteristics of patients in the three dosage groups were similar. The standard range of PK parameters was calculated using non-compartmental methods and appropriate PK computer software. In addition, linearity of ABI-007 was assessed using linear regression analysis of C_{max}, AUC_{0-t} and AUC_{inf} versus doses administered. In addition, the relationship of C_{max}, AUC_{0-t} and AUC_{inf} with the doses was analyzed using a power model, and this was used as the reference for the linear regression assessment.

The pharmacokinetics of paclitaxel (plasma) at ABI-007 doses of 80, 100, and 125 mg/m2 are summarized below in Table 5, and the mean plasma paclitaxel concentration (log) – time profiles for each of the three dose of ABI-007 are shown below in Figure 2. Linearity assessments from the regression analyses were summarized.

Table 5: Study 05DA11 – PK parameters calculated from plasma paclitaxel concentrations.

Pharmacokinetic parameter	Unit	80mg/m² (n=3)			100mg/m² (n=6)			125mg/m² (n=6)		
		Mean	SD	Range	Mean	SD	Range	Mean	SD	Range
t_{max}	hr	0.50	0.00	0.5 — 0.5	0.50	0.00	0.5 — 0.5	0.50	0.00	0.5 — 0.5
C_{max}	ng/mL	4217	594	3690 — 4860	4253	518	3540 — 4840	5397	1008	4310 — 6590
λz	1/hr	0.028	0.002	0.025 — 0.030	0.028	0.006	0.017 — 0.035	0.029	0.005	0.023 — 0.037
$t_{1/2}$	hr	25.2	2.29	23.2 — 27.7	26.1	7.33	19.7 — 40.2	24.6	4.30	18.8 — 29.9
AUC_{0-t}	ng·hr/mL	3822	1277	2918 — 5283	3937	516	3272 — 4868	5246	1628	3124 — 7340
AUC_{inf}	ng·hr/mL	4006	1300	3069 — 5490	4141	538	3376 — 5048	5483	1722	3260 — 7767
CL	L/hr/m²	21.3	5.97	14.6 — 26.1	24.5	3.15	19.8 — 29.6	24.8	8.10	16.1 — 38.3
Vdss	L/m²	267	94.3	159 — 331	311	58.3	229 — 390	280	91.5	177 — 390
Vz	L/m²	781	253	488 — 929	916	248	629 — 1375	893	382	556 — 1548
C_{max} ad	ng/mL/(mg/m²)	52.7	7.45	46.1 — 60.8	42.5	5.18	35.4 — 48.4	43.2	8.1	34.5 — 52.7
AUC_{inf} ad	ng·hr/mL/(mg/m²)	50.1	16.2	38.4 — 68.6	41.4	5.38	33.8 — 50.5	43.9	13.8	26.1 — 62.1
AUC_{extrap}	%	4.8	1.0	3.8 — 5.7	4.9	1.8	3.1 — 8.1	4.3	1.6	2.0 — 6.4

Figure 2: Study 05DA11 – Plasma paclitaxel concentration (log) over time following the three doses of ABI-007.



Note: Mean plasma concentration and standard deviation after: 80 mg/m2 (n = 3) [open square]; 100 mg/m2 (n=6) [open circle]; and 125 mg/m2 (n=6) [open triangle].

Comment: This small Phase I study in Japanese subjects (n=15) with solid cancers showed that the MTD of ABI-007 was 125 mg/m2. The plasma (and blood) paclitaxel concentration – time profiles showed multi-phasic elimination of paclitaxel. Overall, the linearity assessments from the linear regression and the power models showed that C_{max} derived from both paclitaxel blood and plasma concentrations was dose

proportional over the dose range tested, while both the AUC0-t and the AUC_{inf} were not dose proportional based on paclitaxel blood and plasma concentrations. However, the C_{max} results should be interpreted cautiously due to the small number of subjects in the analyses and the very broad 95% CI for the Y intercept in the linear regression analyses. However, the mean plasma CL, Vss and t1/2 values were comparable for the three administered doses suggesting that the plasma pharmacokinetics of paclitaxel are likely to be linear over the dose range 80 to 125 mg/m^2.

4.2.3. Phase I, single-dose study, Japanese patients, solid tumours (05DA13)

Study 05DA13 was a Phase I, multi-centre, open-label, parallel-group, dose-escalation study investigating the pharmacokinetics of ABI-007 administered every three weeks in Japanese patients (n=12) with solid cancers. The study was undertaken in Japan from 14 July 2006 to 31 August 2007, and was translated from Japanese to English on 31 May 2011. The study was carried out according to relevant Japanese regulatory Guidelines.

The study investigated three ABI-007 dose levels of 200 mg/m^2 (n=3), 260 mg/m^2 (n=6) and 300 (n=3) mg/m^2 administered IV over 30 minutes every 3 weeks. The pharmacokinetics of paclitaxel was determined after the first ABI-007 dose (Day 1). Blood sampling time points were before administration, and then after administration at 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 10, 24, 48 and 72 hours. ABI-007 was measured in both blood plasma using validated LC-MS/MS (LLOQ in blood was 5 ng/mL and in plasma was 1 ng/mL). The standard range of PK parameters was calculated using non-compartmental methods and appropriate PK computer software, and linearity was assessed using the same methods summarized above for study 05DA11. All patients in the study were Japanese and the basic demographic characteristics of the three dosage groups were generally similar. However, the 200 mg/m^2 and 300 mg/m^2 dose groups both included males only (3 in each group), while the 260 mg/m^2 dose group included 4 males and 2 females.

The pharmacokinetics of paclitaxel (plasma) at ABI-007 doses of 200, 260 and 300 mg/m^2 is summarized below in Table 6. Linearity assessments from the regression analyses and from the power models were summarized.

Table 6: Study 05DA13 – PK parameters calculated from plasma paclitaxel concentrations.

Pharmacokinetic parameter	Unit	200mg/m^2 (n=3)			260mg/m^2 (n=6)			300mg/m^2 (n=3)		
		Mean	SD	Range	Mean	SD	Range	Mean	SD	Range
t_{max}	hr	0.42	0.14	0.25 – 0.50	0.50	0.00	0.50 – 0.50	0.42	0.14	0.25 – 0.50
C_{max}	ng/mL	9040	3077	6610 – 12500	12000	2111	10300 – 15200	12700	2600	11100 – 15700
λz	1/hr	0.024	0.004	0.020 – 0.027	0.034	0.006	0.025 – 0.042	0.035	0.004	0.032 – 0.039
$t_{1/2}$	hr	29.0	5.13	25.6 – 34.9	20.8	4.06	16.5 – 28.0	19.8	1.93	17.7 – 21.5
AUC_{0-t}	ng·hr/mL	8738	2502	6814 – 11566	13030	2768	9418 – 16967	15941	1695	14940 – 17898
AUC_{inf}	ng·hr/mL	9146	2708	7075 – 12211	13330	2763	9659 – 17272	16271	1822	15133 – 18372
CL	L/hr/m^2	23.1	6.08	16.4 – 28.3	20.2	4.35	15.1 – 26.9	18.6	1.97	16.3 – 19.8
Vdss	L/m^2	240	41.1	194 – 273	172	51.5	117 – 239	144	14.5	129 – 158
Vz	L/m^2	935	109	825 – 1043	620	229	358 – 958	527	37.0	506 – 570
C_{max} ad	ng/mL/(mg/m^2)	45.2	15.4	33.1 – 62.5	46.2	8.13	39.6 – 58.5	42.3	8.64	37.0 – 52.3
AUC_{inf} ad	ng·hr/mL/(mg/m^2)	45.8	13.6	35.4 – 61.1	51.3	10.6	37.1 – 66.4	54.2	6.07	50.4 – 61.2
AUC_{extrap}	%	4.3	0.9	3.7 – 5.3	2.3	1.0	1.1 – 4.1	2.0	0.7	1.3 – 2.6

Comment: The ABI-007 once every three week 200, 260 and 300 mg/m^2 dosage regimens investigated in this small, ascending-dose PK study in Japanese patients (n=12) differed from the once weekly ABI-007 regimen of 100 mg/m^2 combined with carboplatin (AUC = 6) administered every three weeks proposed for the treatment of patients with NSCLC. The plasma (and blood) paclitaxel concentration – time profiles showed multi-phasic elimination of paclitaxel. Using the power model, linearity was shown for paclitaxel C_{max}, AUC_{0-t} and AUC_{inf} in both blood and plasma. Using linear regression analysis, linearity was shown for paclitaxel AUC_{0-t} and AUC_{inf}

in both blood and plasma, and C_{max} in blood but not in plasma. Overall, the results from this study showing dose proportionality for AUC_{0-t}, and AUC_{inf} and suggesting dose proportionality for C_{max} should be interpreted cautiously as subject numbers were small, and the 95% CI of the Y intercepts for the linear regression analyses were wide for each of the parameters tested. Furthermore, in this study there were inconsistencies in the mean plasma CL, V_{ss} and $t_{1/2}$ values for the three administered doses suggesting non-linearity of the pharmacokinetics of ABI-007 over the dose range tested, but inter-subject variability in the parameters was high.

4.2.4. Population pharmacokinetic study BIO-VT-5 (CA031 substudy)

The submission included one "Sparse Pharmacokinetic Report" (BIO-VT-5) dated 31 May 2011 based on substudy PK data from the pivotal Phase III study (CA031). In study CA031, patients treated with ABI-007/carboplatin received ABI-007 at a dose of 100 mg/m^2 IV over approximately 30 minutes without steroid premedication and without G-CSF prophylaxis (in the absence of neutropenic fever or infections associated with neutropenia). The ABI-007 dose was given weekly on Days 1, 8 and 15 of each 21-day cycle, and carboplatin was given at AUC = 6 on Day 1 of each 21-day cycle.

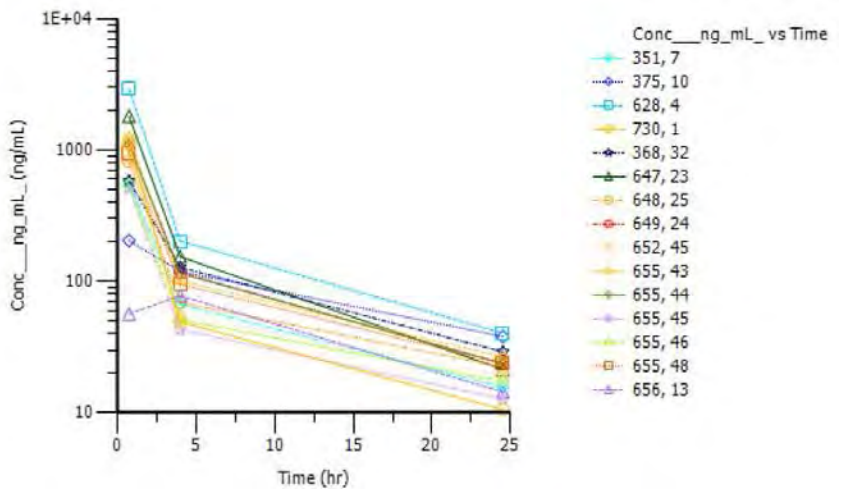
Patients from Canada, Russia, Ukraine, and United States had the option to participate in the sparse PK sampling substudy. Blood samples for PK analyses were taken during Cycle 1 at 0.25, 3.5 and 24 hours post-infusion. PK parameters of $T_{1/2}$, T_{max}, C_{max}, $C_{max/D}$, C_{last}, AUC_{last}, AUC_{inf}, $AUC_{inf/D}$, $AUC_{\%Extrap}$, V_z, CL, V_{ss} were estimated using non-compartmental methods and appropriate PK software. Paclitaxel plasma concentrations were determined using a validated liquid chromatography atmospheric pressure ionization tandem mass spectrometry (LC-API/MS/MS) method. The Lower Limit of Quantitation (LLOQ) was 1 ng/mL and the range was 1 to 500 ng/mL.

4.2.4.1. Results

Of the planned 100 patients randomized to the ABI-007/carboplatin arm, only 15 consented to participate in the optional sparse PK sampling substudy. A sample size of 15 patients was considered insufficient to support the planned population PK analysis. As a result, only individual patient PK data were presented in the report. Of the 15 patients who provided sparse PK samples, 14 were White (Non- Hispanic) and 1 was Black, and there were 10 males and 5 females. Despite the racial mix of 14 White and 1 Black patient the population was referred to by the sponsor as "White" "for ease of discussion". The mean age of the 15 patients was 54.8 years (range: 39 to 68) and the mean weight was 79.4 kg (range: 53 to 125).

The plasma concentration versus time profiles for individual patients is shown below in Figure 3. Except for two patients with exceptionally low plasma paclitaxel concentration at 0.75 hours, patients treated with ABI-007 exhibited similar concentration versus time profiles. However, sampling in the elimination phase was too sparse to adequately describe the pharmacokinetics of paclitaxel during the elimination phase of the drug.

Figure 3: Study BIO-VT-5 – plasma paclitaxel concentration vs time curve; individual patients.



The study included tabulated summary of the PK parameters for each individual patient and mean values for the parameters. However, the individual and mean values are considered to be unreliable due to sparse sampling at only three time points.

Comment: There was no population-pk analysis of the collected data as only 15 patients consented to participate in the substudy. The individual and mean PK parameters are considered to be unreliable due to sparse PK sampling (i.e., three time points Cycle 1 at 0.25, 3.5 and 24 hours post-infusion). The sponsor expressly states that the derived sparse PK parameters should not be used for comparison with PK parameters obtained from full PK studies and should only be used for comparison among patients within study CA031.

4.3. Comparison and analyses of results across studies

4.3.1. Potential for drug-drug interactions between Abraxane and carboplatin

The sponsor considers that various lines of evidence suggest that co-administration of ABI-007 and carboplatin is "not likely to result in pharmacokinetic drug-drug interactions".

Firstly, paclitaxel and carboplatin are not expected to interact with each other by competing for protein binding or competing for the same clearance pathways. The approved Abraxane PI states that *in vitro* studies of binding to human serum proteins, using paclitaxel concentrations ranging from 0.1 to 50 µg/mL, indicate that between 89% to 98% of drug is bound, although studies specifically investigating protein binding with this formulation of paclitaxel have not been conducted. The metabolism of paclitaxel is catalyzed by CYP2C8 and CYP3A4 (Taxol PI), presumably in the liver as hepatic metabolism has been demonstrated in animals. As the drug is metabolized by CYP2C8 and CYP3A4, the pharmacokinetics of the drug may be altered *in vivo* as a result of interactions with compounds that are substrates, inducers, or inhibitors of these two enzymes (approved Abraxane PI). In a Phase III study in patients with metastatic breast cancer (CA012-0), urinary excretion of unchanged paclitaxel accounted for approximately 4% of the dose following ABI-007 260 mg/m^2, while urinary excretion of the two metabolites, 6α-hydroxypaclitaxel and 3'-p-hydroxypaclitaxel, was less than 0.2% of the dose. These results indicate that Abraxane is primarily cleared by non-renal pathways. Faecal excretion was approximately 20% of the total dose administered (approved Abraxane PI). However, the disposition of paclitaxel has not been fully elucidated in humans (Taxol PI). The Baxter Carboplatin PI indicates that excretion of carboplatin is by glomerular filtration and that 65% of

the dose is eliminated in the urine within 24 hours of administration, with 32% of the dose being excreted as unchanged drug. The sponsor states that there have been no reports indicating that carboplatin is an inhibitor or inducer of any CYP enzymes. Consequently, paclitaxel and carboplatin are not expected to interact with each other via competing for protein binding or the same clearance pathways.

Secondly, no pharmacokinetic interactions between solvent–based paclitaxel (Taxol) and carboplatin have been identified in the published literature (Obasaju et al., 1996; Belani et al., 1999). In Obasaju *et al*., 1996, the pharmacokinetics of free carboplatin and total carboplatin were similar in the absence and presence of paclitaxel following carboplatin (AUC = 3.75 mg.min/mL) IV over 30 minutes administered immediately after Taxol 175 mg/m^2 IV over 3 hours. In Belani *et al*., 1999, the pharmacokinetics of paclitaxel were assessed in the presence of carboplatin and the authors concluded that the pharmacokinetics of paclitaxel "were similar in all respects to the pharmacokinetics reported [in the literature] for patients who received paclitaxel as a single agent". However, the authors comment that this "is not surprising for the end-of infusion paclitaxel concentrations, considering that carboplatin had yet to be administered…..However, carboplatin had no noticeable effect on the terminal disposition of paclitaxel". The sponsor also commented that alteration of the infusion sequence for solvent-based paclitaxel and carboplatin (i.e., C⟶P, P⟶C) did not affect either exposure to paclitaxel or degree of neutropenia in NSCLC patients (Huizing *et al*., 1997).

Thirdly, pharmacokinetic drug-drug interactions were not observed between paclitaxel and carboplatin in Japanese patients who received ABI-007/carboplatin combination therapy for the treatment of NSCLC (08DA33). The results of this study have been discussed above in Section 4.2.1 and suggest that, while carboplatin is unlikely to significantly affect the pharmacokinetics of paclitaxel, it is possible that ABI-007 might increase exposure to free plasma carboplatin in Japanese patients.

Comment: Overall, the submitted data suggest that carboplatin administered in combination with ABI-007 is unlikely to significantly affect the plasma pharmacokinetics of paclitaxel. However, study O8DA33 in Japanese patients with NSCLC showed that free plasma carboplatin exposure (AUC_{inf}) was 24% greater than the target value (i.e., 7.41 vs 6 min.mg/mL, respectively). The results from this study in Japanese patients with NSCLC for free plasma carboplatin exposure following treatment with ABI-007/carboplatin differed from the published results from Obasaju et al., 1996 in patients of unknown racial origin with malignant tumours (primarily lung) treated Taxol/carboplatin carboplatin. In Obasaju et al., 1996, exposure to free plasma carboplatin (AUC) in the absence of Taxol did not significantly differ from exposure in the presence of Taxol, and in both situations the AUC agreed with the projected target of 3.75 min.mg/mL.

4.3.2. Relationship between ABI-007 dose and plasma paclitaxel exposure

The sponsor explored dose proportionality from 80 mg/m^2 to 300 mg/m^2 in Japanese patients with NSCLC by using combined ABI-007 dose and mean plasma paclitaxel AUC_{inf} data from studies 05DA11 and 05DA13 according to the following equation:

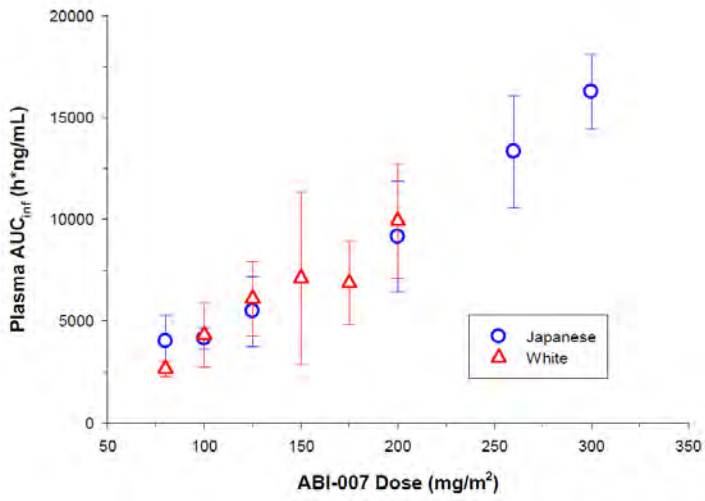
$Ln(AUC_\infty) = a + b \bullet Ln(Dose)$, where a = intercept and b = slope of the regression line.

The slope of $Ln(AUC_\infty)$ versus Ln(Dose) was close to 1 (1.11) and the 90% CI for the slope contained 1 (0.94 to 1.28). Consequently, the results indicated that an increase in ABI-007 dose resulted in an approximately proportional increase in plasma paclitaxel exposure over the dose range 80 to 300 mg/m^2 (see Figure 4, below).

The sponsor also explored dose proportionality from 80 to 200 mg/m^2 in White patients by using the ABI-007 dose and mean plasma paclitaxel AUC_∞ data from studies DMD97-123 and CA005-0. This exploration showed that plasma paclitaxel AUC_∞ was approximately proportional over the ABI-007 dose range 80 to 200 mg/m^2 (see Figure 4, below). Paclitaxel plasma data at

ABI-007 doses > 200 mg/m^2 were lacking in White patients. However, based on the similarity of the pharmacokinetics of paclitaxel in White and Japanese patients the sponsor states that it can be expected that dose proportionality in the two groups can be expected up to an ABI-007 dose of 300 mg/m^2 (as observed in Japanese patients).

Figure 4: Relationship between plasma paclitaxel exposure (AUC_{inf}) and dose of ABI-007.



Data are from Reports 05DA11, 05DA13, DM97-123, and CA005-0. The AUC at 200 mg/m2 for White patients is the mean of the data pooled from DM97-123 and CA005-0.

The Complete Study Reports (CSRs) for the two studies (DM97-123 and CA005-0) used to source the plasma paclitaxel AUC_{inf} data for the dose proportionality analysis in White patients were included in the submission and are briefly summarized below. These two studies were identified as "other study reports", rather than "reports of human pharmacokinetic (PK) studies".

4.3.2.1. Study DM97-123

Study DM97-123 was a Phase I/II study in patients with solid tumours/breast cancer treated with ABI-007 at doses ranging from 135 mg/m^2 to 375 mg/m^2 given IV every three weeks. The objectives of this study were to determine the MTD of ABI-007; evaluate the PK profile of ABI-007; and evaluate the antitumour activity of ABI-007 in patients with advanced solid tumours/breast cancer. Plasma samples for PK analyses were collected from 4 patients assigned to 135 mg/m^2 and 1 patient assigned to 200 g/m^2, and whole blood samples for PK analyses were collected from 2 patients assigned to 200 mg/m^2, 5 patients assigned to 300 mg/m^2 and 4 patients assigned to 375 mg/m^2. Samples were collected predose, at 15, 30, and 60 minutes, and at 1.5, 2, 4, 6, 8, 12, 18, 24, and 48 hours after the start of infusion. Of the 19 enrolled patients, 95% (18/19) were White and the remaining patient was Hispanic. The PK parameters collected in this study were analysed using non-compartmental methods. The paclitaxel PK results (plasma and whole blood) from this study were summarized.

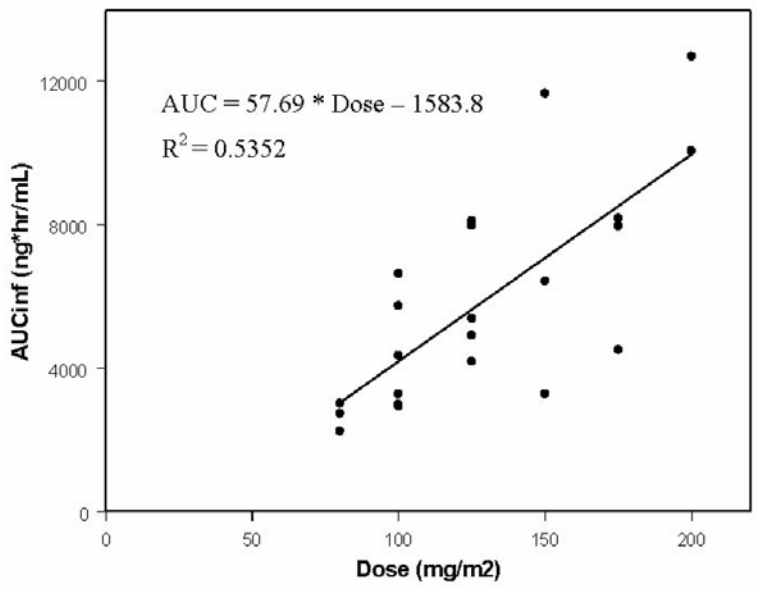
4.3.2.2. Study CA005-0

Study CA005-0 was a Phase I study in patients with advanced non-haematologic malignancies treated with ABI-007 at doses of 80 mg/m^2 to 200 mg/m^2 once weekly for three weeks followed by 1 week of rest and then repeated (i.e., treatment cycles repeated every 28 days). The primary objectives of this study were to determine the MTD of ABI-007; to determine toxicities due to ABI-007; and to determine the PK parameters for ABI-007 when given weekly and to characterize the pharmacokinetics of ABI-007 after the first study dose.

A total of 14 whole blood samples were obtained pre-dose, 15, 30 (immediately prior to the termination of the infusion), and 45 minutes; 1, 1.5, 2, 4, 6, 8, 12, 24, 36, and 48 hours after the first dose of ABI-007. Of the 39 patients enrolled, 85% (n=33) were White, 13% (n=5) were

Hispanic, and 3% (n=1) were Black. The most common tumour types were melanoma (36%) and breast (23%). Of the 39 enrolled patients, there were 23 with PK data; 80 mg/m^2 (n=3), 100 mg/m^2 (n=7), 125 mg/m^2 (n=5), 150 mg/m^2 (n=3), 175 mg /m^2 (n=3), and 200 mg/m^2 (n=2). The mean plasma paclitaxel PK parameters from this study were summarized in the CER and the relationship between exposure (AUC_{inf}) and dose following the first ABI-007 dose is summarized below in Figure 5. The results from this study indicate that paclitaxel exposure increases with ABI-007 dose over the range 80 to 200 mg/m^2 following the first dose.

Figure 5: Study CA005-0 – Linear increase of mean AUC_{inf} following first dose of ABI-007.

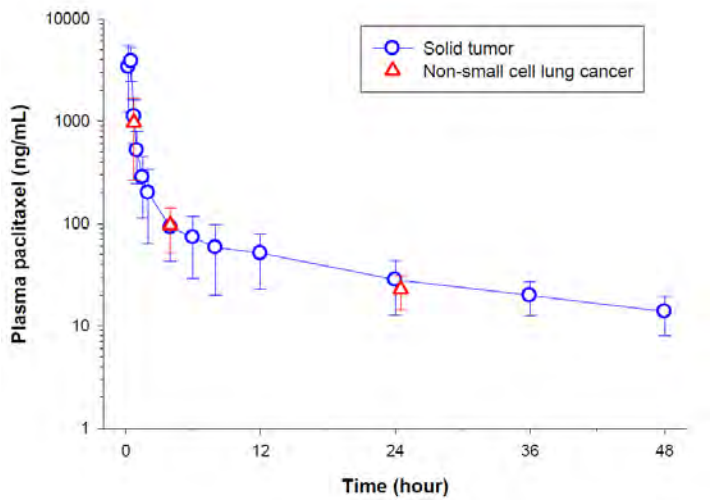


Comment: Overall, the submitted data suggest that plasma paclitaxel exposure (AUC_{inf}) increases proportionally with dose over the ABI-007 dose range 80 mg/m^2 to 300 mg/m^2 in Japanese patients with NSCLC, and over the dose range 80 mg/m^2 to 200 mg/m^2 in White patients with a variety of non-haematologic cancers.

4.3.3. Comparison of pharmacokinetics between patients with solid tumours and NSCLC

The impact of tumour type on the pharmacokinetics of paclitaxel was explored by comparing single-dose PK data in patients with NSCLC (ABI-007/carboplatin) and in patients with solid tumours (ABI-007 alone). The mean plasma concentrations of paclitaxel at 0.75, 4, and 24.5 hours after dosing from European/US NSCLC patients (n=15) treated with ABI-007/carboplatin in the pivotal efficacy and safety study CA031 (report BIO-VT-5) were compared with the mean concentration-time profile from White patients (n=7) with solid tumors (most commonly melanoma [36%] and breast [23%]) who received the same dose of ABI-007 (100 mg/m^2) without concomitant carboplatin (study CA005-0). The plasma concentration – time curves are provided below in Figure 6.

Figure 6: Mean (SD) plasma concentration of paclitaxel for White patients with NSCLC and Solid Tumors (Cycle 1, Day 1).



Data are from CSR CA005-0 (100 mg/m^2 cohort; n=7) and report BIO-VT-5. All patients were "White", except for 1 "Black" patient in report BIO-VT-5.

In addition, the single-dose PK parameters of paclitaxel observed in Japanese NSCLC patients receiving ABI-007 in combination with carboplatin were almost identical to those in the historical data observed in Japanese solid tumor patients receiving ABI-007 alone (see Table 7, below).

Comment: The provided data suggest that the pharmacokinetics of paclitaxel are similar in patients with NSCLC and solid tumours.

4.3.4. Comparison of pharmacokinetics between Japanese and White patients

The demographic characteristics and pharmacokinetics of paclitaxel in White and Japanese patients following a single-dose (100 mg/m^2) of ABI-007 are compared below in Table 7. Mean plasma exposure (C_{max} and AUC_{inf}) and CL was comparable between Japanese and White patients with solid tumors. However, the mean half-life was shorter in White patients than in Japanese patients, and the sponsor states that this difference can be explained by the different PK sampling duration in the two patient groups (48 hours and 72 hours, respectively).

Table 7: Single-dose pharmacokinetics of paclitaxel in plasma in Japanese and White patients following ABI-007 (100 mg/m²).

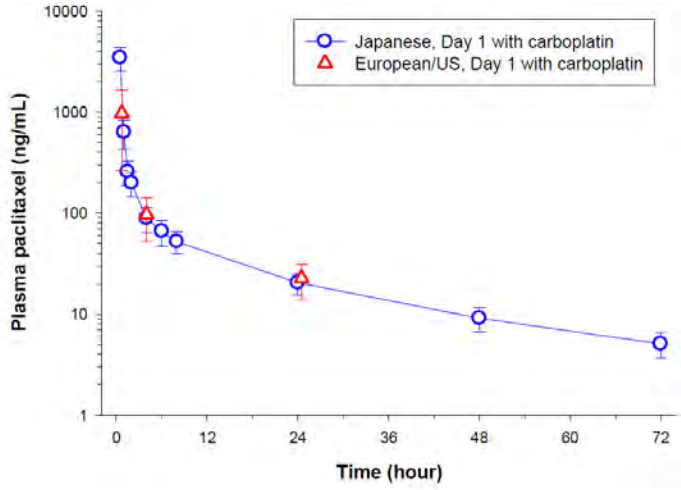
Paclitaxel PK parameter	ABI-007 100 mg/m², Cycle 1 Day 1		
	White Patients Solid Tumors ABI-007 Alone [CSR CA005-0][a]	Japanese Patients Solid Tumors ABI-007 Alone [Report 05DA11]	Japanese Patients NSCLC ABI-007 + Carboplatin [Report 08DA33]
N	6	6	12
Age (year)	57 (38-74)	59 (49-73)	63 (37-72)
Body Surface Area (m^2)	1.90 (1.60-2.14)	1.64 (1.55-1.75)	1.61 (1.41-1.83)
Weight (kg)	80.4 (58.9-101.7)	60.7 (54.7-68.0)	58.9 (49.2-71.7)
AUC_∞ (h•ng/mL)	4311 (1557)	4141 (538)	4073 (929)
C_{max} (ng/mL)	4513 (2002)	4253 (518)	3460 (905)
CL (L/h/m^2)	25.7 (8.3)	24.5 (3.15)	25.9 (6.61)
$t_{1/2}$ (h)[b]	18.2 (3.04)	26.1 (7.33)	24.2 (3.02)
V_{ss} (L/m^2)	Not done	311 (58.3)	324 (108)

a. Excludes 1 patient who had severe obstructive liver disease.
b. Estimated based on 48-hour sampling duration in CA005-0 and 72-hour sampling duration in Report 05DA11 and Report 08DA33.

Mean (SD) data are presented for PK parameters while mean (range) data are present for demographic parameters.

The mean plasma concentrations of paclitaxel from European/US NSCLC patients at 0.75, 4, and 24.5 hours after dosing from study BIO-VT-5 were compared with the mean concentration - time profile from Japanese NSCLC patients from study 08DA33 (see Figure 7, below).

Figure 7: Mean (SD) plasma concentration of paclitaxel for Japanese and European/US NSCLC patients (Cycle 1, Day 1).



Comment: Although the full plasma concentration – time profile of paclitaxel was not available from White NSCLC patients receiving ABI-007, the limited concentration data obtained from these patients (study BIO-VT-5) were comparable with the concentration – time profile from Japanese patients (study 08DA33) who received the same ABI-007 (100 mg/m²)/carboplatin (AUC = 6 min.mg/mL) combination therapy on Day 1 of Cycle 1. The data suggest that the complete concentration – time profile in European/US NSCLC patients is likely to be similar to that in Japanese NSCLC patients. The C_{max}, AUC_{inf} and CL values in White patients with solid tumours were similar to those in Japanese patients, but the half-life was shorter in White patients compared with Japanese patients most likely due to the shorter

sampling time. Overall, the totality of the submitted data suggests that the pharmacokinetics of paclitaxel is similar in White and Japanese patients.

4.4. Evaluator's overall conclusions on pharmacokinetics

The submission included a limited amount of new paclitaxel pharmacokinetic data in patients with NSCLC treated with Abraxane. The pharmacokinetic findings are summarised below.

- The data suggest that co-administration of Abraxane and carboplatin at the proposed dosages in patients with NSCLC are unlikely to significantly affect each others pharmacokinetics when given alone. However, in Japanese patients mean exposure to free carboplatin (AUC_{inf}) was approximately 24% higher than the targeted mean value when ABI-007 was co-administered with carboplatin (study 08DA33). These results were inconsistent with those from the published literature (Obasaju et al., 1996) which showed that exposure to free carboplatin (AUC_{24h}) was similar and consistent with the target value irrespective of whether carboplatin was administered with or without Taxol. The sponsor postulates that the differences between the results observed in study 08DA33 and Obasaju et al., 1996 were due to methodological differences used to calculate the carboplatin dose.
- The data from a cross-study comparison of the plasma pharmacokinetics of paclitaxel in Japanese patients with solid tumours administered ABI-007 100 mg/m^2 (study 05AD11) were comparable with those in Japanese patients with NSCLC administered ABI-007 100 mg/m^2 in combination with carboplatin AUC = 6 min.mg/mL (study 08DA33).
- The data indicate that the pharmacokinetics of paclitaxel following ABI-007 are linear in Japanese patients with NSCLC over the dose range 80 mg/m^2 to 300 mg/m^2 (combined data from studies 05DA11 and 05DA13), and in White patients with solid tumours over the dose range 80 mg/m^2 to 200 mg/m^2 (studies DM1723 and CA005-0).
- The data suggest that the pharmacokinetics of paclitaxel following ABI-007 administered alone are similar in White and Japanese patients with solid tumours (studies CA005-0 and 05DA11), and in White and Japanese patients with NSCLC treated with the same ABI-007/carboplatin regimen (studies BIO-VT-5 and 08DA33).

5. Pharmacodynamics

5.1. SPARC Biomarker Report (BIO-VT-6).

5.1.1. Objectives

The submission included one pharmacodynamic report (SPARC Biomarker Report BIO-VT-6). This secreted protein acidic and rich in cysteine (SPARC) biomarker report was a substudy of the pivotal Phase III efficacy and safety study in patients with advanced NSCLC (study CA031). The objective of the report was to assess SPARC in tumour tissue and to determine the relationship between the biomarker and efficacy outcomes. Patients in study CA031 consented separately to the use of leftover tissue biopsy samples for biomarker analysis, to the collection of blood samples, or both. The report included SPARC data from a total of 71 patients, 35 in the ABI-007/carboplatin treatment arm and 36 in the Taxol/carboplatin treatment arm.

The analyses in the report focused on: (1) the prognostic value of SPARC in the overall 71 patient subset and the two treatment arms with respect to progression-free survival (PFS), overall survival (OS), and overall response rate (ORR); and (2) the predictive value of SPARC for the treatment effect of ABI-007/carboplatin compared with Taxol/carboplatin with respect to PFS, OS, and ORR. The experimental work was started on 9 June 2009 and was completed on 6 June 2011, and the report was released on 7 October 2011.

Comment: SPARC (also known as osteonectin and BM40) is an albumin-binding protein that is overexpressed in NSCLC tumours and is associated with a poor prognosis in NSCLC patients (Koukourakis et al., 2003). In Koukourakis et al., 2003, cancer cells from NSCLC tissue were found to be unreactive in 107 of 113 cases analyzed (95%), whereas substantial production of SPARC by stromal fibroblasts was noted in 42 of 113 cases (37%). Stromal SPARC was significantly linked with tumour necrosis and survival analysis showed a significant association between stromal SPARC and poor prognosis. Due to its albumin binding ability, it has been hypothesized that SPARC expression in tumours results in increased concentration of albumin-bound drugs, such as ABI-007, and may be partly responsible for the greater activity of ABI-007 when compared with conventional formulations (Hawkins, Soon-Shiong, Desain, 2008).

5.1.2. Methods

The expression and cellular distribution of SPARC in biopsies of lung tumour was examined by immunohistochemistry (IHC) techniques in an approved central laboratory located in the USA. The method was a two antibody system with one antibody having preferential staining of tumour SPARC and one antibody having preferential staining of fibroblast SPARC. There were 7 tissue components (tumour cells, fibroblasts, inflammatory cells, acellular stroma/matrix, blood vessels, nerve tissue, and normal tissue) scored within the tumour. For data analysis, nerve tissue and normal tissue within the tumour were excluded as they were absent in the majority of samples examined. For each tissue component and each antibody, 3 measures were recorded independently by two pathologists: maximum intensity, percentage of cells at the maximum intensity, and an overall score calculated from the intensity and percent positivity, providing 30 variables from each pathologist (5 components/tumor x 3 measures/components x 2 antibodies = 30 variables/tumor).

As there is no standard method to classify patients based on SPARC expression status, two methods of analysis were used to classify patients into “high-SPARC” and “low-SPARC” groups. First, all variables were standardized across patients via z-score transformation and averaged between the two pathologists assessing the data. For each patient, an average z-score was calculated across variables. Alternatively, the sum of all the variables (adjusted to 1 and 100) was calculated with high SPARC being classified as values above the median and low SPARC being classified as values below or equal to median. For all 71 patients included in the SPARC analysis, the range of sum of all the variables was 1050 to 2152, with a median of 1720.

5.1.3. Results

5.1.3.1. SPARC subset vs total patient population

The SPARC status was evaluated in 71 patients: 35 in the ABI-007/carboplatin treatment arm and 36 in the Taxol/carboplatin treatment arm. Overall, the 71 patients in the SPARC subset had superior clinical outcomes compared with the total patient population (see Table 8, below).

Table 8: Clinical outcomes of the two treatment arms in SPARC patient subset versus the entire CA031 study and the rest of patients with no SPARC data available.

		N	Median PFS (Months)	Median OS (Months)	ORR N (%)
ABI-007/ carboplatin	SPARC subset	35	7.4	16.4	15 (43%)
	CA031 study	521	6.3	12.1	170 (33%)
	Patients excluding SPARC subset	486	6.0	11.6	155 (32%)
	P-value vs. SPARC subset	-	0.17	0.105	0.194
Taxol/ carboplatin	SPARC subset	36	9.7	17.9	18 (50%)
	CA031 study	531	5.8	11.2	132 (25%)
	Patients excluding SPARC subset	495	5.6	11.0	114 (23%)
	P-value vs. SPARC subset	-	0.001	0.027	0.001

Abbreviations: PFS = progression-free survival; ORR = overall response rate; OS = overall survival.
[1] P-value for PFS and OS was calculated with log-rank test; p-value for response was calculated with Fisher's exact test. P-values were calculated between patients in the SPARC analysis subset and patients who did not have SPARC data available.

Comment: There were differences in clinical outcome between patients in the SPARC subset and the total patient population from which the subset was derived. Overall, the 71 patient subset performed better than the entire CA031 patient population with PFS, OS, and ORR for both treatment arms in the SPARC subset being consistently better than the results from the corresponding treatment arms of the entire population. When compared with the rest of the patients who did not have SPARC data available in the ABI-007/carboplatin arm, the patients in the SPARC subset performed better although the differences did not reach statistical significance. When compared with the rest of the patients who did not have SPARC data available in the Taxol/carboplatin arm, the patients in the SPARC subset performed better and the differences were statistically significant. Overall, the outcome results suggest that the SPARC subset is not representative of the total population of study CA031.

The demographics of the two treatment arms in the SPARC subset were compared separately with the corresponding arms in the entire CA031 study. While the demographics of the Taxol/carboplatin arm in the SPARC subset and the entire CA031 study were similar except for ECOG performance status 0 (31% vs 21%, respectively), the demographics of the ABI-007/carboplatin arm in the SPARC subset had more male patients (86% vs 75%), fewer patients who never smoked (20% vs 26%), more squamous cell NSCLC disease (49% vs 44%), more patients older than 70 years (20% vs 14%), and more patients with ECOG performance status of 0 (40% vs 26%) compared with the corresponding ABI-007/carboplatin arm in the entire CA031 study.

5.1.3.2. Clinical outcomes with different SPARC status (high or low)

In all 71 patients, no statistically significant difference in median PFS or median OS was observed between the high and low SPARC groups when SPARC was classified by applying the average z-score method or the sum of variables method. In the ABI-007/carboplatin group (high SPARC vs low SPARC), no statistically significant differences were observed in median PFS or median OS using the average z-score or sum of variables method. In the Taxol/carboplatin group, a statistically significantly shorter median OS was observed in the low SPARC group compared with the high SPARC group using the average z-score method, but this was not confirmed using the sum of variables method. In the Taxol/carboplatin group (high SPARC vs low SPARC), no statistically significant differences were observed in median PFS using the average z-score or sum of variables method. All results were summarized. No statistically significant differences in the ORR was observed in either the ABI-007/carboplatin arm (high SPARC vs low SPARC) or the Taxol/carboplatin arm (high SPARC vs low SPARC) when SPARC was classified by applying the average z-score method or the sum of variables method.

5.1.3.3. Clinical outcomes between the two treatment arms by SPARC status (high or low)

To assess the predictive value of SPARC status on treatment effect, PFS, OS and ORR were analyzed by treatment arm separately for patients classified as high or low SPARC. No statistically significant results were observed in either the high or low SPARC groups for the comparisons between the ABI-007/carboplatin and Taxol/carboplatin treatment arms when SPARC was classified by applying the average z-score method or the sum of variables method.

5.2. Evaluator's comment on pharmacodynamics

The submission included one exploratory pharmacodynamic substudy investigating the effect of SPARC status (high vs low) on efficacy outcomes of PFS, OS, and ORR in a subset of patients (n=71) from the pivotal Phase III study (CA031). This exploratory substudy showed that SPARC status had no significant effects on the clinical outcomes irrespective of how the data were

analysed. However, the SPARC subset of patients appeared to be unrepresentative of the total patient population from which it was derived as the clinical outcomes (PFS, OS, and ORR) for patients in the subset were superior to those for the total population. The sponsor concludes that "no definitive conclusions about the correlation between clinical outcomes and SPARC status can be drawn" from the subgroup analysis due to the limitations arising from the small sample size. Other exploratory molecular biomarker analysis referred to in the protocol were not undertaken due to the low number of consenting patients with sufficient samples available for study.

6. Dosage selection for the pivotal studies

In the pivotal Phase III study (CA031), the ABI-007 dose was 100 mg/m^2 given weekly. The sponsor stated that results from the Phase I/II studies CA015, CA018 and CA028 suggested that a greater response rate could be anticipated in patients with NSCLC with a once weekly rather than once every three weeks regimen of ABI-007, and with an ABI-007/carboplatin combination rather than ABI-007 alone. Based on the data from the Phase I/II studies and the risk/benefit ratio for dose cohorts in study CA028, the ABI-007 regimen evaluated in the pivotal Phase III study was 100 mg/m^2 given weekly in combination with carboplatin (AUC = 6) every 3 weeks as first-line treatment for patients with metastatic NSCLC.

In the pivotal Phase III study, the Taxol dose was 200 mg/m^2 given once every 3 weeks. The sponsor stated that the 200 mg/m^2 dose was selected for two reasons: (1) the protocol Steering Committee strongly recommended that a Taxol dose of 225 mg/m^2 was not appropriate for the control arm due to toxicity associated with this dose; and (2) 200 mg/m^2 is the dose most commonly administered Taxol dose. In addition, the sponsor stated that the dose of Taxol used in the pivotal Phase III study in combination with carboplatin (AUC = 6) is the same as that used in the study of the doublet-combination of Taxol/carboplatin vs the triplet-combination of Taxol/carboplatin/bevacizumab that resulted in global approval of bevacizumab for the first-line treatment of advanced NSCLC (Sandler et al., 2006). Furthermore, the sponsor stated that the recommended standard of care for first line treatment of NSCLC is Taxol within the range of 175 to 225 mg/m^2 in combination with carboplatin (AUC = 6) (Schiller et al., 2002).

7. Clinical efficacy

7.1. Overview of the clinical efficacy studies

The sponsor submitted four clinical efficacy and safety studies to support the submission to extend the indications of Abraxane to include the treatment of advanced NSCLC. Brief outlines of the basic design features of these four studies were provided.

The Phase III study CA031 was nominated by the sponsor as the pivotal study. This study included 1052 patients and randomized 521 to ABI-007/carboplatin at the proposed dosage regimen and 531 to the control of Taxol/carboplatin. This was a good quality study and it is agreed that it should be considered to be pivotal.

The sponsor nominated the non-randomized, uncontrolled, open-label, dose-escalation Phase II study CA0028 as the key supportive study. However, this study is considered to provide limited supportive data. The study included a cohort of only 25 patients treated with the proposed ABI-007/carboplatin dosage regimen, and the absence of a control arm makes the observed results in these patients difficult to interpret. The sponsor also nominated studies CA015 (Phase I/II) and CA018 (Phase II) as supportive. However, it is considered that neither of these two studies can be considered to provide supportive data as neither included patients treated with the proposed dosage regime. In study CA015, ABI-007 100 mg/m^2 was administered as a single-

agent to 3 patients and in study CA018, ABI-007 was administered as a single-agent at a dose of 260 mg/m^2 once every 3 weeks to 43 patients.

7.2. Pivotal efficacy study (CA031)

7.2.1. Study design, objectives, locations and dates

7.2.1.1. Study design

The pivotal, Phase III, study was a multi-national, multicentred, randomized, active-controlled trial designed to compare the efficacy and safety of ABI-007/carboplatin and Taxol/carboplatin for first-line treatment of advanced NSCLC. The study enrolled 1052 patients from 6 countries and 102 sites (29 sites in Russia, 25 sites in the US, 21 sites in Japan, 16 sites in Ukraine, 6 sites in Canada, and 5 sites in Australia). The first patient was enrolled on 14 December 2007 and the study is ongoing. The study report was dated 26 October 2011. The study was conducted under the sponsorship of Abraxis BioScience, LLC, a wholly owned subsidiary of Celgene Corporation.

The study protocol (including amendments) and informed consent form were approved by site specific Independent Ethics Committees (IEC) and/or Institutional Review Boards (IRB) responsible for local oversight of the trial. The study was conducted in accordance with the Declaration of Helsinki, the ethical principles of GCP according to the ICH Guideline, and country specific regulations and guidelines. All patients provided written informed consent before participating in the study. The study protocol was originally dated 21 February 2007, revised on 16 July 2007, and subsequently amended 4 times.

A total of 525 patients per treatment arm were planned for the intent-to-treat (ITT) analysis. The study consisted of baseline assessments done within 28 days of randomization, a treatment phase, end-of-study (EOS) evaluations and follow-up. The submitted CSR presented the final data for all 1052 patients enrolled in the study. The data cut-off date for analysis of the primary efficacy endpoint of disease response assessed by independent blinded reviewers was 12 October 2009, and the cut-off date for all other efficacy endpoints and for safety/tolerability was 31 January 2011. A Data Monitoring Committee (DMC) was used to provide recommendations relating to increasing the sample size, and continuing or stopping the study based on review of interim safety data. The schedule of events for the study was summarized.

Comment: This study has now been published (Socinski et al., 2012). The study was un-blinded which exposes it to the well known biases associated with studies of this type. However, the study was randomized which mitigates selection bias. Observation bias in this study was mitigated by the use of independent reviewers to assess the primary endpoint of patient response to treatment and the key secondary endpoint of PFS using RECIST criteria (Version 1.0) for computed tomography (CT) scans. The reviewers were blinded to treatment assignment and investigator assessment of response.

The active-control arm was Taxol/carboplatin, an unapproved TGA combination for the treatment of NSCL but a clinically acceptable combination for treatment of advanced NSCLC. It is considered that the use of a placebo-control group in this study would have been unethical, given the availability of clinically acceptable treatments for advanced NSCLC. In this study, treatment of NSCLC was "non-personalized" (i.e., it was not based on individual patient and/or tumour characteristics). It should be noted that there is a move amongst oncologists towards personalized targeted therapy for advanced NSCLC.

7.2.1.2. Study objectives

The primary objective was to compare disease response of ABI-007/carboplatin versus Taxol/carboplatin as first-line therapy in patients with advanced NSCLC using Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (Version 1.0).

The secondary objectives were: (1) to compare the frequency of toxicities graded using the Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0; (2) to compare progression free survival (PFS); (3) to compare overall survival (OS); (4) to compare duration of response in responding patients; (5) to compare SPARC and other molecular biomarkers in tumour tissue and peripheral blood and to determine their possible correlation with efficacy outcomes; and (6) to evaluate PK parameters.

7.2.2. Inclusion and exclusion criteria

The study included male and female patients aged ≥ 18 years of age with histologically or cytologically confirmed stage III or IV NSCLC. Patients were required to have radiographically documented measurable disease (defined by the presence of ≥ 1 radiographically documented measurable lesion). In addition, patients were required not to have received prior chemotherapy for the treatment of metastatic disease, but adjuvant chemotherapy was permitted providing cytotoxic chemotherapy was completed 12 months prior to starting the study. Criteria reflecting adequate haematological, hepatic and renal function were also specified. Patients were also required to have expected survival ≥ 12 weeks and to have Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1. The inclusion criteria were consistent with those seen in oncology studies in patients with advanced malignant disease.

7.2.3. Study treatments

7.2.3.1. Treatment arms – ABI-007/carboplatin vs Taxol/carboplatin

Eligible patients were randomized on Day 1 in a 1:1 ratio into one of two treatment arms and were required to start treatment within 7 days of randomization. Randomization was stratified by disease stage (IIIb vs IV), age (< 70 vs ≥ 70 years), gender (male vs female), histology (adenocarcinoma vs squamous cell vs other), and geographic region. The two treatment arms were:

- Treatment Arm A (ABI-007/carboplatin):

  Patients treated with ABI-007 and carboplatin in combination received ABI-007 at 100 mg/m^2 (unless modified due to toxicity) given IV over approximately 30 minutes without steroid premedication and without G-CSF prophylaxis. The ABI-007 dose was given once weekly on Days 1, 8 and 15 of each 3-week cycle, and carboplatin was given at AUC = 6 mg.min/mL on Day 1 of each 3-week cycle. Day 1 was the only day of each 3-week cycle when ABI-007 was administered in combination with carboplatin.

  In Arm A, a maximum of two dose reductions were allowed from the original dose: first dose reduction (25% reduction) - decrease ABI-007 to 75 mg/m^2 and carboplatin to AUC = 4.5; and second dose reduction (50% reduction) - decrease ABI-007 to 50 mg/m^2 and carboplatin to AUC = 3.0.

- Treatment Arm B (Taxol/carboplatin):

  Patients treated with Taxol and carboplatin in combination were given 200 mg/m^2 Taxol IV (unless modified due to toxicity) administered over approximately 3 hours followed by carboplatin at AUC = 6 mg.min/mL. Cycles of therapy were repeated once every 3 weeks. In this arm, Taxol was administered with standard premedication (as per the prescribing information in the study manual).

  In Arm B, a maximum of two dose reductions were allowed from the original dose: first dose reduction (25% reduction) - decrease Taxol to 150 mg/m^2 and carboplatin to AUC = 4.5; and second dose reduction (50% reduction) - decrease Taxol to 100 mg/m^2 and carboplatin to AUC = 3.0.

Carboplatin dosing was based on the Calvert formula: i.e., carboplatin dose (mg) = (Target AUC) x (glomerular filtration rate [GFR] + 25). For the purposes of this study, the GFR was considered

to be equivalent to the creatinine clearance (calculated by the Cockcroft and Gault, 1976, method). Sites were permitted to use local laboratory values for creatinine or creatinine clearance.

A patient could continue treatment at the investigator's discretion until disease progression, development of an unacceptable toxicity, or withdrawal of consent. If the regimens were tolerated, then, at least 6 treatment cycles were encouraged.

ABI-007, carboplatin, and Taxol were obtained in the US and supplied by the sponsor. Complete blood count, differential, and platelet counts were evaluated weekly for all patients, regardless of treatment or treatment regimen.

Comment: The control arm used in this study of Taxol (200 mg/m^2) in combination with carboplatin (AUC = 6) IV repeated every 3 weeks is not TGA approved for the treatment of NSCLC. Taxol alone at a dose of 175 mg/m^2 administered IV over 3 hours with a 3 week interval between courses is TGA approved for primary or secondary treatment of NSCLC, but carboplatin is not TGA approved for the treatment of NSCL. However, the combination of Taxol and carboplatin is recommended for the treatment of advanced NSCLC in Australian clinical cancer guidelines (e.g., Clinical practice guidelines for treatment of lung cancer, Gunawardana D, Khasraw, and Pavlakis, Cancer Guidelines Wiki, Commissioned by the Australian Government, Cancer Australia; and eviQ, Cancer Treatments Online). The regimen recommended in eviQ is solvent-based paclitaxel 200 mg/m^2 in combination with carboplatin AUC = 6 every 21 days for 4 cycles unless otherwise indicated. In addition, the combination of solvent-based paclitaxel and carboplatin for first-line treatment of stage IV NSCLC is also recommended as a treatment option by the American Society of Clinical Oncology (Azzoli et al., 2011). The sponsor states that, at the time of the study design, "the Taxol/carboplatin regimen was the standard first-line treatment in the US and was a globally well-accepted treatment for advanced NSCLC". Overall, it is considered that the control treatment arm of Taxol (200 mg/m^2) combined with carboplatin (AUC = 6) administered at 3 week intervals is an acceptable comparator treatment.

The sponsor states that at least 6 treatment cycles were encouraged and that this was consistent with clinical practice guidelines in oncology (i.e., the National Comprehensive Cancer Network, ASCO). However, it is noted that the ASCO now recommends that first-line therapy for stage IV NSCLC "should be stopped at disease progression or after four cycles in patients whose disease is stable but not responding to treatment. Two-drug cytotoxic combinations should be administered for no more than six cycles. For patients with stable disease or response after four cycles, immediate treatment with an alternative single agent chemotherapy.....may be considered".

7.2.3.2. Dose adjustments due to toxicities

The protocol and protocol amendments included detailed instructions for administration of study drug to patients with abnormal haematologic or hepatic function, dose reductions for haematologic and non-haematologic toxicities, treatment for hypersensitivity reactions, and rules for dose delays and modified schedules.

The protocol specified that ABI-007 dosing should not be administered at the start of the study or on Day 1 of a cycle until the ANC returns to ≥ 1.5 x 10^9 cells/L and the platelet count returns to ≥ 100 x 10^9 cells/L. For each subsequent weekly dose of ABI-007, patients must have an ANC ≥ 0.5 x 10^9 cells/L and platelets > 50 x 10^9 cells/L. Taxol and carboplatin should not be administered at the start of each cycle until the ANC returns to ≥ 1.5 x 10^9 cells/L and the platelet count returns to >100 x 10^9 cells/L. Protocol specified dose reductions for both treatment arms due to haematological toxicities were summarized. In addition to dose

adjustments for haematological toxicities, the protocol specified that granulocyte colony-stimulating factors (G-CSF) may be given according to institutional guidelines for the treatment of neutropenic fever or infections associated with neutropenia.

Protocol specified dose reductions for both treatment arms due to non-haematological toxicities were summarized. The specified non-haematological toxicities included cutaneous toxicity (Grade 2, 4, or 4), mucositis (Grade 3 or 4), diarrhoea (Grade 3 or 4), and any other non-haematological Grade 3 or 4 toxicity excluding alopecia. The protocol specified that the study drugs should not be administered if hepatic function parameters were outside the range established for entry into the study. Patients who developed severe hypersensitivity reactions to any of the study drugs were not to be re-challenged with the drug, but treatment with the remaining drug alone could continue. The protocol specified that non-haematological toxicities Grade ≤ 2 should be managed symptomatically if possible and treatment should continue without dose reduction. Patients whose next treatment is delayed for ≥ 3 weeks due to persistent toxicity should have subsequent doses reduced by 1 dose level.

The *Dosage and Administration* section of the Abraxane PI includes specific advice on dose reductions of Abraxane and carboplatin in the event of haematologic and non-haematologic toxicities. This advice is comprehensive and is consistent with the protocol specified dosage recommendations for managing toxicities.

7.2.3.3. Prior and concomitant therapy

As ABI-007/carboplatin was being evaluated as first-line therapy, patients were to be naïve to chemotherapy. However, adjuvant chemotherapy was permitted, providing cytotoxic chemotherapy was completed 12 months prior to starting the study. Irradiation was not allowed during study treatment. No additional chemotherapeutic agents were allowed during study treatment. Supportive care such as antiemetic and pain medications was allowed at the investigator's discretion. Concurrent treatment with bisphosphonates was allowed. Erythropoietin could be administered at the investigator's discretion, consistent with institutional guidelines. G-CSF was to be administered according to the guidelines provided in Protocol Amendment 4, and in a manner consistent with European Organisation for Research and Treatment of Cancer (EORTC) guidelines.

7.2.3.4. Removal of patients from therapy or assessment

Patients were withdrawn from the study if any of the following occurred: progressive disease; development of toxicity considered to be unacceptable by the investigator; patient withdrew consent; recurrence of grade 4 neutropenia, or any other haematological toxicity that was grade 3 or 4, or any grade 3 or 4 non-myelosuppressive AE following the second dose reduction unless the investigator considered that continuing benefit to the patient outweighed the risk of recurrent toxicity; initiation of other anticancer therapy; and if the investigator considered that it was in the patient's interest to discontinue.

Patients who were withdrawn due to a laboratory abnormality or AE were to be followed for 30 days after discontinuation of the study drug or to the end of study assessment, whichever came later, and patients whose treatment was discontinued prior to disease progression were followed every 6 weeks with repeat tumour imaging to document continued remission or disease progression.

7.2.4. Efficacy variables and outcomes

7.2.4.1. Primary efficacy variable

The primary efficacy endpoint was the percentage of patients who achieved an objective confirmed complete response (CR) or partial response (PR) based on blinded independent radiological review using RECIST guidelines (Version 1.0). The assessment conventions in relation to RECIST guidelines (Therasse et al., 2000), were provided. In this study, radiology conventions did not constitute actual modifications to the response criteria.

Tumours were assessed by imaging studies every 6 weeks during therapy. For patients who had not progressed by the end of treatment, repeat imaging was performed every 6 weeks until tumour progression was documented or a new anticancer therapy was initiated. Patients were followed for 18 months poststudy to monitor survival. The follow-up consisted of telephone interviews or monthly review of records for 6 months and then every 3 months for 12 months.

Comment: The primary efficacy endpoint in this study of objective confirmed response is inconsistent with the relevant TGA adopted guideline relating to the evaluation of anticancer medicinal products (CPMP/EWP/205/96/Rev.3/Corr.). The TGA approved guideline indicates that Phase III therapeutic confirmatory studies should demonstrate that the investigational product should provide clinical benefit. Furthermore, the guideline specifically states that "acceptable primary endpoints include OS and PFS/DFS. If PFS/DFS is the selected primary endpoint, OS should be reported as a secondary and *vice versa*". It goes on to state that "without further justification, ORR is not an acceptable endpoint for confirmatory trials".

The sponsor considers that in the context of the pivotal study the objective tumour response is a surrogate endpoint for other measures of clinical benefit, including time to event (death or disease progression) and symptom control. In justifying the use of the ORR as the primary endpoint the sponsor states "overall response rate, assessed in a blinded fashion by an independent radiology review, was regarded as an acceptable primary surrogate endpoint for this superiority trial because (1) paclitaxel is an active and effective chemotherapeutic agent in the treatment of NSCLC as evidenced by the global regulatory approvals for paclitaxel in the first-line treatment of advanced NSCLC and, (2) this study was designed as part of a 505(b)(2) registration strategy (FDA Guidance for Industry) under a Special Protocol Assessment in the US". It is considered that it would have been preferable for this study to have used OS or PFS/DFS as the primary endpoint as specified in the relevant TGA adopted guideline. The editorial in the edition of the Journal of Clinical Oncology that accompanied the report of the pivotal study (Socinski et al., 2012) noted that the "use of ORR alone as the primary outcome measure is not commonly done in 2012. Most clinical investigators would not consider this outcome as an adequate choice for a definitive trial evaluating a chemotherapy agent and might choose instead endpoints such as progression free survival or overall survival".

However, despite the concerns relating to the choice of the primary efficacy endpoint it is considered that the sponsor's justification for using the ORR is acceptable based on global regulatory approval of paclitaxel for the first-line treatment of NSCLC, and what appears to be FDA input into the study design. In addition, Australian clinical oncology guidelines include solvent-based paclitaxel in combination with carboplatin as a first-line treatment for advanced NSCLC and, consequently, a non-inferiority study based on the ORR as the primary endpoint is considered to be acceptable.

7.2.4.2. Secondary efficacy variables

Key secondary efficacy endpoints were progression-free survival (PFS) and overall survival (OS). Other secondary efficacy endpoints were: evaluation of PK parameters; percentage of patients with stable disease for ≥ 16 weeks or confirmed CR or PR response (i.e., disease control rate); duration of response in responding patients; and correlation of SPARC and other molecular biomarkers with efficacy outcomes.

7.2.5. Definitions relevant to outcome

7.2.5.1. Measurable and non-measurable lesions

The criteria for defining lesions as measurable were defined in the protocol and Independent Review Charter for imaging (see Appendix 2, pages 147 to 152). The definition of a measurable lesion at baseline was dependent on the technical factors of the imaging studies used to evaluate the patient. The sponsor recommended using 5 mm reconstructions per the RECIST guideline, Version 1.0, but accepted spiral CT images based on the American College of Radiology (ACR) recommendations if that was the standard used at the site. The ACR recommendation is that reconstructions should be < 10 mm, and for spiral CT of the abdomen and pelvis, the recommendation is the slice thickness should be ≤ 8 mm. Cases evaluated using ACR guidelines were not considered protocol deviations and were considered to be measurable lesions. All other lesions that did not meet the criteria for measurable disease, as well as other truly non-measurable lesions, were considered non-measurable.

7.2.5.2. Target and non-target lesions

According to RECIST, up to 10 target lesions (a maximum of 5 per organ) were chosen for measurement over the course of the study, and target lesions must have been measurable at baseline. For cases where there was no identified target lesion, tumour assessment for disease progression was based on protocol specified nontarget lesion assessments or the development of new lesions. Response (PR or CR) and stable disease were not to be assessed in patients where target lesions were not identified at baseline.

7.2.5.3. Antitumour response

Antitumor response was defined as the percentage of patients who achieved an objective response (CR or PR), confirmed by repeat assessments performed no less than 4 weeks after the criteria for response were first met. Disease control rate (stable disease for ≥16 weeks or confirmed CR or PR) was also reported. Response was determined according to RECIST Version 1.0 guidelines (Therasse et al., 2000). The definitions used to evaluate response based on target lesions at each point after baseline are summarized below in Table 9. The definitions for response assessment for non-target lesions were provided and response determinations at each time point assessed as combination of target and non-target response and the presence of new lesions were summarized.

Table 9: Response definitions – target lesions.

CR: Disappearance of all target lesions.
PR: ≥ 30% decrease in the SLD of target lesions, taking as reference the baseline SLD.
Stable Disease: Neither sufficient shrinkage of target lesions to qualify for PR, nor sufficient increase to qualify for PD, taking as reference the nadir SLD since the treatment started.
PD: ≥ 20% increase in the SLD of target lesions, taking as reference the nadir SLD recorded since the treatment started, or, the presence of one or more new lesions.
Unable to Evaluate (UE): A target lesion present at baseline which was not measured or which was unable to be evaluated leading to an inability to determine the status of that particular tumor for the time point in question. If the SLD cannot be determined at a time point, and the rules for PD do not apply, a response of CR, PR or stable disease cannot be assigned for that time point and the time point response will be UE.
Not Applicable (NA): No target lesions were identified at baseline. Patients with no target lesions identified at baseline could not be assessed for response. These patients were assessed for progression only.
Not Done (ND): Scans were not performed at this time point to evaluate the target lesions.

Note: CR = complete response; PR = partial response; SLD = sum of longest diameter; PD = progressive disease.

7.2.6. Randomization and blinding methods

The randomization schedule was generated by a randomization statistician from the sponsor, and randomization was implemented via an ICON Interactive Voice Response (IVR) system. The randomization schedule used a block size of 4 patients. Patients were randomized in a 1:1 ratio and randomization was stratified by: (1) disease stage (IIIb vs IV); (2) age (< 70 vs ≥ 70 years); (3) gender (male vs female); (4) histology (squamous cell carcinoma vs adenocarcinoma vs other histology); and (5) geographic region (North America vs Australia/New Zealand vs Eastern Europe vs Asia/Pacific).

The study was open-label, and the sponsor stated that blinding was not feasible due to the differences in study drug appearance, the frequency and duration of administration, and the required administration of premedications for Taxol. Assessment of the primary endpoint of patient response to treatment and the key secondary endpoint of PFS were evaluated by independent reviewers using RECIST criteria for computed tomography (CT) scans. The independent reviewers were blinded to the treatment assignment and to the investigator assessment of response.

7.2.7. Analysis populations

ITT population: All efficacy analyses were based on the ITT population, which included all randomized patients regardless of whether the patient received any study drug or had any efficacy assessments. The ITT population included 1052 patients (521 in the ABI-007/carboplatin arm and 531 in the Taxol/carboplatin arm).

Treated population: The treated population was the analysis population for all safety analyses, and included all randomized patients who received at least 1 dose of study drug. The treated population included 1038 patients (514 in the ABI-007/carboplatin arm and 524 in the Taxol/carboplatin arm).

No per-protocol efficacy analyses were conducted as only 49 (5%) patients (28 in the ABI-007/carboplatin arm and 21 in the Taxol/carboplatin arm) were considered not to be evaluable. These 49 patients included 14 who were randomized but did not receive study drug and 35 with major protocol violations.

7.2.8. Sample size

7.2.8.1. Response rate (primary efficacy endpoint)

The sponsor referred to Phase III data on Taxol plus carboplatin that showed a response rate of 17% in patients previously untreated for advanced NSCLC (Schiller et al., 2002). Based on the improved antitumour activity over Taxol demonstrated in metastatic breast cancer, it was assumed that ABI-007/carboplatin would have a response rate of 24% (a relative improvement of approximately 40% over Taxol plus carboplatin). Based on this assumption, the 525 ITT patients per arm provided 80% power with a 2-sided Type 1 error of 0.049 to reject the null hypothesis that the ABI-007/carboplatin response rate was equal to that of Taxol/carboplatin.

A pre-specified interim analysis of response rate was performed after 200 patients per arm had completed the second response assessment. The purpose of this interim analysis was to evaluate the initial assumption of treatment difference in response rate (24%, ABI-007/carboplatin vs 17%, Taxol/carboplatin). If the treatment difference at the interim analysis was lower than assumed, the sample size was to be increased accordingly. The maximum allowed sample size was 990 patients per arm, which was based on a minimum treatment difference of 22% vs 17% (relative improvement of approximately 30%). An alpha spending function was utilized to preserve the overall Type 1 error at 0.050. This spending function allocated alpha values of 0.001 and 0.049 at the interim and final analyses of the response rate, respectively. An independent DMC was established with responsibilities for evaluating the initial assumption of treatment difference in response, as well as safeguarding the interests of study participants and monitoring the overall conduct of the study. The DMC met on 31 August 2009 and determined that the treatment difference at the interim analysis was not lower than assumed, and recommended that the sample size should not be changed.

7.2.8.2. Progression free survival and overall survival

The final analysis for PFS was to be conducted once 70% of patients had an event of disease progression or death (any cause). This was equivalent to 735 events, which provided 85% power with a 2-sided Type 1 error of 0.049 to detect hazard ratio (HR) of ABI-007/carboplatin to Taxol/carboplatin (i.e., $HR_{A/T}$) of 0.80. At the time of the final response rate analysis an interim analysis of PFS was reported. An alpha spending function was utilized to preserve the overall Type 1 error at 0.050 for the analysis of PFS. This spending function allocated alpha values of 0.001 and 0.049 at the interim and final analyses of PFS, respectively. Due to a higher than expected rate of censoring, the final PFS analysis was performed with 609 events rather than 735 events.

The final analysis for OS was to be conducted once 70% of patients had died. This was equivalent to 735 deaths, which provided 85% power with a 2-sided Type 1 error of 0.049 to detect a $HR_{A/T}$ of 0.80. At the time of the final response rate analysis an interim analysis of OS was reported. An alpha spending function was utilized to preserve the overall Type 1 error at 0.050 for the analysis of OS. This spending function allocated alpha values of 0.001 and 0.049 at the interim and final analyses of OS, respectively.

7.2.9. Statistical methods

7.2.9.1. Primary efficacy endpoint

The primary efficacy endpoint was the percentage of patients who achieved an objective confirmed CR or PR based on the blinded radiological review. The null hypothesis was that the ABI-007/carboplatin regimen response rate was equal to that of the Taxol/carboplatin regimen. Superiority of ABI-007/carboplatin to Taxol/carboplatin was to be established if the lower

bound of the two-sided 95.1% CI of the ratio for the relative response rates of the two treatment arms was greater than 1 (i.e., pA/pT > 1.0). Treatment regimen comparison of response rates was tested using the chi-square test.

The primary analysis of response was not adjusted for covariates. However, pre-specified (SAP) exploratory subgroup analyses were performed to assess the potential influence of a number of prognostic factors on the primary efficacy endpoint of objective response. The effect on objective response of each prognostic factor was tested using a logistic regression model with effects for treatment regimen, prognostic factor, and treatment regimen-by-prognostic factor interaction.

If a patient was randomized but never received study drug, discontinued from the study prior to a response evaluation, or had non-evaluable response evaluations during the study, that patient was analyzed as a non-responder in the response rate efficacy analysis.

7.2.9.2. Key secondary efficacy endpoints (PFS and OS)

7.2.9.2.1. Superiority analysis of PFS and OS

Secondary efficacy endpoints were to be analyzed only if the primary efficacy endpoint displayed superiority of ABI-007/carboplatin over Taxol/carboplatin. To control the overall family-wise Type I error rate at a 2-sided alpha of 0.050 for the 2 key secondary efficacy endpoints, PFS was tested first at an alpha of 0.050, and OS was tested second at an alpha of 0.050 only if PFS showed significant improvement.

PFS was defined as the time from the day of randomization to the start of disease progression or death (any cause), whichever occurred first, based on the blinded radiological review assessment of response. It was analyzed using Kaplan-Meier (KM) methods, and patients who did not have disease progression or had not died were censored at the last known time that the patient was progression-free. The ABI-007/carboplatin to Taxol/carboplatin hazard ratio ($HR_{A/T}$) and 95.1% CI for PFS was presented.

OS was defined as the time from the day of randomization to patient death (any cause), and was analyzed in a similar manner to PFS. The final analysis for OS was conducted once 70% of patients had died.

7.2.9.2.2. Non-inferiority analysis of PFS and OS:

An addendum to the Statistical Analysis Plan (SAP), finalized on 11 April 2011, was developed to outline additional analyses specific for the European Union (EU) submission to address: (1) PFS per European Medicines Agency (EMA) methodological considerations for PFS endpoint guidelines (EMEA/CHMP/EWP/27944/2008); (2) non-inferiority analysis consistent with recommendations of EMA guidelines (EMEA/CHMP/EWP/205/95/ Rev.3/Corr; and EMEA/CPMP/EWP/2158/99); and (3) supportive analysis of non-inferiority based on OS.

Cox proportional hazard models, stratified by geographic region and primary diagnosis were used to estimate the hazard ratio and 95% confidence interval (CI) of both PFS and OS. PFS was chosen as the primary endpoint of the non-inferiority analyses. For the primary non-inferiority PFS analysis and the supportive non-inferiority OS analysis, the non-inferiority margin was chosen as 15% (i.e., when the upper bound of the 95% CI of the $HR_{A/T}$ was less than 1.176, then non-inferiority was considered met). The selection of the non-inferiority margin for the PFS and OS analyses was based on data from studies with Alimta and Xeloda, and an assessment of clinical benefit based on a meta-analysis of relevant historical studies.

In a previous study comparing Alimta/cisplatin with gemcitabine/cisplatin for first-line treatment of NSCLC, the non-inferiority criterion for OS was an upper bound 95% CI for the hazard ratio of less than 1.17645. In addition, the sponsor noted that in the Xeloda clinical program for metastatic colorectal cancer, metastatic gastric cancer and adjuvant colon cancer, analyses for PFS and/or OS used upper 95% CI limits of 1.2 to 1.3 for the relevant hazard ratios.

To evaluate the impact of the 15% non-inferiority margin, the relative efficacy of ABI-007/carboplatin over "Placebo" (i.e., etoposide + cisplatin combination in this case) was projected using data from a series of HRs from relevant regimens in comparable populations. This analysis suggested that if ABI-007/carboplatin loses 15% efficacy compared with Taxol/carboplatin (i.e., the PFS and OR of the $HR_{A/T}$ is 1.176) then the projected PFS and OS would still indicate a marginal positive effect for ABI-007/carboplatin over "placebo" (i.e., etoposide + cisplatin) with the respective HRs being 0.92 and 0.99.

Comment: The non-inferiority analyses of PFS and OS specified in the SAP addendum were not specified in the original protocol and SAP. There was no plan for multiple comparisons adjustment for these analyses as they were produced "only to facilitate the EMEA review" (SAP addendum). The decision to introduce non-inferiority analyses at such a late stage in the study is unusual. However, the addendum was prepared prior to the final database lock and prior to the PFS and OS analyses. Consequently, it is considered that the non-inferiority analyses of the PFS and OS are acceptable. The rationale for the 15% non-inferiority margin appears reasonable, but the sponsor acknowledges that this margin was decided after the pre-specified interim analysis.

7.2.9.3. Other secondary efficacy endpoints

- Investigator assessment of response and PFS were analyzed in the same manner as the assessment of these parameters based on blinded radiological review.
- Disease control (stable disease ≥16 weeks or confirmed CR or PR) was analyzed in the same manner as objective response based on both independent radiological review and investigator assessment.
- PFS for patients who achieved an objective response was presented as a measure of duration of response, and was based on both independent radiological review and investigator assessment.

7.2.10. Participant flow

Patient disposition is summarized below in Table 10.

Table 10: Study CA031 – Patient disposition.

Variable / Category	ABI-007/ carboplatin (N=521)	Taxol/ carboplatin (N=531)	All Patients (N=1052)
Intent-to-treat Patients, N	521	531	1052
Patients Treated, n (%)	514 (99%)	524 (99%)	1038 (99%)
Therapy Ongoing, n (%)	3 (< 1%)	0	3 (<1%)
Therapy Discontinued, n (%)	511 (> 99%)	524 (100%)	1035 (>99%)
Reason for Therapy Discontinuation, N	511	524	1035
Progressive Disease, n (%)	275 (54%)	265 (51%)	540 (52%)
Unacceptable Toxicity, n (%)	61 (12%)	62 (12%)	123 (12%)
Adverse Event, n (%)	20 (4%)	24 (5%)	44 (4%)
Investigator Discretion, n (%)	86 (17%)	99 (19%)	185 (18%)
Protocol Deviation, n (%)	3 (<1%)	4 (<1%)	7 (<1%)
Lost to Follow-up, n (%)	1 (<1%)	1 (<1%)	2 (<1%)
Patient Discretion, n (%)	65 (13%)	67 (13%)	132 (13%)
Other[a], n (%)	0 (<1%)	2 (<1%)	2 (<1%)

[a] The "Other" category included GCP deviation, study drug Taxol not available, Taxol no longer available, and high bilirubin.

Comment: Patient disposition was well balanced between the two treatment arms. As of the data cut-off date (31 January 2011), approximately 99% (n=1038/1052) of randomized patients in the ITT population had been treated, and > 99% (n=1035/1038) of these patients had completed treatment while therapy was ongoing in the remaining 3 patients. Overall, 14 patients were randomized but not treated (7 in each treatment am). Of these 14 patients, 7 were not treated due to investigator discretion, 3 due to adverse events, 3 due to protocol deviation and 1 due to withdrawal of consent. The most common reason for treatment discontinuation was progressive disease (52% overall). Only 2 patients (1 in each treatment arm) had been lost to follow-up. Overall, 5% (n=49/1052) of patients discontinued due to completion of 6 Cycles of therapy (4%, n=21 in the ABI-007/carboplatin arm and 5%, n=28, in the Taxol/carboplatin arm).

7.2.11. Major protocol violations/deviations

Overall, major protocol violations were reported in 36 patients (3.4%) with the most common violation being dosing errors (28 patients). Major protocol violations were reported in 21 patients (4.0%) in the ABI-007/carboplatin arm and 15 patients (2.8%) in the Taxol/carboplatin arm.

A total of 62 patients were randomized via the IVR system with an inaccurate stratification factor consisting of 32 disease stage errors, 31 histology errors, 1 date of birth error resulting in mis-stratification by age, and 1 gender error. Information in the IVR system was compared with patient information in the clinical database, and all inaccurate stratification factor information was corrected in the clinical database which was used for all stratified and subgroup analyses.

7.2.12. Baseline data

Baseline demographics were comparable between the two treatment arms in the ITT population, and representative of the targeted population. The median age was 60 years in both treatment arms, and the age range for all patients was 24 to 84 years. Overall, the majority of patients were < 65 years of age (67%) and only 3% of patients were aged ≥ 75 years. The majority of patients in both treatment arms were male (75%), and approximately 80% of patients in both treatment arms were “White, non-Hispanic and Non-Latino”, with the majority of the remaining patients being “Asian”. Most patients (73%) were current smokers or had been smokers and had quit smoking, and most patients (76%) had an ECOG performance status of 1 (i.e., restrictive but ambulatory) at baseline. The Physician Assessment of Sensory Neuropathy at baseline was zero for 95% of patients. The majority of patients had normal SAP, ALT, AST, total bilirubin, Hb, and creatinine levels at baseline. Overall, 45% of patients were enrolled in Russia, 24% in the Ukraine, 14% in Japan, 12% in the US, 4% in Canada, and 1% in Australia. Treatment arm assignments were balanced for each country.

Cancer history at enrollment was comparable between the two treatment arms in the ITT population. In both treatment arms, the majority of patients were randomized within one month of lung cancer diagnosis, with a median time from primary diagnosis to enrollment of 0.7 months, and a median time from first documented metastasis/relapse to study entry of 0.5 months. In compliance with the protocol, NSCLC disease stage at randomization was primarily Stage IV (79%) with the remainder being Stage IIIb (21%). The anatomic site of the primary diagnosis was lung for approximately 93% of all patients, and “other” anatomic sites of the primary diagnosis were most commonly lymph nodes. Histology of the primary diagnosis was most commonly carcinoma/adenocarcinoma (49%) or squamous cell carcinoma (43%). The most common sites of metastasis/relapse at randomization (observed in ≥ 20% of patients) were thorax (> 99%), abdomen/peritoneum (25%), liver (20%) and bone (20%). In both treatment arms nearly all patients (> 99%) had visceral disease.

Blinded baseline target and non-target lesions assessments in the ITT population were generally comparable between the two treatment arms. A spiral CT scan was used to assess

lesions in > 99% of patients in both treatment arms, and lesion status was generally comparable between the two treatment arms in the ITT population. The median number of lesions in the Taxol/carboplatin arm was larger than in the ABI-007/carboplatin arm (5 [range: 1, 27] vs 4 [range: 1, 30], respectively, p=0.011). However, the median sum of the individual longest target lesion diameters was similar in the Taxol/carboplatin and ABI-007/carboplatin arms (11.60 cm [range: 1.3, 40.0] vs 11.80 cm [range: 1.1, 41.7], respectively, p=0.386). The main site of lesions were lung in both the ABI-007/carboplatin and Taxol/carboplatin arms (94% vs 93% respectively), followed by non-axillary lymph nodes (80% vs 84%, respectively).

Pretreatment diagnoses, signs and symptoms were reported in > 99% of patients in both treatment arms and grouped system disorders and individual conditions were well balanced between the two arms. The most commonly occurring pretreatment disorders in both the ABI-007/carboplatin and Taxol/carboplatin treatment arms were "respiratory, thoracic, and mediastinal" (84% vs 83%, respectively), consisting primarily of cough and dyspnoea.

Prior therapies for cancer were uncommon in both treatment arms and were well balanced between the two arms. Prior chemotherapy had been received by only 3% of patients in the ABI-007/carboplatin arm and 2% of patients in the Taxol/carboplatin arm. Prior neoadjuvant therapy had been received by <1% of patients in both treatment arms, prior adjuvant therapy had been received by 2% of patients in both treatment arms, and prior metastatic therapy by only 2 patients (<1%), both in the Taxol/carboplatin arm. Less than 1% of all patients had received prior hormonal therapy and no patient in either treatment arm had received prior monoclonal antibody therapy. Prior radiation therapy was reported in 7% of patients in the ABI-007/carboplatin arm and 9% of patients in the Taxol/carboplatin arm. The radiation therapy sites treated in ≥ 1% of patients in either arm (ABI-007/carboplatin vs Taxol/carboplatin) were lung/thoracic (3% vs 5%), bone (2% for both arms), and CNS/brain (1% vs 2%).

Prior medications were taken by 38% of patients in the ABI-007/carboplatin arm and 41% of patients in the Taxol/carboplatin arm. Prior medication classes taken by ≥ 10% of patients in either treatment arm (ABI-007/carboplatin vs Taxol/carboplatin) were blood substitutes and perfusion solutions (14% vs 12%), anaesthetics (12% vs 13%), analgesics (11% both arms), antibacterials for systemic use (11% vs 15%), contrast media (11% vs 10%), and drugs for functional gastrointestinal disorders (10% vs 9%).

Selected, pre-dosing concomitant medications (i.e., corticosteroids, anti-histamines, and anti-emetics) taken on the of or the day before dosing and summarized by patients and cycle were notably lower in the ABI-007/carboplatin arm than in the Taxol/carboplatin arm. The high rate of corticosteroid and antihistamine use in the Taxol/carboplatin arm was consistent with the protocol instructions to administer premedication to patients randomized to this arm to prevent severe hypersensitivity reactions associated with Taxol. In contrast, no corresponding protocol instructions were specified for patients in the ABI-007/carboplatin arm, but concomitant medication could be administered at the investigator's discretion. The most common reason provided by the investigator for administering corticosteroids to patients in the ABI-007/carboplatin arm was as a pre-medication for carboplatin, indicating that it was used for anti-emetic prophylaxis.

Concomitant medications were those medications taken on or after the date of the first dose of study drug and were taken by 90% of patients in the ABI-007/carboplatin arm and > 99% of patients in the Taxol/carboplatin arm. A smaller percentage of patients in the ABI-007/carboplatin arm compared with patients in the Taxol/carboplatin arm used anti-emetics and anti-nauseants (74% vs 93%), corticosteroids (45% vs 99%), drugs for acid-related disorders (31% vs 96%), anti-inflammatory and anti-rheumatic products (25% vs 36%), and anti-histamines (19% vs 95%). A higher percentage of patients in the ABI-007/carboplatin arm compared with patients in the Taxol/carboplatin arm used anti-anaemic preparations (35% vs

20%), blood substitutes and perfusion solutions (33% vs 29%), and human blood transfusion products (16% vs 4%).

7.2.13. Results for the primary efficacy endpoint

The analysis of the primary efficacy endpoint of the ORR determined by blinded radiology assessment showed that the response was statistically significantly greater for patients in the ABI-007/carboplatin arm compared with the Taxol/carboplatin arm (see Table 11 below).

Table 11: Study CA031 – Blinded assessment of the ORR; ITT population.

Variable Category/Statistic	ABI-007/ carboplatin (N=521)	Taxol/ carboplatin (N=531)	Response Rate Ratio (p_A/p_T)	P-value
Patients with Confirmed Complete or Partial Overall Response				
n (%)	170 (33%)	132 (25%)	1.313	0.005*
Confidence Interval (CI) [a]	28.6, 36.7	21.2, 28.5	1.082, 1.593	
Complete Response	0	1 (< 1%)		
Partial Response	170 (33%)	131 (25%)		

a 95% CI of response rate and 95.1% CI of response rate ratio.
* Indicates p-value < 0.049; p-value is based on a chi-square test.

A waterfall plot of the maximum percent tumor shrinkage assessed by independent review for both treatment arms is displayed in the CER. The waterfall plot shows that a greater number of patients achieved a maximum shrinkage of ≥ 30% in the ABI-007/carboplatin arm than in the Taxol/carboplatin arm, consistent with the increased response rate observed in the ABI-007/carboplatin arm.

Comment: The primary efficacy analysis of the ORR based on blinded radiological assessment showed a statistically superior greater response in the ABI-007/carboplatin arm (33%, n=170/521) compared with the Taxol/carboplatin arm (25%, n=132/531); p=0.005. The study specified that superiority of ABI-007/carboplatin relative to Taxol/carboplatin was to be established if the lower bound of the two-sided 95.1% CI of response rate ratio (p_A/p_T) was greater than 1.0. The lower bound 95.1% of response ratio was 1.082 indicating that in this study ABI-007/carboplatin was superior to Taxol/carboplatin for the treatment of patients with stage IIIb or IV NSCLC. The absolute difference between the two treatment arms was 8% in favour of ABI-007/carboplatin, and the clinical significance of this difference is uncertain.

The Clinical Overview (Module 2) included a non-protocol specified (but TGA requested) analysis of the difference between the ORR in the two treatment arms in the ITT population. This analysis showed that the 95% CI of the 8% difference in the ORR between the two treatment arms was 2.3% to 13.2%.

7.2.14. Results for other efficacy endpoints

7.2.14.1. Key secondary efficacy endpoints

7.2.14.1.1. Progression-free survival (first key secondary efficacy endpoint)

7.2.14.1.1.1. Superiority analysis

The analysis of the first key secondary efficacy of PFS determined by blinded radiological assessment failed to demonstrate superiority of ABI-007/carboplatin over Taxol/carboplatin (see Table 12, below).

Table 12: Study CA031 – Primary analysis of PFS determined by blinded radiology assessment; ITT population.

Variable	ABI-007/carboplatin (N=521)	Taxol/carboplatin (N=531)	Hazard Ratio ($HR_{A/T}$)	P-value
Number of Patients who Died or had Progression	297 (57%)	312 (59%)		
Median Progression-Free Survival (months)	6.3	5.8	0.902	0.214
Confidence Interval [1]	5.6, 7.0	5.6, 6.7	0.767, 1.060	
Time points				
Month 6				
Number of Patients at Risk	167	162		
KM Estimate (95% CI)	52% (47%, 57%)	49% (44%, 54%)		
Month 12				
Number of Patients at Risk	38	40		
KM Estimate (95% CI)	22% (17%, 27%)	19% (15%, 24%)		
Month 18				
Number of Patients at Risk	10	10		
KM Estimate (95% CI)	11% (6%, 16%)	9% (6%, 14%)		
Month 24				
Number of Patients at Risk	0	2		
KM Estimate (95% CI)	--	7% (4%, 12%)		

[1] 95% confidence interval of median value and 95.1% confidence interval of hazard ratio. P-value is based on a stratified log-rank test stratified by geographic region (North America/Australia, Eastern Europe, or Asia/Pacific) and histology of primary diagnosis (squamous cell carcinoma or non-squamous cell carcinoma).

The KM curve for PFS for each treatment regimen was presented. The KM curves show that the estimated risk of progression is slightly reduced for patients in the ABI-007/carboplatin treatment arm compared with the Taxol/carboplatin arm, although the reduction is not statistically significantly superior (log-rank, p = 0.214). PFS based on KM estimates was higher in the ABI-007/carboplatin arm compared with the Taxol/carboplatin arm at 6 months (52% vs 49%), 12 months (22% vs 19%), and 18 months (11% vs 9%).

Censoring in the blinded radiology assessment PFS was summarized. Patients who did not have disease progression or who were alive were censored at the last known time that the patient was progression free. If palliative radiotherapy or lesion site surgery occurred, the patient was censored at the last assessment prior to the date of radiotherapy or surgery. A patient who began a new anticancer therapy, or with two or more missing response assessments prior to documented progression, was censored at the last assessment when the patient was progression free. Censoring occurred in 43% of patients in the ABI-007/carboplatin arm and 41% of patients in the Taxol/carboplatin arm. In both treatment arms, the two most common reasons for censoring were discontinuation of scanning by the investigator due to progressive disease (ABI-007/carboplatin, 28% vs Taxol/carboplatin, 25%) and new anti-cancer therapy or lesion site surgery (8% for both arms). The median follow-up time for PFS in censored patients was approximately 4 months in both treatment arms.

Three sensitivity analyses for PFS were performed. First (#1), a sensitivity analysis for the blinded radiology assessment of PFS in which patients who had disease progression or were censored at an unscheduled/off-scheduled response assessment were evaluated as having progressed or were censored at the time of next regularly scheduled response. Second (#2), a sensitivity analysis for PFS was performed in which patients with a single missing/unevaluable response assessment prior to documented disease progression were censored at the last response assessment where the patient was documented as progression free. Third (#3), a sensitivity analysis was performed in which patients with a single missing/unevaluable response assessment prior to documented disease progression were evaluated as having progressed at the time of the missing/unevaluable response assessment. All three sensitivity analyses showed no statistically significant difference in PFS between the two treatment arms.

Comment: In the primary PFS superiority analysis, median PFS was 6.3 months (95% CI: 5.6, 7.0) in the ABI-007/carboplatin arm compared with 5.8 months (95% CI: 5.6, 6.7) in the Taxol/carboplatin arm, p = 0.214; $HR_{A/T}$ = 0.902 (95.1% CI: 0.767, 1.060). The primary analysis failed to demonstrated statistically significant superiority of PFS in the ABI/carboplatin arm compared with the Taxol/carboplatin arm, and the 0.5 months improvement in median PFS in favour of ABI-007/carboplatin is considered to be not clinically meaningful. The Clinical Overview (Module 2) included a non-protocol specified (but TGA requested) analysis of the difference in median PFS between the two treatment arms in the ITT population. This analysis showed that the 95% CI of the median difference in PFS between the two arms of 0.56 months was -0.34 to 1.46 months.

7.2.14.1.1.2. Non-inferiority analysis

The results for the non-inferiority analysis of PFS are summarized below in Table 13. For this non-inferiority PFS analysis, the censoring rules followed EMEA guidelines for using PFS as primary endpoint in confirmatory trials for registration. The non-inferiority analysis of PFS did not censor PFS events preceded by missing response evaluations or by initiation of new therapy. Consequently, the censoring rules in the non-inferiority analysis differ from those in the primary analysis where strict censoring rules were applied for missing response assessments and initiation of new therapy.

Table 13: Study CA031 - PFS determined by blinded radiology assessment – non-inferiority analysis; ITT population.

Variable	ABI-007/carboplatin (N=521)	Taxol/carboplatin (N=531)	Hazard Ratio ($HR_{A/T}$)
Number of Patients who Died or had Progression	429 (82%)	442 (83%)	
Median Progression-Free Survival (months)	6.8	6.5	0.949
95% Confidence Interval	5.7, 7.7	5.7, 6.9	0.830, 1.086
Time points			
Month 6			
Number of Patients at Risk	246	245	
KM Estimate (95% CI)	54% (49%, 58%)	52% (47%, 56%)	
Month 12			
Number of Patients at Risk	90	89	
KM Estimate (95% CI)	23% (19%, 27%)	22% (18%, 25%)	
Month 18			
Number of Patients at Risk	25	25	
KM Estimate (95% CI)	8% (6%, 11%)	8% (5%, 11%)	
Month 24			
Number of Patients at Risk	1	5	
KM Estimate (95% CI)	1% (0%, 4%)	3% (1%, 5%)	

Note: Missing observations or initiation of subsequent new therapy was not used to censor PFS event for this analysis.

Comment: In the PFS non-inferiority analysis, median PFS was 6.8 months (95% CI: 5.7, 7.7) in the ABI-007/carboplatin arm compared with 6.5 months (95% CI: 5.7, 6.9) in the Taxol/carboplatin arm; $HR_{A/T}$ = 0.949 (95% CI: 0.830, 1.086). Non-inferiority of ABI-007/carboplatin compared with Taxol/carboplatin for PFS was assessed based on the upper bound of the 95% CI of the $HR_{A/T}$. If the upper bound was less than 1.176, then non-inferiority was considered met. In the non-inferiority analysis, the upper bound of the 95% CI of the $HR_{A/T}$ (1.086) was less than 1.176 and consequently non-inferiority has been met (i.e., PFS in the ABI-007/carboplatin arm is non-inferior to the Taxol/carboplatin). The upper bound 95% CI for the superiority analysis where strict PFS censoring rules were applied was also less than 1.176.

7.2.14.1.2. Overall survival (OS)

The protocol (SAP) specified that formal superiority statistical testing of OS was to be undertaken only if PFS in the ABI-007/carboplatin arm was statistically significantly superior to PFS in the Taxol/carboplatin arm. Consequently, the results of the primary analysis of OS should be considered to be exploratory rather than confirmatory. The results of the OS analysis are summarized below in Table 14, the KM curves and the censoring data for the OS analysis were provided.

Table 14: Study CA031 – OS primary analysis; ITT population.

Variable	ABI-007/carboplatin (N=521)	Taxol/carboplatin (N=531)	Hazard Ratio ($HR_{A/T}$)	P-value
Number of Patient Deaths	360 (69%)	384 (72%)		
Median Survival (months)	12.1	11.2	0.922	0.271
Confidence Interval [1]	10.8, 12.9	10.3, 12.6	0.797, 1.066	

Note: Patients that did not die were censored at the last known time the patient was alive.
Note: P-value is based on a stratified log-rank test stratified by geographic region (North America/Australia, Eastern Europe, or Asia/Pacific) and histology of primary diagnosis (Squamous cell carcinoma or Non-squamous cell carcinoma).
[1] 95% confidence interval of median value and 95.1% confidence interval of hazard ratio.

Comment: The primary analysis of OS (formally considered to be exploratory rather than confirmatory) showed no statistically significant difference between the ABI-007/carboplatin and the Taxol/carboplatin arms. The median survival was 12.1 months (95% CI: 10.8, 12.9) in the ABI-007/carboplatin arm and 11.2 months (95%: 10.3, 12.6) months in the Taxol/carboplatin arm, p=0.271; $HR_{A/T}$ = 0.922 (95.1%CI: 0.797, 1.066). The absolute difference in OS of 0.9 months between the two treatment arms in favour of ABI-007/carboplatin is considered not to be clinically meaningful. The upper bound of the 95.1% CI was less than 1.176 and, consequently, it was concluded that ABI-007/carboplatin was non-inferior to Taxol/carboplatin. The CSR stated that recalculation of the 95% CI for OS was to be done only if the 95.1% CI was not sufficient to meet the non-inferiority criterion. Consequently, the results of the 95% CI of the $HR_{A/T}$ for the OS could not be identified in the CSR. However, data provided in the Clinical Overview (Module 2) indicates that the 95% CI of the $HR_{A/T}$ for the OS is identical to the 95.1% CI (i.e., $HR_{A/T}$ = 0.922 [95% CI: 0.797, 1.066]). The Clinical Overview (Module 2) also included a non-protocol specified (but TGA requested) analysis of the difference in median OS between the two treatment arms in the ITT population. This analysis showed that the 95% CI of the difference between the two treatment arms for OS of 0.89 months was -0.77 to 2.54 months.

7.2.14.2. Results for other secondary efficacy endpoints

ORR (investigator assessed): The percentage of patients with an ORR (confirmed complete or partial response) was 38% (95% CI: 34.2, 42.6) in the ABI-007/carboplatin arm and 30% (95% CI: 26.2, 34.0) in the Taxol/carboplatin arm; p=0.005, the response rate ratio (p_A/p_T) was 1.274 (95% CI: 1.076, 1.509). Of the 200 patients with an ORR in the ABI-007/carboplatin arm, complete response was reported in 2 patients and partial response in 198 patients. Of the 160 patients with an ORR in the Taxol/carboplatin arm, complete response was reported in 4 patients and partial response in 156 patients.

Discordance between the blinded radiology assessment and the investigator assessment of the best overall response was ≤ 25% for each of the response assessment categories (see Table 15, below). The percent discordance between PR and PD was low (2% and 1%), while the percent

discordance between PR and stable disease (9% and 4%) and between stable disease and PD (3% and 4%) were slightly higher.

Table 15: Study CA013 - Discordance of best overall response between blinded radiology assessment and investigator assessment; ITT population.

	Investigator Assessment					
Blinded Radiology Assessment (N=969)	Confirmed Complete Response	Confirmed Partial Response	Confirmed Stable Disease	Unconfirmed Response	Disease Progression	Unable to Evaluate
Confirmed Complete Response	0	1 (<1%)	0	0	0	0
Confirmed Partial Response	4 (<1%)	239 (25%)	43 (4%)	0	14 (1%)	1 (<1%)
Confirmed Stable Disease	2 (<1%)	92 (9%)	244 (25%)	2 (<1%)	41 (4%)	0
Unconfirmed Response	0	2 (<1%)	0	36 (4%)	63 (7%)	2 (<1%)
Disease Progression	0	19 (2%)	26 (3%)	6 (<1%)	119 (12%)	1 (<1%)
Unable to Evaluate	0	1 (<1%)	2 (<1%)	1 (<1%)	5 (<1%)	3 (<1%)

Note: In the ITT population, there are 83 patients with no post-baseline blinded radiology assessments.
Note: Analysis based on final response data (October 12, 2009 cut-off date).

PFS (investigator assessed): Median investigator assessed PFS was 5.5 months (95% CI: 5.1, 5.7) in the ABI-007/carboplatin arm compared with 5.4 months (95% CI = 5.1, 5.6 months) in the Taxol/carboplatin arm, p = 0.371, $HR_{A/T}$ = 0.939 (95% CI: 0.818, 1.078).

Disease control rate (secondary efficacy endpoint): Disease control rate was defined as the percentage of patients with stable disease for ≥ 16 weeks or confirmed complete or partial overall response. The disease control rate was comparable for patients in the ABI-007/carboplatin and Taxol/carboplatin arms (53% [274/521] vs 49% [260/531], respectively, p = 0.239; $p_Ap_{/T}$= 1.074 [95% CI = 0.953, 1.210]).

Duration of response (secondary efficacy endpoint): PFS (determined by blinded review) for patients with an objective response was presented as a measure of duration of response. The median duration of response (PFS) in patients with an objective response was similar in both arms; 9.6 months (95% CI: 8.3, 10.8) in the ABI-007/carboplatin arm compared with 9.5 months (95% CI: 8.1, 11.0) in the Taxol/carboplatin arm, p = 0.551 (stratified log-rank test). The $HR_{A/T}$ was 0.901 (95% CI: 0.652, 1.244).

7.2.14.3. Results for exploratory subgroup analyses based on stratification factors

Randomization was stratified based on disease stage (IIIb vs IV), age (< 70 vs > 70 years), gender (male vs female), histology (squamous cell carcinoma vs adenocarcinoma vs other histology), and geographic region (North America vs Australia/New Zealand vs Eastern Europe vs Asia/Pacific). The study included exploratory analyses of ORR, PFS, and OS in the stratification subgroups. The results for the stratification factor subgroup analyses are considered to be of clinical interest and have been summarized in a series of tables including: disease stage - ORR, PFS, and OS; age - ORR, PFS, and OS; histology - ORR, PFS, and OS; gender - ORR, PFS, and OS; and geographic regions - ORR, PFS, and OS. The results for the Australia/New Zealand region are not shown as no meaningful conclusions can be drawn due to the small total patient number (n=14).

In the stratification factor subgroup analyses, statistically significantly superior results in the ABI-007/carboplatin arm compared with the Taxol/carboplatin arm were observed for the following endpoints and subgroups: **ORR** - patients with stage IV disease; patients aged < 70 years; patients with squamous cell carcinoma; male patients; and patients from Eastern Europe; **OS** - patients aged ≥ 70 years; and patients from North America. There were no statistically significant differences between the two treatment arms in the stratification factor subgroup analyses of PFS.

7.2.14.4. Results for exploratory subgroup based on prognostic factors

7.2.14.4.1. ORR (blinded radiological assessment)

As pre-specified in the SAP, exploratory analyses were performed to assess the potential influence of the following prognostic factors on the primary efficacy endpoint of objective response: region (North America, Eastern Europe, Australia/New Zealand, or Asia/Pacific); gender (male or female); race (Asian, White, or Other; age (years); smoking status (patient never smoked, quit smoking, or currently smokes; baseline ECOG status (0, 1, or 2); time (years) from date of primary diagnosis to date of study entry; stage at primary diagnosis (I, II, IIIa, IIIb, or IV); histology at primary diagnosis (carcinoma/adenocarcinoma, squamous cell carcinoma, large cell carcinoma, or other); time (years) from date of first documented metastasis/relapse to date of study entry; stage at current diagnosis (IIIb or IV); and number of lesions (target + non-target). For each prognostic factor, the effect on objective response was tested using a logistic regression model with effects for treatment regimen, prognostic factor, and treatment regimen-by-prognostic factor interaction. If the interaction was significant then the nature of the interaction was evaluated.

Prognostic factors that showed a significant interaction (performed at the significance level of 0.100 [SAP]) with ORR (determined by the blinded radiology assessment) based on a logistic regression model are presented below in Table 16. Two factors showed an interaction with treatment effect on ORR: (1) time interval from date of primary diagnosis to date of study entry randomization; and (2) histology at primary diagnosis. There were no interactions for the following baseline factors: region, gender, race, age, smoking status, baseline ECOG status, stage at primary diagnosis, time from date of first documented metastasis/relapse to date of study entry, stage at current diagnosis, and number of lesions. The forest plot of all prognostic factors analyzed for ORR (blinded radiological assessment) was provided.

Table 16: Study CA031 – Effect of prognostic factors on ORR (blinded radiology assessment); ITT population.

Prognostic Factor Category/Statistic	ABI-007/ carboplatin (N=521)	Taxol/ carboplatin (N=531)	Interaction P-value
Time from Date of Primary Diagnosis to Date of Study Entry			0.092
< 1 month	109/347 (31%)	93/345 (27%)	
1-3 months	36/116 (31%)	26/118 (22%)	
≥ 3 months	25/58 (43%)	13/68 (19%)	
Histology at Primary Diagnosis			0.036
Carcinoma/Adenocarcinoma	66/254 (26%)	71/264 (27%)	
Squamous Cell Carcinoma	94/229 (41%)	54/221 (24%)	
Large Cell Carcinoma	3/9 (33%)	2/13 (15%)	
Other	7/29 (24%)	5/33 (15%)	
Histology at primary Diagnosis			0.010
Squamous Cell Carcinoma	94/229 (41%)	54/221 (24%)	
Non-squamous Cell Carcinoma	76/292 (26%)	78/310 (25%)	

P-value is based on a logistic regression model with effects for treatment regimen, prognostic factor, and treatment regimen-by- prognostic factor interaction. A non-significant interaction p-value (i.e., p-value ≥ 0.100) indicates the treatment regimen effect was consistent within a prognostic factor.

Comment: The two prognostic factors with a significant effect on the ORR assessed by blinded radiological review were time from date of primary diagnosis to date of study entry, and histology at primary diagnosis. The longer the time interval between the date of primary diagnosis and study entry, the greater the treatment effect in the ABI-

007/carboplatin arm compared with the Taxol/carboplatin arm as measured by ORR. Patients in the ABI-007/carboplatin arm with squamous cell carcinoma, large cell carcinoma, or other histologies had higher ORRs compared with patients in the Taxol/carboplatin arm, while patients in the two treatment arms with carcinoma/adenocarcinoma showed no difference in ORR. The ORR was notably higher in patients with squamous cell carcinoma in the ABI-007/carboplatin arm than in the Taxol/carboplatin arm, while the ORR was similar in patients with non-squamous carcinoma in both treatment arms.

7.2.14.4.2. PFS (blinded radiological assessment)

Prognostic factors (unplanned analysis) showing a significant interaction ($p<0.100$) with PFS (determined by the blinded radiology assessment) based on a Cox regression model were time from date of primary diagnosis to date of study entry (< 1 month; 1-3 months; and ≥ 3 months) and time from date of first documented metastasis/relapse to date of study entry (< 1 month; ≥ 1 month). For the factor of date of primary diagnosis to date of study entry, there was no difference between treatment arms in PFS for patients who entered the study at < 1 month, while patients in the ABI-007/carboplatin arm who entered the study at 1-3 months and ≥ 3 months had longer median PFS times than patients in the Taxol/carboplatin arm. For the factor of time from date of first documented metastasis/relapse to data of study entry, there was no difference between treatment arms in PFS for patients with times < 1 month, while patients in the ABI-007/carboplatin arm with times ≥ 1 month had longer median PFS times than patients in the Taxol/carboplatin arm.

Factors that did not show an interaction with the treatment effect on PFS were region, gender, race, age, smoking status, baseline ECOG performance status, stage at primary diagnosis, histology at primary diagnosis, stage at current diagnosis, and number of lesions. However, for the majority of prognostic factors, PFS hazard ratios favoured the ABI-007 treatment arm (see Section 18.2, Figure 13, page 142). With the exception of patients with < 1 month between primary diagnosis to study entry, primary Stage I or Stage II NSCLC, or with 3 or 4 lesions, all subgroups of patients in the ABI-007/carboplatin arm demonstrated a reduced risk of progression. No statistically significant differences in PFS (blinded radiological assessment) were observed between the two treatment arms for subgroups defined by demographic or baseline characteristics.

7.2.14.4.3. OS

Prognostic factors (unplanned analysis) showing a significant interaction with OS based on a Cox regression model were region (Asia/Pacific; Eastern Europe; North America), age (< 70 years; ≥ 70 years), and smoking status (never smoked; quit smoking; currently smokes). While patients enrolled in Asia/Pacific and Eastern Europe showed no difference in OS between treatment arms, patients enrolled in North America showed increased OS when treated with ABI-007/carboplatin vs Taxol/carboplatin. OS was similar for patients < 70 years of age in both treatment arms, while patients in the ABI-007/carboplatin arm ≥ 70 years of age showed increased OS compared with patients in the Taxol/carboplatin arm. Patients who had never smoked or who had quit smoking showed increased OS in the Taxol/carboplatin arm, while patients who currently smoked showed increased OS in the ABI-007/carboplatin arm.

Factors that did not show a significant interaction with the treatment effect on OS were gender, race, baseline ECOG status, time from date of primary diagnosis to date of study entry, stage at primary diagnosis, histology at primary diagnosis, time from date of first documented metastasis/relapse to date of study entry, stage at current diagnosis, and number of lesions. For the majority of prognostic factors, OS rates favoured the ABI-007 treatment arm. With the exception of patients enrolled in Eastern Europe, patients who never smoked or quit smoking, patients with Stage II or Stage IIIb NSCLC, patients with large cell histology, or patients with

"other histology", all patient subgroups showed a reduced risk of death in the ABI-007/carboplatin treatment arm.

7.3. Other efficacy studies

7.3.1. Study CA028 (primary supportive study)

7.3.1.1. Design

Study CA028 was nominated by the sponsor as the primary supportive study. The study was a Phase II, single-country (Russia), multi-centre (13 sites), open-label trial with escalating ABI-007 doses plus carboplatin (AUC = 6) in cohorts of 25 patients with advanced NSCLC. The first patient was enrolled on 15 March 2005 and the last completed on 1 June 2007, with the CSR final date being 30 July 2009. The study complied with all ethical requirements.

7.3.1.2. Objectives

The primary objectives were to obtain preliminary data on the antitumour activity and adverse events (AEs) of ABI 007 in combination with carboplatin (AUC=6) in patients with advanced NSCLC. The secondary objectives were to evaluate the percentage of patients with stable disease (SD) for ≥ 16 weeks, or complete or partial overall response (i.e., total response); progression-free survival (PFS); duration of response; and patient survival.

7.3.1.3. Inclusion and exclusion criteria

The study included patients aged ≥ 18 years with histologically or cytologically confirmed NSCLC stage IIIB with pleural effusion or evidence of inoperable local recurrence or metastasis (stage IV). Patients were also required to have measurable disease (defined by the presence of at least 1 measurable lesion). In addition, patients were expected to survive more than 12 weeks and have ECOG performance status 0 or 1. The inclusion and exclusion criteria have been examined and are considered to be consistent with those for the pivotal Phase III study (CA031), as were the criteria for removing patients from the study.

7.3.1.4. Study treatments

Patients were enrolled in 7 escalating ABI-007 dose cohorts of 25 patients. ABI-007 was given IV over approximately 30 minutes without steroid premedication and without G-CSF prophylaxis every 3 weeks [q3w] at doses of 225, 260, 300, and 340 mg/m^2 for cohorts 1 to 4, on Days 1 and 8 of a 21-day cycle (q2/3w) at a dose of 140 mg/m^2 for cohort 5, and on Days 1, 8, and 15 of a 21-day cycle (weekly) at doses of 100 or 125 mg/m^2 for cohorts 6 and 7. In addition, the study included an extension phase in 76 patients treated with an ABI-007 dose of 340 mg/m^2 every 3 weeks (cohort 8). Carboplatin (AUC=6) was administered on Day 1 of the 21-day cycle for all cohorts. Patients continued receiving treatment in the absence of disease progression or unacceptable toxicity.

7.3.1.5. Efficacy endpoints

The **primary efficacy endpoint** was the percentage of patients who achieved an objective confirmed complete or partial overall response based on RECIST (Version 1.0) response criteria.

The **secondary efficacy endpoints** were percentage of patients with stable disease (SD) for ≥ 16 weeks, or complete or partial overall response (i.e., total response); progression-free survival; duration of response; and patient survival.

7.3.1.6. Statistical methods

The "enrolled population" consisted of all enrolled patients even if they were not treated or had no treatment evaluations, and the "treated population" consisted of enrolled patients that received at least one dose of study drug. All analyses, unless noted otherwise, were performed on the treated population.

There were no planned formal interim analyses. Accrual to the next dose level occurred in the absence of unexpected SAEs. No statistical comparisons of dose levels were planned, although the clinical relevance of differences between dose levels was assessed. The day of the first dose of study drug was defined as Day 1. Baseline value was defined as the last value before the first dose of study drug. Final Evaluation was defined as the last on-treatment value.

The ORR was summarized by the number and percentage of patients with confirmed complete or partial response, and the 95% CI. The number and percentage of patients with SD for ≥16 weeks, or confirmed complete or partial overall response was presented. TTP and PFS were analyzed using Kaplan-Meier methods as was patient survival. Patients alive at the end of follow-up were censored at the last known time that the patient was alive. Patient survival was summarized by sample size, number of deaths, median survival time, and 95% CI of the median survival time.

There were no formal sample size calculations. However, based on an assumed ORR of 20% and a sample size of 25 patients (or 100 patients in the case of the optimal q3w dosing regimen), the 95% CI for the ORR was estimated to be 4% to 36% (or 12% to 28% for a sample size of 100 patients).

7.3.1.7. Patient disposition

The study enrolled 254 patients, 251 (99%) received treatment and 227 (90%) had a least one response assessment. There are no ongoing patients in the study.

In the 251 patients who received treatment, the mean age was 60 years (range: 34, 81) and 63% (n=159) of patients were < 65 years of age. A total of 202 patients (80%) were male and 49 patients (20%) were female. Nearly all patients (n=250) were "White, non-Hispanic, non-Latino" with the remaining patient (n=1) being "White, Hispanic, or Latino". ECOG Performance Status was 0 (fully active) in 38 patients (15%) and 1 (restrictive but ambulatory) in 213 patients (85%). A total of 11 (4%) patients had Grade 1 pre-existing peripheral neuropathy, and all other 240 (96%) patients had Grade 0 pre-existing neuropathy. No important differences across individual cohorts were noted in patient demographics. Prior chemotherapy had been administered to a total of 5 (2%) patients in the treated population, with 2 (<1%) patients having received prior neoadjuvant therapy and 3 (1%) patients having received prior adjuvant therapy. No patients had received prior therapy for metastatic disease.

Of the 227 (90%) patients who had at least one response assessment, 155 (88%) were in the q3w groups and 72 (96%) were in the weekly groups. Progressive disease (without unacceptable toxicity) was the most common reason for therapy discontinuation and occurred in 43% (n=107/251) of patients. There were 25 patients only in the cohort treated with the proposed dose of ABI-007 (100 mg/m^2 on Days 1, 8, and 15 of a 21-day cycle) combined with carboplatin (AUC=6) Day 1 of each 21-day cycle. There were no major protocol violations during the study.

7.3.1.8. Efficacy results

ORR (investigator assessment): The ORR in the ABI-007 100 mg/m^2 weekly regimen (n=25) was 48.0% (95% CI: 28.4, 67.6), and the 12 patients with an ORR included 1 (4%) with a complete response and 11 (44%) with a partial response. The response rate ranged from 24% in the 260 and 300 mg/m^2 q3w groups (n = 25 each) to 56% in the 140 mg/m^2 q2/3w group (n = 25). There was no apparent direct dose proportional relationship observed in ORR across the q3w or weekly cohorts in terms of ABI-007 dose. Results are summarized below in Table 17.

Table 17: Study CA028 – ORR (investigator assessment) by dose cohort.

	225 mg/m² q3w (C1; n = 25)	260 mg/m² q3w (C2; n = 25)	300 mg/m² q3w (C3; n = 25)	340 mg/m² q3w (C4; n = 25)[a]	140 mg/m² q2/3w (C5; n = 25)	100 mg/m² weekly (C6; n = 25)	125 mg/m² weekly (C7; n = 25)	340 mg/m² q3w (C4 + C8; n = 101)[b]
Complete Response	0	1 (4%)	0	0	0	1 (4%)	1 (4%)	1 (<1%)
Partial Response	10 (40%)	5 (20%)	6 (24%)	8 (32%)	14 (56%)	11 (44%)	8 (32%)	32 (32%)
Patients with Confirmed Complete or Partial Overall Response	10 (40.0%)	6 (24.0%)	6 (24.0%)	8 (32.0%)	14 (56.0%)	12 (48.0%)	9 (36.0%)	33 (32.7%)
95% Confidence Interval	20.80 – 59.20	7.26 – 40.74	7.26 – 40.74	13.71 – 50.29	36.54 – 75.46	28.42 – 67.58	17.18 – 54.82	23.53 – 41.82

a Includes patients treated at 340 mg/m² q3w during dose escalation phase of the study.
b Includes all patients treated at 340 mg/m² q3w.

PFS (investigator assessed): The median PFS in the ABI-007 100 mg/m² weekly cohort (n=25) was 6.2 months (95% CI: 4.2, 9.7). The median PFS ranged from 4.8 months in the 340 mg/m² q3w cohort to 6.9 months in the 225 mg/m² q3w cohort. There was no apparent direct dose proportional relationship observed in PFS across the q3w or weekly cohorts in terms of ABI-007 dose. Results are summarized below in Table 18.

Table 18: Study CA028 – PFS (investigator assessment) by dose cohort.

	225 mg/m² q3w (C1; n = 25)	260 mg/m² q3w (C2; n = 25)	300 mg/m² q3w (C3; n = 25)	340 mg/m² q3w (C4; n = 25)[a]	140 mg/m² q2/3w (C5; n = 25)	100 mg/m² weekly (C6; n = 25)	125 mg/m² weekly (C7; n = 25)	340 mg/m² q3w (C4 + C8; n = 101)[b]
Number of Patients who Died or had Progression	20 (80%)	19 (76%)	20 (80%)	20 (80%)	21 (84%)	18 (72%)	17 (68%)	73 (72%)
Median Progression-Free Survival (months)	6.9	6.5	5.3	4.8	5.6	6.2	6.4	6.2
95% Confidence Interval	4.2 – 9.6	4.3 – 9.1	2.2 – 8.5	3.9 – 7.8	3.9 – 7.7	4.2 – 9.7	4.2 – 7.9	5.1 – 7.8

a Includes patients treated at 340 mg/m² q3w during dose escalation phase of the study.
b Includes all patients treated at 340 mg/m² q3w.

OS: The median OS in the ABI-007 100 mg/m² weekly cohort (n=25) was 11.3 months (95% CI: 7.8, >20.1). The median OS ranged from 8.3 months in the 300 mg/m² cohort to 15.0 months in the 125 mg/m² weekly cohort. There were no marked differences in median OS across the dose cohorts. Results are summarized below in Table 19.

Table 19: Study CA028 – PFS (investigator assessment) by dose cohort.

	225 mg/m² q3w (C1; n = 25)	260 mg/m² q3w (C2; n = 25)	300 mg/m² q3w (C3; n = 25)	340 mg/m² q3w (C4; n = 25)[a]	140 mg/m² q2/3w (C5; n = 25)	100 mg/m² weekly (C6; n = 25)	125 mg/m² weekly (C7; n = 25)	340 mg/m² q3w (C4 + C8; n = 101)[b]
Number of Patient Deaths	20 (80%)	18 (72%)	20 (80%)	19 (76%)	20 (80%)	17 (68%)	13 (52%)	52 (51%)
Median Survival (months)	10.7	12.2	8.3	14.6	12.0	11.3	15.0	13.8
95% Confidence Interval	8.7 – 17.0	8.5 – 21.9	4.2 – 15.4	7.6 – 17.2	6.5 – 17.1	7.8 – >20.1	10.0 – >18.4	11.9 – 16.1

a Includes patients treated at 340 mg/m² q3w during dose escalation phase of the study.
b Includes all patients treated at 340 mg/m² q3w.

7.3.2. Studies CA015 and CA018

7.3.2.1. Study CA015

Study CA015 was a Phase I/II single-centre (USA), open-label study of AB1-007 administered weekly in chemotherapy naïve patients with advanced NSCLC. The primary objectives of this study were to determine the maximum tolerated dose (MTD) and dose limiting toxicity (DLT) of weekly ABI-007 treatment in patients with advanced stage IV non-small cell lung cancer (NSCLC), to determine anti-tumour activity of ABI-007, and to evaluate the safety/tolerability of

ABI-007 in this patient population. The secondary objectives of this study were to evaluate time to disease progression, response to ABI-007 and survival in patients with NSCLC.

Three doses of ABI-007 (100, 125 and 150 mg/m^2) were evaluated and the MTD was determined to be 125 mg/m^2. The primary efficacy analysis was based on the percentage of patients in the Treated Population who achieved an objective confirmed complete response (CR) or partial response (PR) overall as defined using the RECIST guidelines. Secondary efficacy endpoints included percentage of patients with SD for ≥ 16 weeks, or complete or partial overall response (disease control rate or total response); time to disease progression; duration of response; and patient survival.

Of the 75 treated patients, 35 experienced complete response (CR), partial response (PR) or stable disease (SD). The ORRs ranged from 14.3% to 33.3%, the disease control rate (i.e., SD ≥ 16 weeks, or confirmed CR or PR) ranged from 14.3% to 66.7%, and the median time to death ranged from 10.6 to 18.3 months. The study included only 3 patients who received ABI-007 100 mg/m^2, and no patients in the study received ABI-007 in combination with carboplatin. Of the 3 patients treated with ABI-007, 1 patient experienced a partial response, 2 patients experienced disease control, median PFS was 11.8 months, and the median time to death was 18.3 months. Overall, as only three patients in this study were administered ANI-007 alone it is considered that the study provides no meaningful efficacy data supporting the proposed treatment regimen.

7.3.2.2. Study CA018

This was a Phase II, single-country (Russia), multi-centre (7 sites), non-randomized, uncontrolled, open-label study designed to evaluate the safety and anti-tumour activity of single-agent ABI-007 260 mg/m^2 administered IV every three weeks to patients with NSCLC. This study is considered to provide not supportive data as the treatment regimen in this study was markedly different from that being proposed.

7.4. Analyses performed across trials (pooled analyses and meta-analyses)

There were no pooled analyses or meta-analyses.

7.5. Evaluator's conclusions on clinical efficacy for advanced NSCLC

7.5.1. Pivotal Phase III study (CA031)

In the pivotal Phase III study (CA031), the primary efficacy endpoint was the ORR including patients who achieved a confirmed CR or PR based on blinded radiological assessment using RECIST guidelines. In this study, all efficacy evaluations were based on the ITT population (n=1052), including 521 patients in ABI-007 arm and 531 patients in the Taxol/carboplatin arm. The ORR in patients with advanced NSCLC was statistically significantly higher in the ABI-007/carboplatin arm (33% [95% CI: 28.6, 36.7]) than in the Taxol/carboplatin arm (25% [95% CI: 21.2, 28.5]), p=0.005; p_A/p_T = 1.313 (95.1% CI: 1.082, 1.593). However, the clinical significance of the absolute difference between the two treatment arms of 8% in favour of ABI-007/carboplatin is unlikely to be clinically meaningful in the absence of statistically significant differences between the two arms in the clinical benefit outcomes of PFS and OS.

The primary superiority analysis of the first key secondary efficacy endpoint of PFS (blinded radiological assessment) showed that the difference between median PFS duration in the two treatment arms was not statistically significant: 6.3 months in the ABI-007/carboplatin arm and 5.8 months in the Taxol/carboplatin arm, p=0.214; $HR_{A/T}$ = 0.902 (95.1% CI: 0.767, 1.060). The primary superiority analysis of the second key secondary efficacy endpoint of OS also showed no statistically significant difference in median survival time between the two treatment arms: 12.1 months in the ABI-007/carboplatin arm and 11.2 months in the Taxol/carboplatin arm,

p=0.271; $HR_{A/T}$ = 0.922 (95.1% CI: 0.797, 1.066). However, this analysis is considered to be exploratory rather than confirmatory as the protocol specified that superiority testing of OS should proceed only if initial superiority testing of PFS had demonstrated a statistically significant result in favour of the ABI-007/carboplatin arm relative to the Taxol/carboplatin arm.

The non-inferiority analysis of PFS and OS showed that the ABI-007/carboplatin arm was non-inferior to the Taxol/carboplatin for both parameters. In the PFS (blinded radiological assessment) non-inferiority analysis, median PFS was 6.8 months in the ABI-007/carboplatin arm and 6.5 months in the Taxol/carboplatin arm; $HR_{A/T}$ = 0.949 (95% CI: 0.830, 1.086). In the OS non-inferiority analysis, median OS was 12.1 months in the ABI-007/carboplatin arm and 11.2 months in the Taxol/carboplatin arm; $HR_{A/T}$ = 0.922 (95% CI: 0.797, 1.066). In the non-inferiority analyses of both the PFS and the OS, the upper bound of the 95% CI of the $HR_{A/T}$ was less than the pre-specified non-inferiority margin of 1.176 (i.e., non-inferiority margin of 15%).

The results for the secondary efficacy endpoints of investigator assessed ORR and PFS were consistent with the primary analysis of these endpoint based on blinded assessment. In addition, there was no statistically significant difference between the two treatment arms as regards the secondary efficacy endpoints of disease control rate and duration of response.

The planned exploratory analysis of the effect of baseline stratification factors on the ORR (blinded radiological assessment) showed that the ORR was statistically significantly higher in the ABI-007/carboplatin arm compared with the Taxol/carboplatin arm in patients with squamous cell carcinoma (41% vs 24%, p < 0.001), patients with stage IV disease (31% vs 23%, p=0.015), male patients (33% vs 24%, p=0.011), patients aged < 70 years (32% vs 25%, p=0.013), and patients from Eastern Europe (34% vs 27%, p=0.014). The planned exploratory analysis of the effect of baseline stratification factors on OS showed that median survival was longer in the ABI-007/carboplatin arm compared with the Taxol/carboplatin in North American patients (12.7 vs 9.8 months, p=0.008; $HR_{A/T}$ = 0.622 [95% CI: 0.436, 0.866]), and patients aged ≥ 70 years (19.9 vs 10.4 months, p=0.009; HRA/T = 0.583 [95% CI: 0.388, 0.975]). The planned exploratory analysis of the effect of baseline stratification factors on PFS (blinded radiological assessment) showed no statistically significant difference between the two treatment arms for any of the factors.

Overall, the exploratory analyses of the effect of baseline stratification factors (planned) and other baseline prognostic factors (unplanned) on ORR, PFS and OS showed consistent benefits for patients in the ABI-007/carboplatin arm compared with the Taxol/carboplatin arm.

7.5.2. Phase I/II studies nominated by the sponsor as supportive (CA028, CA015, CA018)

The sponsor nominated the Phase II study CA028 as the "primary supportive" efficacy study. However, this preliminary, single-country (Russia), multi-site, non-randomized, open-label, single-arm, dose escalation study in patients with advanced NSCLC is considered to provide only limited supportive efficacy data. The study included one cohort of 25 patients treated with the proposed ABI-007/carboplatin treatment regimen. The key efficacy results for this regimen were ORR (investigator assessed RECIST) 48.0% (95% CI: 28.4, 67.58), PFS (investigator assessed RECIST) 6.2 months (95% CI: 4.2, 9.7), and OS 11.3 months (95% CI: 7.8, > 20.1). The ORR (investigator assessed) in the supportive Phase II study for the proposed ABI-007/carboplatin treatment regimen was greater than the comparable endpoint from the pivotal Phase III study (48% vs 38%), while median PFS (investigator assessed) values for the two studies were 6.3 and 5.5 months, respectively, and median OS values were 11.3 and 12.1 months, respectively. However, in the absence of a comparator arm in the Phase II study (CA028), it is difficult to interpret the clinical relevance of the ORR, PFS and OS results from this study.

The sponsor nominated the Phase I/II study CA015 as supportive. However, this single-site (USA), non-randomized, uncontrolled, open-label, dose-escalating study in patients with advanced NSCLC included only three patients treated with single-agent ABI-007 100 mg/m^2. Consequently, this study is considered to provide no meaningful clinical data on the ABI-007/carboplatin combination proposed for registration for the treatment of advanced NSCLC.

The sponsor nominated the Phase II study CA018 as supportive. However, this single-country (Russia), multi-centre (7 sites), non-randomized, uncontrolled, open-label study in patients with advanced NSCLC did not investigate the ABI-007/carboplatin combination proposed for registration. The study investigated single-agent ABI-007 260 mg/m^2 administered once every three weeks to 43 treated patients. This regimen is markedly different from that being proposed. Consequently, this study is considered to provide no meaningful clinical data on the ABI-007/carboplatin combination proposed for registration for the treatment of advanced NSCLC.

8. Clinical safety

8.1. Studies providing evaluable safety data

The submission included safety data from four studies in patients with advanced NSCLC (CA031, CA028, CA015, and CA018). The number of patients exposed to ABI-007 by dosing regimen, dose and study for the treatment of NSCLC is summarized below in Table 20.

Table 20: Summary of patients with NSCLC exposed to ABI-007.

Regimen	Number of Patients Exposed										
	ABI-007 Weekly (mg/m^2)					ABI-007 Every 3 Week (mg/m^2)					ABI-007 Weekly or Every 3 Weeks (mg/m^2)
Dose	**100**	**125**	**140**	**150**	**All**	**225**	**260**	**300**	**340**	**All**	**All**
ABI-007/carboplatin therapy											
Phase 3, CA031	514	-	-	-	**514**	-	-	-	-	-	514
Phase 2, CA028	25	25	25	-	**75**	25	25	25	101	**176**	251
Total	539	25	25	-	**589**	25	25	25	101	**176**	**765**
ABI-007 Monotherapy											
Phase 2, CA015	3	65	-	7	**75**	-	-	-	-	-	75
Phase 2, CA018	-	-	-	-	-	-	43	-	-	**43**	43
Total	3	65	-	7	**75**	0	43	-	-	**43**	**118**

The submission included a total of 539 patients exposed to ABI-007/carboplatin at the proposed dosage regimen (514 from the pivotal study [CA031] and 25 from the sponsor nominated key supportive study [CA028]). The pivotal safety data is derived from study CA031. This study includes safety data on 514 patients with advanced NSCLC treated with ABI-007/carboplatin at the proposed dosage regimen and 524 patients treated with Taxol/carboplatin. The evaluation of the safety data for the proposed combination focuses on the pivotal Phase III study (CA031).

8.1.1. Pivotal study CA031

8.1.1.1. Introductory comments

Adverse events (AEs) were recorded on the case report form (CRF) by the investigator using the verbatim term that best described the event. Grading of severity was based on the NCI CTCAE

(V3.0), and the secondary objectives of the pivotal study included comparison of the frequencies of toxicities between the two treatment arms using this grading system. However, all AEs were also coded to a MedDRA term (SOC, preferred term) by the sponsor, and all MedDRA (lower level) terms were mapped into the appropriate NCI CTCAE term. It is noted that the safety data in the proposed Abraxane PI focuses on AEs classified by the MedDRA system, as does the review of safety in the sponsor's Clinical Overview (Module 2.5). In this CER, the description of AEs focuses primarily on events described by MedDRA (SOC, preferred terms) terminology, with descriptions of adverse events classified by NCI CTCAE terminology being provided where considered relevant.

Adverse events/toxicities were summarized as either treatment-emergent or treatment-related. The definition of a treatment-related adverse event was any adverse event that began or worsened in grade after the start of study drug through 30 days after the last dose of study drug or end of study (EOS), whichever was later. A treatment-related adverse event was one considered by the investigator to be possibly, probably or definitely related to study drug. Statistical testing of treatment regimen differences was performed using Fisher's exact test for all toxicities/AEs and the CMH test for all toxicities/AEs by intensity.

8.2. Exposure

A total of 1038 patients received at least 1 dose of study drug and were included in the "treated population". The median number of treatment cycles was 6 in both treatment arms. The median number of ABI-007 doses was 2.5 times higher than the median number of Taxol doses due to the different administration regimens for the taxanes (15 vs 6 doses, respectively), while the median number of carboplatin doses was the same in both treatment arms (6 doses in both arms). Exposure in the two treatment arms is summarized below in Table 21. All patients in both treatment arms received 1 cycle; 4 cycles were received by 75% of patients in the ABI-007/carboplatin arm and 73% of patients in the Taxol/carboplatin arm; and 6 cycles were received by 52% and 54% of patients in the two treatment arms respectively.

Table 21: Study CA031 – Number of cycles and study drug administered; treated population.

Variable Category / Statistic	ABI-007/ carboplatin (N=514)	Taxol/ carboplatin (N=524)
Number of Cycles Administered		
Mean (SD)	6.3 (4.57)	6.1 (4.30)
Median (Min, Max)	6.0 (1, 31)	6.0 (1, 30)
Number of Taxane Doses Administered		
Mean (SD)	17.3 (13.03)	6.1 (4.30)
Median (Min, Max)	15.0 (1, 85)	6.0 (1, 30)
Number of Carboplatin Doses Administered		
Mean (SD)	6.2 (4.40)	6.1 (4.26)
Median (Min, Max)	6.0 (1, 28)	6.0 (1, 30)

Note: Patients with multiple dose modifications can be in more than one category.
Note: Cycle length is defined as time between Day 1 of two sequential cycles.

The median cumulative taxane dose and the median average taxane dose intensity were higher in the ABI-007/carboplatin arm (1325.0 mg/m^2 and 81.98 mg/m^2/week, respectively) relative to the Taxol/carboplatin arm (1125.0 mg/m^2 and 65.12 mg/m^2/week, respectively). The percentage of the protocol specified dose administered and proportion of patients receiving ≥ 90% of the protocol specified taxane dose was lower in the ABI-007/carboplatin treatment arm (81.98% and 34%, respectively) relative to the Taxol/carboplatin treatment arm (97.67% and 73%, respectively).

The median cumulative dose and the median average carboplatin dose intensity were lower in the ABI-007/carboplatin treatment arm (3140.5 mg and 166.14 mg/week, respectively) relative to the Taxol/carboplatin treatment arm (3315.0 mg and 203.61 mg/week, respectively). The median percentage of the protocol specified carboplatin dose administered was comparable in the ABI-007/carboplatin and the Taxol/carboplatin arms (99.77% and 100.00%, respectively), but the percentage of patients with ≥ 90% protocol specified dose was lower in the ABI-007/carboplatin arm (65%) relative to Taxol/carboplatin arm (87%).

8.2.1. Dose modifications

8.2.1.1. Dose reductions and interruptions

The proportion of patients who experienced reduction of the taxane or carboplatin dose was higher in the ABI-007/carboplatin arm (46% for both components) than in the Taxol/carboplatin arm (23% for both components). The majority of patients in the ABI-007/carboplatin and the Taxol/carboplatin arms had 1 dose reduction (58% vs 69%, respectively), while 2 dose reductions were reported in 42% of patients in both arms and no patients in either treatment arm had more than 2 dose reductions. Dose interruptions of the taxane and carboplatin components of both treatment arms were infrequent (< 1% of patients). Dose reductions and dose interruptions in the two treatment arms were summarized.

The greater incidence of taxane dose reductions in patients in the ABI-007/carboplatin arm (43%) compared with the Taxol/carboplatin arm (23%) were most likely due to the once weekly ABI-007/carboplatin dosing schedule in the ABI/carboplatin arm compared with the once every three weeks Taxol dosing schedule in the Taxol/carboplatin arm. The difference in the dosing schedule between the two treatment arms provided for greater opportunities of protocol-specified taxane dose reductions due to haematological and/or non-haematological toxicities. In the ABI-007/carboplatin arm, taxane dose reductions occurred notably more frequently (≥ 2%) than in the Taxol/carboplatin arm due to neutropenia (24% vs 9%), thrombocytopaenia (13% vs 4%), anaemia (6% vs < 1%), and neutrophil count decreased (4% vs 1%). In the Taxol/carboplatin arm, taxane dose reductions occurred notably more frequently (≥ 2%) than in the ABI-007/carboplatin arm due to peripheral sensory neuropathy (5% vs <1%).

8.2.1.2. Dose delays/doses not given

The proportion of patients with taxane dose delays/doses not given was higher in the ABI-007/carboplatin arm than in the Taxol/carboplatin arm (82% vs 54%, respectively), as was proportion of patients with carboplatin dose delays/doses not given (72% vs 54% respectively). Dose delays/doses not given due to AE/toxicity related to the taxane component of the combination occurred more frequently in the ABI-007/carboplatin arm than in the Taxol/carboplatin arm (87% vs 75%, respectively), and for the carboplatin component (88% vs 76%, respectively). In the ABI-007/carboplatin arm, taxane dose delays occurred notably more frequently (≥ 2% more patients) than in the Taxol/carboplatin arm due to neutropenia (41% vs 12%), thrombocytopenia (30% vs 12%), anaemia (16% vs 1%), leucopenia (6% vs 1%), neutrophil count decreased (8% vs 2%), platelet count decreased (4% vs 2%), ALT increased (4% vs 2%), pneumonia (3% vs 1%), and fatigue (3% vs < 1%). In the Taxol/carboplatin arm, taxane dose delays occurred notably more frequently (≥ 2% more patients) than in the ABI-007/carboplatin arm due to peripheral sensory neuropathy (5% vs 1%).

8.3. Adverse events

8.3.1. Overview

Most patients in both treatment arms experienced at least 1 TEAE. In general, the percentage of patients who experienced AEs was comparable in the ABI-007/carboplatin and Taxol/carboplatin arms for most event categories (see Table 22, below). The main differences

between the two treatment arms was the higher proportion of patients in the ABI-007/carboplatin arm compared with the Taxol/carboplatin arm with at least 1 AE resulting in the taxane dose being delayed (71% vs 41%), and patients with at least 1 AE resulting in the taxane dose being reduced (46% vs 23%, respectively).

Table 22: Study CA031 – Overview of all treatment-emergent adverse events; treated population.

Category	ABI-007/ carboplatin (N=514)	Taxol/ carboplatin (N=524)
	n (%)	n (%)
Patients with at least 1 AE	483 (94%)	504 (96%)
Patients with at least 1 AE after 6 cycles of therapy	143 (28%)	143 (27%)
Patients with at least 1 grade 3 or higher AE	360 (70%)	355 (68%)
Patients with at least 1 treatment-related AE	469 (91%)	481 (92%)
Patients with at least 1 treatment-related grade 3 or higher AE	321 (62%)	315 (60%)
Patients with at least 1 serious AE	93 (18%)	80 (15%)
Patients with at least 1 treatment-related serious AE	37 (7%)	30 (6%)
Patients with at least 1 AE with action of taxane permanently discontinued	80 (16%)	84 (16%)
Patients with at least 1 AE with action of taxane dosage reduced	237 (46%)	120 (23%)
Patients with at least 1 AE with action of taxane interrupted	0	5 (<1%)
Patients with at least 1 AE with action of taxane delayed	365 (71%)	214 (41%)

8.3.1.1. TEAEs reported in ≥ 10% of patients in either treatment arm

TEAEs reported in ≥ 10% of patients in either treatment arm were summarized. TEAEs reported in ≥ 30% of patients in at least one of the two treatment arms (ABI-007/carboplatin vs Taxol/carboplatin) were alopecia (56% vs 60%), neutropenia (51% vs 48%), anaemia (44% vs 21%), thrombocytopenia (40% vs 23%) and peripheral sensory neuropathy (26% vs 40%).

TEAEs reported statistically significantly more frequently in patients in the ABI-007/carboplatin (vs patients in the Taxol/carboplatin arm) were anaemia (44% vs 21%, p<0.001), thrombocytopenia (40% vs 23%, p<0.001), peripheral oedema (10% vs 4%, p<0.001), epistaxis (7% vs 2%, p<0.001), haemoglobin decreased (11% vs 6%, p=0.015), upper abdominal pain (3% vs 1%, p=0.039), nail disorder (2% vs <1%, p=0.002), and haemorrhoids (2% vs <1%, p=0.020).

TEAEs reported statistically significantly more frequently in patients in the Taxol/carboplatin arm (vs patients in the ABI-007/carboplatin arm) were peripheral sensory neuropathy (40% vs 26%, p<0.001), arthralgia (25% vs 13%, p<0.001), myalgia (19% vs 10%, p < 0.001), and pruritus (4% vs 2%, p=0.050).

8.3.1.2. Grade 3 or higher TEAEs

Grade 3 or higher TEAEs reported in ≥ 5% of patients in either treatment arm are summarized below in Table 23. The proportion of patients with at least one grade 3 or higher TEAE was similar in the ABI-007/carboplatin and Taxol/carboplatin arms (70% vs 68%, respectively).

TEAEs (grade 3 or higher) reported statistically significantly more commonly in patients in the ABI-007/carboplatin arm compared with the Taxol/carboplatin arm were anaemia (25% vs 6%, p<0.001), thrombocytopenia (17% vs 6%, p<0.001), haemoglobin decreased (4% vs < 1%, p=0.006), ALT increased (2% vs < 1%, p=0.032), and platelet count decreased (2% vs < 1%, p=0.020).

TEAEs (grade 3 or higher) reported statistically significantly more commonly in patients in the Taxol/carboplatin arm compared with the ABI-007/carboplatin arm were peripheral

neuropathy (5% vs 2%, p=0.018), peripheral sensory neuropathy (7% vs < 1%, p<0.001), arthralgia (2% vs < 1%, p=0.021), and myalgia (2% vs < 1%, p=0.011).

Table 23: Study CA031 – TEAE grade 3 or higher reported in at least 5% of patients in either treatment arm; treated population.

System Organ Class / Preferred Term	ABI-007/ carboplatin (N=514) n (%)	Taxol/ carboplatin (N=524) n (%)	p-value [a]
Patients with at least 1 grade 3 or higher AE	360 (70%)	355 (68%)	0.461
Patients with an AE by MedDRA (Version 12.1) System Organ Class and Preferred Term			
Blood and lymphatic system disorders	274 (53%)	245 (47%)	0.040*
Neutropenia	185 (36%)	212 (40%)	0.142
Anaemia	127 (25%)	32 (6%)	<0.001*
Thrombocytopenia	87 (17%)	34 (6%)	<0.001*
Leukopenia	44 (9%)	44 (8%)	>0.999
Investigations	75 (15%)	74 (14%)	0.860
Neutrophil count decreased	36 (7%)	50 (10%)	0.145
White blood cell count decreased	30 (6%)	28 (5%)	0.788
Nervous system disorders	37 (7%)	68 (13%)	0.002*
Neuropathy peripheral	11 (2%)	26 (5%)	0.018*
Peripheral sensory neuropathy	5 (<1%)	38 (7%)	<0.001*

a P-values are based on a Fisher's exact test.
* Indicates statistically significant p-values.
Events are ordered by decreasing system organ class incidence in the ABI-007/carboplatin arm.

8.3.1.3. Treatment-related TEAEs

Treatment-related TEAEs in at least 5% of patients in either treatment arm.

The proportion of patients with at least one treatment-related TEAE was similar in the ABI-007/carboplatin and Taxol/carboplatin arms (91% vs 92%, respectively) for treatment-related TEAEs reported in at least 5% of patients in either arm. Treatment related AEs reported in ≥ 30% of patients in either treatment arm (ABI-007/carboplatin vs Taxol/carboplatin) were alopecia (56% vs 60%), neutropenia (51% vs 48%), thrombocytopenia (40% vs 23%), anaemia (39% vs 19%), and peripheral sensory neuropathy (26% vs 40%).

Treatment-related TEAES occurring statistically significantly more frequently in the ABI-007/carboplatin arm than in the Taxol/carboplatin arm were thrombocytopenia (40% vs 23%, p<0.001), anaemia (39% vs 19%, p<0.001), haemoglobin decreased (11% vs 6%, p=0.019), peripheral oedema (5% vs 2%, p=0.014), and epistaxis (6% vs <1%, p<0.001). Treatment-related TEAES occurring statistically significantly more frequently in the Taxol/carboplatin arm than in the ABI-007/carboplatin arm were peripheral sensory neuropathy (40% vs 26%, p<0.001), arthralgia (24% vs 12%, p<0.001), myalgia (18% vs 9%, p<0.001), pain in extremity (4% vs 1%, p<0.001), and chest pain (2% vs <1%, p<0.001).

8.3.1.4. Grade 3 or higher treatment-related TEAEs

The majority of treatment-related TEAEs in both treatment arms were grade 3 or higher events (62%, ABI-007/carboplatin vs 60%, Taxol/carboplatin). The proportion of patients with grade 1, 2, 3, 4, and 5 treatment-related TEAEs in the ABI-007/carboplatin arm compared with the Taxol/carboplatin arm was: Grade 1 (7%, n=36 vs 7%, n=39); Grade 2 (22%, n=112 vs 24%, n=127); Grade 3 (42%, n=218 vs 33%, n=175); Grade 4 (20%, n=102 vs 27%, n=139); Grade 5 (<1%, n=1 vs <1%, n=1).

Grade 3 or higher treatment-related TEAEs reported in at least 5% of patients in either treatment arm are summarized below in Table 24. The proportion of patients with at least one Grade 3 or higher treatment-related TEAEs was similar in the ABI-007/carboplatin and Taxol/carboplatin arms (62% vs 60%, respectively). Treatment-related TEAEs of grade 3, 4, or 5 severity and reported in at least 2% of patients in either treatment arm were summarized. In

both treatment arms, grade 3 events occurred more frequently than grade 4 or 5 events. In the ABI-007/carboplatin compared with the Taxol/carboplatin arm, grade 3 events occurred in 42% (n=218) and 33% (n=175) of patients respectively, and the corresponding percentages for grade 4 events were 20% (n=102) and 27% (n=139), respectively. Grade 5 treatment-related TEAEs occurred in 1 patient (<1%) in each of the two treatment arms.

Table 24: Study CA013 – Grade 3 or higher treatment-related TEAEs reported in at least 5% of patients in either treatment arm; treated population.

System Organ Class / Preferred Term	ABI-007/ carboplatin (N=514) n (%)	Taxol/ carboplatin (N=524) n (%)	p-value[a]
Patients with at Least 1 Treatment-related Grade 3 or Higher AE	321 (62%)	315 (60%)	0.445
Patients with an AE by MedDRA (Version 12.1) System Organ Class and Preferred Term			
Blood and lymphatic system disorders	264 (51%)	241 (46%)	0.094
Neutropenia	185 (36%)	212 (40%)	0.142
Anaemia	107 (21%)	28 (5%)	<0.001*
Thrombocytopenia	87 (17%)	34 (6%)	<0.001*
Leukopenia	44 (9%)	44 (8%)	>0.999
Investigations	67 (13%)	65 (12%)	0.780
Neutrophil count decreased	36 (7%)	50 (10%)	0.145
White blood cell count decreased	30 (6%)	27 (5%)	0.684
Nervous system disorders	22 (4%)	64 (12%)	<0.001*
Neuropathy peripheral	11 (2%)	25 (5%)	0.026*
Peripheral sensory neuropathy	5 (<1%)	37 (7%)	<0.001*

a P-values tested using Fisher's exact test.
* Indicates statistically significant p-values.
Note: Events are ordered by decreasing system organ class incidence in the ABI-007/carboplatin arm.
Note: Treatment-related adverse events include adverse events with relationship to study drug of possible, probable, or definite.

Treatment-related grade 3 or higher TEAEs occurring in a statistically significantly greater percentage of patients in the ABI-007/carboplatin than in the Taxol/carboplatin arm (Fisher's exact test) were anaemia (21% vs 5%, p<0.001), thrombocytopenia (17% vs 6%, p< 0.001), haemoglobin decreased (4% vs <1%, p=0.006), and platelet count decreased (2% vs <1%, p=0.020).

Treatment-related grade 3 or higher TEAEs occurring in a statistically significantly greater percentage of patients in the Taxol/carboplatin arm than in the ABI-007/carboplatin arm (Fisher's exact test) were peripheral sensory neuropathy (7% vs <1%, p<0.001), peripheral neuropathy (5% vs 2%, p=0.026), myalgia (2% vs <1%, p=0.001), and arthralgia (2% vs 0%, p=0.008).

8.3.2. Adverse events of special interest

8.3.2.1. Haematological toxicities

8.3.2.1.1. Anaemia

In the analysis of adverse events of special interest, the term anaemia included the MedDRA preferred terms of anaemia, haemoglobin decreased, haematocrit decreased, and red blood cell count decreased. Anaemia (all grades) occurred more commonly in the ABI-007/carboplatin arm than in the Taxol/carboplatin arm (54% vs 24%, respectively), as did grade 3 or higher events (28% vs 7%, respectively). The overall median nadir for the haemoglobin concentration was lower in the ABI-007/carboplatin arm relative to the Taxol/carboplatin carboplatin arm (89 g/L [range: 48, 151] vs 104 g/L [range: 32, 159], respectively).

Anti-anemic preparations during the study were administered to a higher proportion of patients in the ABI-007/carboplatin arm (35%, n=181) than in the Taxol/carboplatin arm (20%, n=107). Specifically, erythropoietin use occurred more frequently in the ABI-007/carboplatin arm than in the Taxol/carboplatin arm (epoetin alfa = 11% vs 3%; darbepoetin alfa = 4% vs 1%; and epoetin beta = 2% vs < 1%, respectively). Similarly, more ABI-007/carboplatin treated patients had a concomitant blood transfusion during the study than Taxol/carboplatin treated patients (16% vs 4%, respectively). Of the patients who had a concomitant blood transfusion, the majority had 1 transfusion (62%, ABI-007/carboplatin vs 79%, Taxol/carboplatin arm). The median time to the first blood transfusion was 65 days (i.e., at the beginning of Cycle 4), in both treatment arms. The incidence of haemorrhagic AEs was similar in the ABI-007/carboplatin arm and the Taxol/carboplatin arm (13% vs 10%, respectively).

In the ABI-007/carboplatin arm, discontinuation of ABI-007 or carboplatin due to anaemia (preferred term) occurred in 3% of patients for each drug, while in the Taxol/carboplatin arm no discontinuations were reported due to anaemia. In the ABI-007/carboplatin arm, dose reductions of ABI-007 or carboplatin due to anaemia (preferred term) were reported in 6% of patients for each drug, with the corresponding results for the Taxol/carboplatin arm being <1% for both Taxol and carboplatin. In the ABI-007/carboplatin arm, dose delays/doses not given of ABI-007 or carboplatin due to anaemia (preferred term) were reported in 16% of patients for ABI-007 and 12% of patients for carboplatin, and the corresponding results for the Taxol/carboplatin arm were 1% for both Taxol and carboplatin.

8.3.2.1.2. Neutropenia

The primary analysis of neutropenia was based on laboratory assessments to ensure that neutropenia events were not under-reported. Overall, there were statistically significantly lower severities of neutropenia (most severe NCI- CTCAE) in the ABI-007/carboplatin arm compared with the Taxol/carboplatin arm for all grades (p<0.007) and grades 3/4 (p<0.001) (see Table 25, below).

Table 25: Study CA031 – Most severe NCI-CTCAE for absolute neutrophil count.

Most Severe NCI CTCAE Grade	ABI-007/ carboplatin (N=521)	Taxol/ carboplatin (N=531)	P-value[a]	P-value[b]
N	508	513	0.007*	< 0.001*
Grade 0	78 (15%)	89 (17%)		
Grade 1	58 (11%)	39 (8%)		
Grade 2	133 (26%)	89 (17%)		
Grade 3	169 (33%)	164 (32%)		
Grade 4	70 (14%)	132 (26%)		

a P-values are based a CMH test across all grades and a two sample t-test for nadir.
b P-values are based on a Fisher's exact test for grade 3 and grade 4.
Note: Asterisk indicates a significant p-value (p < 0.05).

The incidence of infection and infestations (SOC) was similar in patients in both treatment arms (23%, ABI-007/carboplatin vs 18%, Taxol/carboplatin), suggesting that the increased incidence of grade 3/4 neutropenia in the Taxol/carboplatin arm did not result in increased rates of infection. Immunostimulant use was similar in both treatment arms (12%, ABI-007/carboplatin vs 10%, Taxol/carboplatin), suggesting that the difference in neutropenic events is not due to differences in the use of these agents.

The median time to ANC nadir (time from first dose of study drug to first occurrence of overall nadir) was 43 days (95% CI: 43, 56.0) in the ABI-007/carboplatin arm (i.e., at the start of cycle 3) and 57 days (95% CI: 57, 59) in the Taxol/carboplatin arm (i.e., towards the end of cycle 3); p=0.194 (log-rank test).ANC nadir below the lower limit of normal (LLN) was reported in a

similar percentage of patients in the ABI-007/carboplatin and Taxol/carboplatin arms (80% vs 79%, respectively). The median time to recovery of ANC (time from first occurrence of overall nadir to first occurrence of a value at or above the LLN) was 9 days (95%CI: 8, 12) in the ABI-007/carboplatin arm and 8 days (95%: not calculable) in the Taxol/carboplatin arm. The overall median nadir of ANC values was higher in the ABI-007/carboplatin arm (1.0 x 109/L [range: 0, 24.4) than in the Taxol/carboplatin arm (0.8 x 109/L [range: 0, 10.5]).

The analysis of neutropenia using MedDRA preferred terms of neutropenia, granulocytopenia, neutrophil count decreased, and granulocyte count decreased showed that the incidence of neutropenia (all grades) was higher in patients in the ABI-007/carboplatin arm compared with the Taxol/carboplatin arm (59%, n=305 vs 56%, n=294, respectively), while the incidence of neutropenia grade 3 or higher was higher in patients in the Taxol/carboplatin arm compared with the ABI-007/carboplatin arm (48%, n=251 vs 42%, n=218, respectively).

In the ABI-007/carboplatin arm, discontinuations of ABI-007 or carboplatin due to neutropenia (preferred term) were reported in 3% of patients for each drug, with the corresponding results for the Taxol/carboplatin arm being 2% for both Taxol and carboplatin. In the ABI-007/carboplatin arm, dose reductions of ABI-007 or carboplatin due to neutropenia (preferred term) were reported in 24% of patients for each drug, and the corresponding results for the Taxol/carboplatin arm were 9% for both Taxol and carboplatin. In the ABI-007/carboplatin arm, dose delays/doses not given of ABI-007 or carboplatin due to neutropenia (preferred term) were reported in 41% of patients for ABI-007 and 38% of patients for carboplatin, and the corresponding results for the Taxol/carboplatin arm were 12% for both Taxol and carboplatin.

8.3.2.1.3. Febrile neutropenia

Febrile neutropenia (preferred term) was reported by 1% (n=6) of patients in the ABI-007/carboplatin arm and 2% (n=8) of patients in the Taxol/carboplatin arm. In the ABI-007/carboplatin arm, grade 3 events occurred in 3 (< 1%) patients and grade 4 events in 2 (< 1%) patients, and the respective figures for the Taxol/carboplatin arm were 6 (1%) and 1 (<1%) patients. Febrile neutropenia (grade 3) resulted in permanent discontinuation of ABI-007 and carboplatin in 1 (< 1%) patient in the ABI-007 treatment arm, while no patients in the Taxol/carboplatin arm discontinued due to febrile anaemia. Febrile neutropenia resulted in delayed taxane dosing in 4 (< 1%) patients in the ABI-007/carboplatin arm and 2 (< 1%) patients in the Taxol/carboplatin arm.

8.3.2.1.4. Thrombocytopenia

In this analysis, the term thrombocytopenia included the MedDRA preferred terms thrombocytopenia and platelet count decreased. Thrombocytopenia (all grades) was reported more commonly in the ABI-007/carboplatin arm than in the Taxol/carboplatin (45%, n=230 vs 27%, n=143, respectively), as did grade 3 or higher thrombocytopenia (18%, n=94 vs 7%, n=35). The majority of thrombocytopenia events led to taxane dose delays in both treatment arms (34%, ABI-007/carboplatin vs 14%, Taxol/carboplatin), and a minority led to taxane dose reductions (13% vs 4%, respectively) or taxane discontinuations (3% vs < 1%, respectively). The overall median nadir of platelet values was lower for ABI-007/carboplatin (97 x 10^9/L [range: 6, 682]) than for Taxol/carboplatin (120 x 10^9/L [range: 11, 618]). There was an increase in haemorrhagic events in ABI-007/carboplatin treated patients compared with Taxol/carboplatin treated patients (13% vs 10%, respectively), but this relatively small difference did not appear to reflect the more than 2-fold increase in grade 3 or higher thrombocytopenic events observed in the ABI-007/carboplatin arm relative to the Taxol/carboplatin arm.

8.3.2.2. Peripheral neuropathy

In the analysis of adverse events of special interest, peripheral neuropathy was defined using the Standardized MedDRA Query (SMQ) neuropathy (broad scope), and the results are

summarized below in Table 26. Each peripheral neuropathy category occurred more frequently in the Taxol/carboplatin arm than in the ABI-007/carboplatin arm. The individual peripheral neuropathy conditions were summarized. The majority of disorders in both treatment arms were classified as peripheral sensory neuropathy (26%, ABI-007/carboplatin vs 40%, Taxol/carboplatin, p<0.001), and peripheral neuropathy (20% vs 23%, respectively, p=0.405).

Table 26: Study CA031 – Overview of peripheral neuropathy; treated population.

Category	ABI-007/ carboplatin (N=514) n (%)	Taxol/ carboplatin (N=524) n (%)	p-value[a]
Patients with at Least 1 Peripheral Neuropathy Event	246 (48%)	333 (64%)	< 0.001*
Patients with at Least 1 Treatment-related Peripheral Neuropathy Event	240 (47%)	328 (63%)	<0.001*
Patients with at Least 1 Treatment-related Peripheral Neuropathy Event after 6 Cycles of Therapy	49 (10%)	71 (14%)	0.052
Patients with at Least 1 Treatment-related Grade 3 or Higher Peripheral Neuropathy Event	17 (3%)	62 (12%)	< 0.001*

a P-values tested using Fisher's exact test. Statistically significant treatment differences are marked with an asterisk.

The relative time to onset of the first occurrence of treatment-related peripheral neuropathy (any grade) occurred statistically significantly later in the ABI-007/carboplatin arm compared with Taxol/carboplatin arm (49 vs 37.5 days, respectively; p<0.001). The median time to first occurrence of treatment-related peripheral neuropathy (grade ≥ 2) was also statistically significantly longer in the ABI-007/carboplatin arm than in the Taxol/carboplatin arm (105 vs 78 days, respectively; p = 0.040). Time to first occurrence and time to first improvement of various categories of treatment-related peripheral neuropathy for the two treatment arms were summarized.

The physician assessment of peripheral neuropathy based on NCI CTCAE grade at baseline, the final evaluation, and overall (i.e., the most severe grade any time after the first study drug dose) was summarized. At baseline, most patients (≥ 95%) in both treatment arms were assessed as not having peripheral neuropathy (grade 0). However, at the final and overall evaluation there were significant treatment differences favouring ABI-007/carboplatin, with fewer patients in the ABI-007/carboplatin arm shifting from grade 0 to grades 1 to 4 relative to the Taxol/carboplatin arm (p<0.001). In addition, the patient assessment of peripheral neuropathy using the Functional Assessment of Cancer Therapy (FACT-Taxane) Quality of Life (QOL) instrument showed that patients in the ABI-007/carboplatin arm reported significantly fewer peripheral neuropathy symptoms, pain in the hands and feet, and hearing loss compared with the Taxol/carboplatin arm.

8.3.2.3. Arthralgia and myalgia

Arthralgia was reported in a greater proportion of patients in the Taxol/carboplatin arm than in the ABI-007/carboplatin arm (25%, n=129 vs 13%, n=65; p<0.001), and the majority of events in both arms were considered to be treatment-related (24% vs 12%, respectively). A total of 2 patients in the Taxol/carboplatin arm discontinued due to arthralgia and a total of 5 patients had their dose reduced, while no patients in the AB0-007/carboplatin arm discontinued treatment or had their dose reduced because of arthralgia.

Myalgia was also reported in a greater proportion of patients in the Taxol/carboplatin carboplatin arm than in the ABI-007/carboplatin arm (19%, n=97 vs 10%, n=50; p<0.001), and the majority of events in both arms were considered to be treatment-related (18% vs 9%, respectively). One patient in the Taxol/carboplatin arm discontinued due to myalgia and 7 patients had their dose reduced compared with no patients in the ABI-007/carboplatin arm, while one patient in both treatment arms experienced a dose delay due to myalgia.

8.3.2.4. Drug hypersensitivity

MedDRA preferred terms of drug hypersensitivity and hypersensitivity were both reported in 2 patients (< 1%) in the ABI-007/carboplatin arm, and in 8 (2%) patients and 6 (1%) patients, respectively, in the Taxol/carboplatin arm. Taxane-related drug hypersensitivity or hypersensitivity was reported in 2 (< 1%) patients and 1 (< 1%) patient, respectively in the ABI-007/carboplatin arm, and in 6 (1%) patients and 4 (< 1%) patients, respectively in the Taxol/carboplatin arm. Drug hypersensitivity or hypersensitivity ≥ grade 3 was not reported in the ABI-007/carboplatin arm, but was reported in 3 (<1%) and 1 (<1%) patients, respectively in the Taxol/carboplatin arm. Of the 3 grade ≥ 3 drug hypersensitivity events in the Taxol/ carboplatin arm, 2 were grade 3 events and 1 was a grade 4 SAE.

In the Taxol/carboplatin arm, drug hypersensitivity/hypersensitivity resulted in treatment discontinuation in 2 (<1%) patients compared with no patients in the ABI-007/carboplatin arm. In the Taxol/carboplatin arm, drug hypersensitivity/hypersensitivity resulted in interruptions to taxane treatment in 4 (<1%) patients and to carboplatin treatment in 2 (<1%) patients, compared with no and 1 patients, respectively, in the ABI-007/carboplatin arm.

8.3.2.5. Skin and subcutaneous disorders

Skin and subcutaneous tissue disorders were defined using the MedDRA system organ class (SOC). The overall incidence of skin and subcutaneous tissue disorders was comparable between the ABI-007/carboplatin and Taxol/carboplatin arms (61% vs 64%, respectively). The most commonly reported (≥ 5% of patients) skin and subcutaneous tissue disorder TEAEs in the ABI-007/carboplatin and Taxol/carboplatin arms were alopecia (56% vs 60%, respectively) and rash (10% vs 8%, respectively). The only skin and subcutaneous tissue TEAEs for which the differences between the two treatment arms were statistically significant were nail disorder (2%, ABI-007/carboplatin vs <1%, Taxol/carboplatin, p=0.002), and pruritus (4%, Taxol/carboplatin vs 2%, ABI-007/carboplatin, p=0.050). The only skin and subcutaneous tissue adverse events for which the differences between the two treatment arms were statistically significant were nail disorder (2%, ABI-007/carboplatin vs <1%, Taxol/carboplatin, p=0.002), and pruritus (4%, Taxol/carboplatin vs 2%, ABI-007/carboplatin, p=0.050). In both treatment arms, nearly all skin and subcutaneous tissue disorders were considered to be treatment-related (59%, ABI-007/carboplatin vs 62%, Taxol/carboplatin).

Less than 1% of patients in either treatment arm experienced a grade 3 or higher skin and subcutaneous tissue disorder, and few had new or worsened disorders after 6 cycles (5%, ABI-007/carboplatin vs 2%, Taxol/carboplatin). There were no instances of Stevens-Johnson syndrome or toxic epidermal necrolysis. There were no SAE skin and subcutaneous tissue disorders, and < 1% of patients in each treatment arm discontinued due a skin and subcutaneous tissue disorder. Few patients in the ABI-007/carboplatin or Taxol/carboplatin arms had dose reductions due to skin and subcutaneous tissue disorders (2% vs < 1%, respectively), and few patients had a dose delay due to these disorders (2% vs 1%, respectively).

8.3.2.6. Gastrointestinal disorders

Gastrointestinal disorders were defined using the MedDRA system organ class. There was no significant difference in the proportion of patients with gastrointestinal disorders in the ABI-007/carboplatin and Taxol/carboplatin arms (41% vs 38%, respectively). The most commonly reported (≥ 5% of patients) gastrointestinal TEAEs (ABI-007/carboplatin vs Taxol/carboplatin) were nausea (27% vs 25%), constipation (16% vs 13%), diarrhoea (15% vs 11%), vomiting (12%, both), and stomatitis (6% vs 4%). The only gastrointestinal TEAEs for which the differences between the two treatment arms were statistically significant were upper abdominal pain (3%, ABI-007/carboplatin vs 1%, Taxol/carboplatin, p=0.039), and haemorrhoids (2%, ABI-007/carboplatin vs <1%, Taxol/carboplatin, p=0.020). In both

treatment arms, the majority of gastrointestinal disorders were considered to be treatment-related (37%, ABI-007/carboplatin vs 34%, Taxol/carboplatin).

Only 3% of patients in either treatment arm experienced a grade 3 or higher gastrointestinal disorder, and few patients had a new or worsened AE after 6 cycles (5%, ABI-007/carboplatin vs 4%, Taxol/carboplatin). Approximately 1% of patients in each treatment arm experienced a SAE gastrointestinal disorder, and 1 patient in the Taxol/carboplatin arm discontinued due to gastrointestinal hemorrhage. Few patients in the ABI-007/carboplatin or Taxol/carboplatin arms had their dose reduced due to gastrointestinal disorders (< 1%, both arms), and few patients required a dose delay (2%, ABI-007/carboplatin vs < 1%, Taxol/carboplatin).

8.3.2.7. Cardiac disorders

Treatment-emergent cardiac disorders (SOC) occurred in a similar proportion of patients in both treatment arms (6%, ABI-007/carboplatin vs 5%, Taxol/carboplatin). There were no statistically significant differences between the two treatment arms in cardiac TEAEs (preferred terms).

8.3.3. Deaths and serious adverse events

8.3.3.1. Deaths

TEAEs with an outcome of death within 30 days of the last treatment occurred in 18 (4%) patients in the ABI-007/carboplatin arm and 19 (4%) patients in the Taxol/carboplatin arm. No TEAE with an outcome of death was reported at the preferred term level for ≥ 1% of patients in either treatment arm. Events with outcome of death in more than 1 patient in the ABI-007/carboplatin arm were pulmonary embolism (4 patients), pulmonary hemorrhage (2 patients), and cardiac arrest (2 patients). Events with outcome of death in more than 1 patient in the Taxol/carboplatin arm were pulmonary embolism (4 patients) and pulmonary hemorrhage (3 patients). There were 2 treatment-related TEAEs with an outcome of death; one in each arm (1x multi-organ failure, ABI-007/carboplatin, and 1x gastrointestinal haemorrhage, Taxol/carboplatin).

In the pooled data from studies CA031 and CA028, treatment-related SAEs occurred in 8 (1%) of the 765 patients receiving ABI-007/carboplatin (1 patient from study CA031 referred to in the above paragraph and 7 patients from study CA028). The 7 deaths in study CA028 were due to pneumonia (x2), cardiopulmonary failure (x1), cerebrovascular accident (x1), disease progression (x1), endotoxic shock (x1) and pulmonary haemorrhage (x1). No treatment-related fatal SAEs occurred during ABI-007 monotherapy (n=236).

8.3.3.2. Serious adverse events (fatal and non-fatal)

Treatment-emergent SAEs (fatal and non-fatal) reported in ≥ 1% of patients in either treatment arms are summarized below in Table 27. SAEs were reported in 18% (n=93) of patients in the ABI-007/carboplatin arm and 15% (n=80) of patients in the Taxol/carboplatin arm. Anaemia was reported as an SAE more often in patients in the ABI-007/carboplatin arm than in the Taxol/carboplatin arm (4% vs < 1%). All other SAES occurred in a comparable proportion of patients in the two treatment arms.

Table 27: Study CA031 – Treatment-emergent SAEs (fatal and non-fatal) reported in at least 1% of patients in both treatment arms; treated population.

System Organ Class Preferred Term	ABI-007 100mg/m² Weekly/ carboplatin (N = 514) n (%)	Taxol 200mg/m² Every 3 weeks/ carboplatin (N = 524) n (%)
Patients with ≥ 1 SAE	93 (18%)	80 (15%)
Blood and Lymphatic System Disorders	**26 (5%)**	**12 (2%)**
Anaemia	19 (4%)	3 (< 1%)
Infections and Infestations	**21 (4%)**	**16 (3%)**
Pneumonia	14 (3%)	11 (2%)
Respiratory, Thoracic and Mediastinal Disorders	**18 (4%)**	**26 (5%)**
Dyspnoea	4 (< 1%)	6 (1%)
Pulmonary embolism	4 (< 1%)	8 (2%)

Treatment-related SAEs occurred in a similar proportion of patients in the ABI-007/carboplatin and Taxol/carboplatin arms (7%, n=37 vs 6%, n=30, respectively). Treatment related SAEs reported in more than 1 patient in either treatment arm (ABI-007/carboplatin vs Taxol/carboplatin) were anaemia (3%, n=16 vs < 1%, n=2), febrile neutropenia (<1%, n=4 vs <1%, n=5), neutropenia (<1%, n=1 vs <1%, n=2), and pneumonia (<1%, n=1 vs <1%, n=4).

8.4. Discontinuations, interruptions, and dose delays/dose not given due to adverse events

8.4.1. Discontinuation

The proportion of patients with at least 1 TEAE resulting in discontinuation was comparable for the two treatment arms for discontinuation of both the taxane component (16% for both ABI-007/carboplatin and Taxol/carboplatin) and the carboplatin component (16% for ABI-007/carboplatin and 15% for Taxol/carboplatin. The most common TEAEs resulting in taxane and carboplatin discontinuation in the ABI-007/carboplatin arm were neutropenia (3% for both) and thrombocytopenia (3% for both), and in the Taxol/carboplatin arm the most common TEAEs resulting in discontinuation was peripheral sensory neuropathy (4% and 3%, respectively). All other TEAEs resulting in treatment discontinuation were reported in ≤ 2% of patients in either treatment arm for discontinuation of both taxane and carboplatin.

8.4.2. Dose interruptions

There were no interruptions in ABI-007 dosing due to TEAEs for the 514 patients in the ABI-007/carboplatin arm, and only 1 (<1%) patient in this arm had an interruption in carboplatin dosing (drug hypersensitivity). In the Taxol/carboplatin arm, Taxol dosing was interrupted due to TEAEs in < 1% of patients (drug hypersensitivity 3 patients, hypersensitivity 1 patient, hypertensive crisis/pyrexia 1 patient), and carboplatin was interrupted in < 1% of patients (drug hypersensitivity 2 patients, asthma 1 patient).

8.4.3. Dose delays/dose not given

The incidence of TEAEs resulting in taxane dose delay/dose not given was substantially higher in the ABI-007/carboplatin arm than in the Taxol/carboplatin arm (71% vs 41%, respectively),as were TEAEs resulting in carboplatin dose delay/dose not given (64% vs 41%, respectively). TEAEs resulting in taxane dose delays/dose not given in ≥ 10% of patients in

either treatment arm (ABI-007/carboplatin vs Taxol/carboplatin) were neutropenia (41% vs 12%), thrombocytopenia (30% vs 12%), and anaemia (16% vs 1%).

8.5. Long-term safety (treatment for > 6 cycles)

In order to identify TEAEs potentially associated with long-term treatment the frequency of TEAEs reported after 6 treatment cycles were compared for both treatment arms. TEAEs reported in at least 2% of patients in either treatment arm after 6 cycles were summarized. The percentage of patients with TEAEs occurring after 6 cycles was similar in both treatment arms (28%, ABI/carboplatin vs 27%, Taxol/carboplatin). TEAEs after 6 cycles occurring statistically significantly more frequently in patients in the ABI-007/carboplatin arm compared with the Taxol/carboplatin arm were anemia (9% vs 4%, p=0.005), peripheral oedema (3% vs <1%, p=0.004), and constipation (2% vs 0%, p=0.004). TEAEs after 6 cycles occurring more frequently in patients in the Taxol/carboplatin arm compared with the ABI-007/carboplatin arm were arthralgia (2% vs <1%, p=0.034) and myalgia (2% vs <1%, p=0.020).

The incidence of grade 3 or higher TEAEs after 6 cycles of therapy was marginally greater in the Taxol/carboplatin arm than in the ABI-007/carboplatin arm (18% vs 14%, p=0.063). TEAEs Grade 3 or higher after 6 cycles reported statistically significantly more frequently in patients in the Taxol/carboplatin arm than in the ABI-007/carboplatin arm were neutropenia (12% vs 7%, p=0.005), and peripheral sensory neuropathy (3% vs <1%, p=0.002). There were no grade 3 or higher TEAEs after 6 cycles reported statistically significantly more frequently in patients in the ABI-007/carboplatin arm than in the Taxol/carboplatin arm.

The proportion of patients with at least one treatment-related TEAE after 6 cycles was similar in the ABI-007/carboplatin and Taxol/carboplatin arms (26% vs 25%, respectively). Treatment-related TEAEs occurring in at least 5% of patients in either treatment arm (ABI-007/carboplatin vs Taxol/carboplatin) were: neutropenia (12% vs 15%); thrombocytopenia (11% vs 7%); anaemia (8% vs 4%); peripheral sensory neuropathy (5% vs 8%); and peripheral neuropathy (5% vs 6%).

The incidence of treatment-related TEAEs of grade 3 or higher after 6 cycles was 12% of patients in the ABI-007/carboplatin arm and 17% of patients in the Taxol/carboplatin arm (p=0.029). In general, these events occurred infrequently and were comparable in the two treatment arms at the MedDRA term level, apart from nervous system disorders (SOC) which were reported significantly more frequently in the Taxol/carboplatin arm than the ABI-007/carboplatin arm (5% vs 2%, p=0.012). There were no preferred term grade 3 or higher TEAEs reported statistically significantly more frequently in patients in the ABI-007/carboplatin arm compared with the Taxol/carboplatin arm. The preferred term grade 3 or higher TEAEs reported statistically significantly more frequently in the Taxol/carboplatin arm compared with the ABI-007/carboplatin arm were neutropenia (12% vs 7%; n=0.005) and peripheral sensory neuropathy (3% vs < 1%, p=0.002).

8.6. Clinical laboratory findings

8.6.1. Haematological toxicities

Haematological toxicities have been described above.

8.6.2. Clinical chemistry

Hepatic and renal function was summarized using the NCI CTCAE (Version 3) most severe grade for alkaline phosphatase, ALT, AST, total bilirubin, and creatinine, but no shift tables were provided for clinical chemistry abnormalities. There were no significant differences between the two treatment arms in the most severe hepatic and renal function events recorded during the study. In the majority of patients in both arms, treatment appeared to have no marked effect

on SAP, ALT, AST or total bilirubin levels with the most severe TEAE grade in the majority of patient being grade 0. Similarly, the most severe creatinine TEAE grade was grade 0 in > 90% of patients with nearly all other patients being grade 1. Clinically significant clinical chemistry values occurring after the start of treatment are summarized below in Table 28.

Table 28: Study CA031 – Clinically significant clinical chemistry values occurring after start of treatment; treated population.

Parameter	NCI CTCAE Grade	ABI-007/carboplatin (N=514)	Taxol/carboplatin (N=524)
Alkaline Phosphatase	H3	5 (<1%)	5 (<1%)
ALT (SGPT)	H3	6 (1%)	3 (<1%)
	H4	0	1 (<1%)
AST (SGOT)	H3	5 (<1%)	3 (<1%)
	H4	1 (<1%)	1 (<1%)
Total Bilirubin	H3	0	1 (<1%)
	H4	0	1 (<1%)
Albumin	L3	2 (<1%)	0
Calcium	L3	1 (<1%)	1 (<1%)
Glucose	H3	8 (2%)	17 (3%)
	L4	0	1 (<1%)
Potassium	H3	0	2 (<1%)
	L3	2 (<1%)	2 (<1%)
Sodium	L3	4 (<1%)	4 (<1%)
	L4	1 (<1%)	0

H = high; L = low. Patients with both grade 3 and grade 4 values for a specific parameter were tabulated as grade 4. Patients with both L3 and L4 values for a specific parameter were tabulated as L4. Patients with both H3 and H4 values for a specific parameter were tabulated as H4.

8.6.3. Vital signs

Vital signs were assessed at baseline, Days 1, 8 and 15, EOS, and AE resolution/follow-up. No summary report or tabulations were provided for vital signs, with reference in the study report being made only to vital sign listings. The electrocardiograms (ECGs) performed at baseline were evaluated locally, but no systemic evaluation of ECG changes during the study appears to have been undertaken. The schedule of assessments indicates that ECG was to be performed at baseline and at any other stage in the cycle as determined to be clinically significant by the investigator.

8.7. Adverse events in special groups

8.7.1. Age

In the ABI-007/carboplatin arm vs Taxol/carboplatin arm, there were 356 vs 343 patients aged < 65 years, 158 vs 181 patients aged ≥ 65 years, 73 patients vs 81 aged ≥ 70 years, and 18 vs 17 patients aged ≥ 75 years. The submission included a comparison of TEAEs in patients < 65 years of age compared with those aged ≥ 65 years, and those aged < 70 years compared with those aged ≥ 70 years. However, due to the relatively small number of patients aged ≥ 70 years the adverse event profile in this population should be interpreted cautiously. Consequently, the safety data from study CA031 reviewed in this section focuses on the comparison between patients aged < 65 years and those aged ≥ 65 years. TEAEs (preferred term) occurring in ≥ 5% of patient in any of the treatment groups by age (< 65 and ≥ 65 years) reported in the pivotal Phase III study CA031 were summarized.

8.7.1.1. Exposure

In the ABI-007/carboplatin arm, the median number of cycles administered was higher in patients aged < 65 years (6.0 [range: 1. 27]) than in patients aged ≥ 65 years (5.0 [range: 1, 31]). In the ABI-007/carboplatin arm, the mean±SD cumulative ABI-007 dose during the study in

patients aged < 65 years was higher than in patients aged ≥ 65 years (1590±1061 vs 1393±993 mg/m^2, respectively), as was the mean±SD ABI-007 dose intensity (81.6±16.3 vs 74.9±18.8 mg/m^2/weekly, respectively). In the ABI-007/carboplatin arm, the mean cumulative carboplatin dose and the mean carboplatin dose intensity were also both higher in patients aged < 65 years compared with patients aged ≥ 65 years.

8.7.1.2. TEAEs (all grades)

In the ABI-007/carboplatin treatment arm, the overall incidence of TEAEs was similar in patients aged < 65 years compared with patients aged ≥ 65 years (93% vs 97%), and a similar pattern was seen in the Taxol/carboplatin arm (95% vs 98%, respectively). In the ABI-007/carboplatin arm, TEAEs reported in ≥ 5% more patients aged ≥ 65 years vs patients aged < 65 years were: neutropenia (55% vs 49%); anaemia (55% vs 49%); thrombocytopaenia (44% vs 39%); fatigue (39% vs 18%); nausea (35% vs 24%); peripheral sensory neuropathy (31% vs 24%); constipation (28% vs 11%); decreased appetite (26% vs 13%) diarrhoea (24% vs 10%); haemoglobin decreased (20% vs 7%); white blood cell decreased (20% vs 8%); arthralgia (20% vs 9%); neutrophil decreased (17% vs 8%); rash (16% vs 7%); dyspnoea (16% vs 11%) oedema peripheral (16% vs 8%); weight decreased (15% vs 6%); pyrexia (13% vs 8%); epistaxis (12% vs 5%); dysgeusia (12% vs 5%); platelet count decreased (11% vs 4%); dizziness (10% vs 4%); insomnia (9% vs 4%); and haematocrit decreased (8% vs 2%). In the ABI-007/carboplatin arm, the only TEAE reported ≥ 5% more frequently in patients aged < 65 years (vs patients aged ≥ 65 years) was asthenia (18% vs 13%).

8.7.1.3. TEAEs grade 3 or higher

In the ABI-007/carboplatin arm, the overall incidence of patients with grade 3 or higher TEAEs was greater in the patients aged ≥ 65 years compared with patients aged < 65 years (80%, 127/158 vs 65%, 233/356), and a similar pattern was seen in the Taxol/carboplatin arm (79%, 143/181 vs 62%, 212/343). In the ABI-007/carboplatin arm, TEAEs grade 3 or higher reported in ≥ 2% more patients aged ≥ 65 years vs patients aged < 65 years were: neutropenia (44% vs 32%); neutrophil count decreased (11% vs 5%); white blood cell count decreased (11% vs 3%); leukopenia (10% vs 8%); haemoglobin decreased (6% vs 2%); fatigue (5% vs 3%); platelet count decreased (4% vs < 1%); pneumonia (4% vs <1%); dehydration (3% vs <1%); and back pain (2% vs 0%). There were no TEAEs grade 3 or higher reported in ≥ 2% more patients in the < 65 years group compared with the ≥ 65 years group.

Similar to the overall population, patients aged ≥ 65 years in the ABI-007/carboplatin had statistically significantly higher incidences than patients in the Taxol/carboplatin arm of grade 3 or greater anaemia (24% vs 4%, p<0.001), thrombocytopenia (17% vs 7%, p=0.003), haemoglobin decreased (6% vs 1%), and platelet count decreased (4% vs 0%, p=0.010). Similar to the overall population, patients aged ≥ 65 years in the Taxol/carboplatin arm had statistically significantly higher incidences than patients in the ABI-007/carboplatin arm of grade 3 or greater peripheral sensory neuropathy (12% vs 1%, p<0.001), and arthralgia (3% vs 0%, p=0.032).

8.7.2. Gender

In the ABI-007/carboplatin arm, 96% (121/126) of female patients experienced at least one TEAE compared with 93% (362/388) of male patients. In the Taxol/carboplatin arm, 95% (373/391) of male patients experienced at least one TEAE compared with 98% (131/133) of female patients. In the ABI-007/carboplatin arm, women compared with men experienced higher rates of treatment-emergent gastrointestinal disorders (56% vs 37%), including nausea (44% vs 22%), vomiting (20% vs 10%), constipation (22% vs 14%), and diarrhoea (22% vs 12%). Similarly, in the Taxol/carboplatin arm a greater proportion of women compared with men experienced treatment-emergent gastrointestinal disorders (46% vs 36%), including nausea (35% vs 21%), constipation (20% vs 10%), and vomiting (19% vs 10%). In addition, a greater proportion of women compared with men experienced at least one treatment emergent

blood and lymphatic disorder (79% vs 72%) including neutropenia (52% vs 50%) and anaemia (43% vs 39%). Furthermore, a greater proportion of women experienced increased ALT levels compared with men (16% vs 7%). Trends were similar in the Taxol/carboplatin arm. Overall, women had a higher incidence of grade 3 or higher leukopenia than men (13% vs 7%), and women in the Taxol/carboplatin arm had higher rates of grade 3 or higher neutropenia than women in the ABI-007/carboplatin arm (50% vs 39%).

8.7.3. Race

The TEAE profiles were compared for "White, non-Hispanic and non-Latino", and "Asian" patients. There was no separation of the Asian patients into genetic subgroups (e.g., Chinese [including subgroups], Korean, Japanese). In the ABI-007/carboplatin arm, anaemia was more common in White relative to Asian patients. However, adverse events reported more frequently in Asian patients compares with White patients in both treatment arms included alopecia, rash, peripheral sensory neuropathy, dysgeusia, headache, peripheral motor neuropathy, fatigue, pyrexia, influenza-like illness, nausea, constipation, diarrhea, vomiting, stomatitis, hiccups, arthralgia, myalgia, decreased appetite, hyponatraemia, hypoalbuminaemia, and insomnia. The incidence of grade 3 or higher anaemia in the ABI-007/carboplatin arm was higher in White patients relative to Asian patients, while the rates of this adverse event were comparable in the Taxol/carboplatin arm. The incidences of grade 3 or higher leukopenia, decreased ANC, WBC, haemoglobin, and decreased appetite were higher in Asian patients relative to White patients in both treatment arms.

8.8. Safety across all studies

The key safety data relating to the proposed dose for the proposed indication are derived from the pivotal Phase III efficacy and safety study CA031. The overall safety profile for ABI-007 from all submitted studies was summarized. In addition, treatment-related adverse events (all grades) and grade 3 or higher in at least 5% of patients in any dosing regimen or dosing schedule were also summarized.

8.9. Post-marketing data

The submission included a summary of the post-marketing experience of Abraxane from the International Birth Date of the drug (7 January 2005) to the most recent Periodic Safety Update Report cut-off date (6 July 2011). During this time interval, approximately 116,527 patients were exposed to commercial Abraxane, including 103,614 patients from the US and 12,913 patients from outside the US. The recommended dose of single-agent Abraxane for patients with metastatic breast cancer is 260 mg/m^2 administered intravenously over 30 minutes every 3 weeks. The sponsor estimates that the number of vials per cycle over the assessed time interval for all patients is 4.4, and that the average number of treatment cycles per patient is 5.5.

The sponsor states that the major risks associated with the use of Abraxane for the treatment of patients with metastatic breast cancer reflect the known toxicities of paclitaxel. These risks include alopecia, haematologic toxicities (neutropenia and anaemia), peripheral sensory neuropathy, myalgia/arthralgia, fatigue/asthenia, hypersensitivity reactions, gastrointestinal events (nausea and diarrhoea), infections, elevated aspartate aminotransferase, elevated alkaline phosphatase, and abnormal electrocardiogram.

8.9.1. Results - All patients (i.e., including lung cancer plus all other conditions)

During the period from the International Birth Date of Abraxane (07 January 2005) to the most recent Periodic Safety Update Report cut-off date (06 July 2011) 2,611 adverse drug reactions (ADRs) from 1,645 unique adverse event reports have been received from: (a) contract pharmacies; (b) spontaneous sources; (c) regulatory authorities; and (d) the scientific literature.

Of the 1,645 unique adverse event reports, 20 reports were received from 11 patients treated with Abraxane specifically for lung cancer. For these 11 patients, Abraxane was used as monotherapy in 6 cases, in combination with carboplatin in 2 cases, in combination with sunitinib in 2 cases, and in combination with bevacizumab in 1 case. Medically ADRs by MedDRA term SOC in lung cancer patients compared with all patients were summarized. ADRs (MedDRA SOCs) occurring in ≥ 10% of all patients were blood and lymphatic system disorders (15.55%), investigations (12.52%), general disorders and administration site conditions (11.22%), and gastrointestinal disorders (10.61%).

Of the 20 ADRs reported in lung cancer patients, 12 were expected events and 6 were unexpected events, while 2 were reported as "lack of efficacy" and "counterfeit drug administered." The 12 ADRs classified as expected events included 2 reports for fatigue, and 1 report each for alopecia, peripheral neuropathy, dyspnoea, neutrophil count decreased, haemoglobin decreased, platelet count decreased, chest pain, back pain, flushing, and infusion site extravasation. The 6 ADRs classified as unexpected events included 2 reports for decreased appetite, and 1 report each for constipation, skin peeling from hand, blindness in one eye, and allergic dermatitis. All ADRs in patients with lung cancer, expected and unexpected, were reported as non-serious except for one serious event of blindness in one eye for which limited information is available.

The 20 post-marketing ADRs reported for the subset of lung cancer patients who received Abraxane were also reported in the pivotal NSCLC study CA031. In study CA031, the frequency of TEAEs reported in the Abraxane/carboplatin arm and considered to be expected events based on post-marketing data included fatigue (25%), alopecia (56%), peripheral sensory neuropathy (26%), dyspnoea (12%), neutrophil count decreased (11%), haemoglobin decreased (11%), platelet count decreased (7%), chest pain (5%), back pain (4%), flushing (< 1%), and infusion site extravasation (< 1%). In study CA031, the frequency of TEAEs reported in the Abraxane/carboplatin arm and considered to be unexpected events based on post-marketing data included decreased appetite (17%), constipation (16%), skin exfoliation (< 1%), blindness (< 1%), and allergic dermatitis (< 1%).

Overall, the post-marketing data for Abraxane administered for the treatment of lung cancer are insufficient to conclude that the safety profile of the drug for this condition is consistent with the safety profile of the drug for the treatment of metastatic breast cancer.

8.10. Evaluator's overall conclusions on clinical safety

Overall, the submission included safety data on ABI-007 from a total of 4 studies in 883 patients with NSCLC treated with ABI-007 administered weekly or once every 3 weeks combined with carboplatin (n=765) or as monotherapy (n=118), and 1 study in 32 patients with metastatic breast cancer treated with ABI007/Herceptin weekly combined with carboplatin administered once every 3 weeks. In general, the safety profile of ABI-007 was consistent in the 5 submitted studies.

The pivotal safety data for ABI-007/carboplatin at the proposed dose for the proposed indication are derived from the pivotal Phase III efficacy and safety study CA031. In this study, 514 patients were treated with ABI-007 administered weekly at a dose of 100 mg/m^2 on days 1, 8, and 15 of each 21-day cycle combined with carboplatin (AUC = 6) administered on day 1 of each 21-day cycle. The safety data from these 514 patients was compared with the safety data from 524 patients in the pivotal study treated with Taxol administered at a dose of 200 mg/m^2 combined with carboplatin (AUC = 6) on day 1 of each 21-day cycle. The safety data summarized below refers to the data from the pivotal Phase III efficacy and safety study CA031 unless otherwise stated.

Exposure to ABI-007/carboplatin and Taxol/carboplatin in study CA031 is considered sufficient to adequately characterize the safety profile of the two treatment arms. In each treatment arm

the median number of 21-day treatment cycles was 6.0. However, the median cumulative taxane dose was 17.8% higher with ABI-007 administered weekly (1325 mg/m^2) relative to Taxol administered every 3 weeks (1125 mg/m^2). In addition, the median average taxane dose intensity per week was 25.9% higher with ABI-007 weekly (81.98 mg/m^2/week) relative to Taxol every 3 weeks (65.12 mg/m^2/week).

TEAEs (all grades) were reported in nearly all patients in both the ABI-007/carboplatin and Taxol/carboplatin arms (94% and 96%, respectively). The most commonly reported TEAEs (all grades) occurring in ≥ 20% of patients in the ABI-007/carboplatin vs the Taxol/carboplatin arm were alopecia (56% vs 60%), neutropenia (51% vs 48%), anaemia (44% vs 21%), thrombocytopenia (40% vs 23%), nausea (27% vs 25%), peripheral sensory neuropathy (26% vs 40%), fatigue (25% vs 23%), and peripheral neuropathy (20% vs 23%).

TEAEs (all grades) reported statistically significantly more commonly in patients in the ABI-007/carboplatin arm compared with the Taxol/carboplatin arm were anaemia (44% vs 21%, p<0.001), thrombocytopenia (40% vs 23%, p<0.001), peripheral oedema (10% vs 4%, p<0.001), epistaxis (7% vs 2%, p<0.001), haemoglobin decreased (11% vs 6%, p=0.015), upper abdominal pain (3% vs 1%, p=0.039), haemorrhoids (2% vs < 1%, p=0.020), and nail disorder (2% vs <1%, p=0.002). TEAEs (all grades) reported statistically significantly more commonly in patients in the Taxol/carboplatin arm compared with the ABI-007/carboplatin arm were peripheral sensory neuropathy (40% vs 26%, p<0.001), arthralgia (25% vs 13%, p<0.001), myalgia (19% vs 10%, p<0.001), and pruritus (4% vs 2%, p=0.050). The pattern of treatment-related AEs (all grades) in both treatment arms was consistent with that for TEAEs (all grades), and the majority of events were considered to be treatment-related.

TEAEs (grade 3 or higher) were reported in a similar proportion of patients in the ABI-007/carboplatin and Taxol/carboplatin arms (70% vs 68%, respectively). The most commonly reported TEAEs (all grades) occurring in ≥ 20% of patients in the ABI-007/carboplatin vs the Taxol/carboplatin arm were neutropenia (36% vs 40%) and anaemia (25% vs 6%). TEAEs (grade 3 or higher) reported statistically significantly more commonly in patients in the ABI-007/carboplatin arm compared with the Taxol/carboplatin arm were anaemia (25% vs 6%, p<0.001), thrombocytopenia (17% vs 6%, p<0.001), haemoglobin decreased (4% vs < 1%, p=0.006), ALT increased (2% vs < 1%, p=0.032), and platelet count decreased (2% vs < 1%, p=0.020). TEAEs (grade 3 or higher) reported statistically significantly more commonly in patients in the Taxol/carboplatin arm compared with the ABI-007/carboplatin arm were peripheral neuropathy (5% vs 2%, p=0.018), peripheral sensory neuropathy (7% vs < 1%, p<0.001), arthralgia (2% vs < 1%, p=0.021), and myalgia (2% vs < 1%, p=0.011). The pattern of treatment-related AEs (grade 3 or higher) in both treatment arms was consistent with that for TEAEs (all grades), and the majority of events were considered to be treatment-related.

The study included specific analyses of a number of adverse events of special interest. Anaemia (including preferred terms of anaemia, haemoglobin decreased, haematocrit decreased, and red blood cell count decreased) occurred in a greater proportion of patients in the ABI-007/carboplatin arm compared with the Taxol/carboplatin arm for all grades (54% vs 24%) and for grade 3 or higher (28% vs 7%). The percentage of patients in the ABI-007/carboplatin arm who received a blood transfusion during the study was greater than in the Taxol/carboplatin arm (16% vs 4%, respectively), and the majority of transfused patients in both treatment arms required only 1 transfusion. In the ABI-007/carboplatin arm, greater percentages of patients discontinued, had dose reductions, or dose delays/dose not given due to anaemia than patients in the Taxol/carboplatin arm.

Most severe neutropenia (NCI CTCAE) showed a statistically significant reduction in severity across all grades (p=0.007) and for grades 3/4 (p<0.001) in patients in the ABI-007/carboplatin arm relative to the Taxol/carboplatin arm (p=0.007). The analysis of neutropenia using combined MedDRA preferred terms of neutropenia, granulocytopenia, neutrophil count decreased, and granulocyte count decreased showed that neutropenia (all grades) occurred

more commonly in patients in the ABI-007/carboplatin arm than in the Taxol/carboplatin arm (59% vs 56%, respectively), while Grade 3 of higher events occurred more commonly in patients in the Taxol/carboplatin arm than in the ABI-007/carboplatin arm (48% vs 42%). There were very few neutropenia SAEs (< 1% for both arms), and the proportion of patients discontinuing taxane due to neutropenia (preferred term) was 3% in the ABI-007/carboplatin arm and 2% in the Taxol/carboplatin arm. Febrile neutropenia was reported in 1% and 2% of the ABI-007/carboplatin and Taxol/carboplatin arms, respectively. Infection and infestation (MedDRA SOC) treatment emergent SAEs occurred in a similar proportion of patients in the ABI-007/carboplatin and Taxol/carboplatin arms (4% vs 3%, respectively).

Thrombocytopenia (preferred terms thrombocytopenia and platelet count decreased) occurred in a greater proportion of patients in the ABI-007/carboplatin arm compared with the Taxol/carboplatin arm for all grades (45% vs 27%) and for grade 3 or higher (18% vs 7%). The majority of thrombocytopenic events resulted in taxane dose delays in both treatment arms, with a minority resulting in taxane dose reductions and small number in discontinuations of taxane.

Peripheral neuropathy (broad scope) occurred in a statistically significantly greater proportion of patients in the Taxol/carboplatin arm than in the ABI-007/carboplatin arm (64% vs 48%, $p<0.001$). The time to onset of treatment-related peripheral neuropathy (any grade) was statistically significantly shorter in the Taxol/carboplatin arm compared with the ABI-007/carboplatin arm (37.5 vs 49 days, $p<0.001$). The median time to improvement of grade ≥ 3 treatment-related peripheral neuropathy to grade 1 was shorter in the ABI-007/carboplatin arm than in the Taxol/carboplatin arm (38 vs 104 days, $p=0.326$). In addition, both physician assessment of peripheral neuropathy at every visit and patient reported outcome using the FACT-Taxane assessment instrument significantly favoured patients in the ABI-007/carboplatin arm compared with the Taxol/carboplatin arm. Peripheral sensory neuropathy was the most common TEAE (preferred term) resulting in taxane discontinuation in the Taxol/carboplatin arm 4% (vs 1% in the ABI-007/carboplatin arm), followed by peripheral neuropathy (2%, Taxol/carboplatin vs < 1%, ABI-007/carboplatin) and neutropenia (2%, Taxol/carboplatin vs 3%, ABI-007/carboplatin).

Arthralgia was reported in a greater proportion of patients in the Taxol/carboplatin arm than in the ABI-007/carboplatin arm (25% vs 13%; $p<0.001$), as was myalgia (19% vs 10%; $p<0.001$). However, few patients in both treatment arms had treatment discontinued or doses reduced or delayed due to arthralgia or myalgia.

Skin and subcutaneous tissue disorders (MedDRA, SOC term) occurred frequently in both treatment arms and in a comparable proportion of patients (61%, ABI-007/carboplatin vs 64%, Taxol/carboplatin). The most common TEAEs reported in this SOC (≥ 5% of patients) in the ABI-007/carboplatin vs Taxol/carboplatin arms were alopecia (56% vs 60%, respectively) and rash (10% vs 8%, respectively). There were no reports of Stevens-Johnson syndrome or toxic epidermal necrolysis. Few patients in both treatment arms had treatment discontinued or doses reduced or delayed due to skin and subcutaneous tissue disorders.

Gastrointestinal disorders (MedDRA, SOC term) occurred in a comparable proportion of patients in both treatment arms (41%, ABI-007/carboplatin vs 38%, Taxol/carboplatin). Few patients in both treatment arms had treatment discontinued or doses reduced or delayed due to skin and subcutaneous tissue disorders.

Drug hypersensitivity and hypersensitivity occurred infrequently in both the ABI-007/carboplatin and Taxol/carboplatin arms, although these events were more common in the Taxol/carboplatin arm than in the ABI-007/carboplatin arm. Drug hypersensitivity and hypersensitivity were reported in 2 patients each (< 1%) in the ABI-007/carboplatin arm, and in 8 (2%) and 6 (1%) patients, respectively, in the Taxol/carboplatin arm. The majority of cases of drug hypersensitivity/hypersensitivity in both treatment arms were related to the taxane

component of the combinations with very small numbers of cases being related to carboplatin. Drug hypersensitivity/hypersensitivity ≥ grade 3 was not reported in the ABI-007/carboplatin arm, but was reported in 4 (<1%) patients in the Taxol/carboplatin arm. There were very few treatment discontinuations and dose interruptions due to drug hypersensitivity/hypersensitivity, with nearly all reported events occurring in the Taxol/carboplatin arm.

TEAEs with an outcome of death within 30 days of the last treatment occurred in 18 (4%) patients in the ABI-007/carboplatin arm and 19 (4%) patients in the Taxol/carboplatin arm. No TEAE with an outcome of death was reported at the preferred term level for ≥ 1% of patients in either treatment arm. Treatment-emergent SAEs (fatal and non-fatal) were reported in 18% of patients in the ABI-007/carboplatin arm and 15% of patients in Taxol/carboplatin arm. The main difference between the two treatment arms as regards treatment-emergent SAEs (fatal and non-fatal) was the higher percentage of patients with anaemia in the ABI-007/carboplatin arm (4%) compared with the Taxol/carboplatin arm (<1%).

The proportion of patients discontinuing the taxane component of the combination due to TEAEs was identical (16%) in both treatment arms, while the proportion of patients discontinuing carboplatin was similar in the ABI-007/carboplatin and Taxol/carboplatin arms (16% and 15%, respectively). The most common TEAEs resulting in taxane and carboplatin discontinuation in the ABI-007/carboplatin arm were neutropenia (3% for both) and thrombocytopenia (3% for both), and in the Taxol/carboplatin arm the most common event resulting in discontinuation was peripheral sensory neuropathy (4%, Taxol and 3%, carboplatin). All other TEAEs resulting in treatment discontinuation related to taxane and carboplatin were reported in ≤ 2% of patients in either treatment arm.

The proportion of patients who had their taxane dose reduced was 2-fold higher in the ABI-007/carboplatin arm compared with the Taxol/carboplatin arm (46% vs 23%, respectively). This difference was most likely due to the greater frequency of taxane dosing in the ABI-007/carboplatin arm (once weekly) than in the Taxol/carboplatin arm (once every three weeks), resulting in more opportunities for protocol-specified dose reductions due to taxane induced toxicities. In both treatment arms, nearly all taxane dose reductions were due to AEs/toxicities. In the ABI-007/carboplatin arm, taxane dose reductions occurred notably more frequently (≥ 2% more patients) than in the Taxol/carboplatin arm for the TEAEs of neutropenia (24% vs 9%), thrombocytopenia (13% vs 4%), anaemia (6% vs < 1%), and neutrophil count decreased (4% vs 1%). In the Taxol/carboplatin arm, taxane dose reductions occurred notably more frequently (≥ 2% more patients) than in the ABI-007/carboplatin arm for the TEAE of peripheral sensory neuropathy (5% vs <1%).

The proportion of patients with delayed/not given taxane doses was also higher in the ABI-carboplatin arm (82%) than in the Taxol/carboplatin arm (54%), as was delayed/not given carboplatin doses (72% vs 54%). In both treatment arms, the majority of delayed/not given taxane dose were due to AEs/toxicities. In the ABI-007/carboplatin arm, taxane dose delays occurred notably more frequently (≥ 2% more patients) than in the Taxol/carboplatin arm for the TEAEs of neutropenia (41% vs 12%), thrombocytopenia (30% vs 12%), anaemia (16% vs 1%), leucopenia (6% vs 1%), neutrophil count decreased (8% vs 2%), platelet count decreased (4% vs 2%), ALT increased (4% vs 2%), pneumonia (3% vs 1%), and fatigue (3% vs < 1%). In the Taxol/carboplatin arm, taxane dose delays occurred notably more frequently (≥ 2% more patients) than in the ABI-007/carboplatin arm for the TEAE of peripheral sensory neuropathy (5% vs 1%). Dosing interruptions at the time of infusion of taxane or carboplatin were uncommon occurring in < 1% of patients and < 1% of cycles in both treatment arms.

TEAEs (all grades) reported or worsening after 6 treatment cycles occurred in a similar proportion of patients in the ABI-007/carboplatin arm (28%) and the Taxol/carboplatin arm (27%), and the proportion of patients with TEAEs (grade 3 or greater) was higher in the Taxol/carboplatin arm (18%) compared with the ABI-007/carboplatin arm (14%). The general

pattern of TEAEs reported or worsening after 6 treatment cycles was consistent with the overall pattern of TEAEs.

There were no marked differences between the two treatment arms as regards clinical laboratory assessment of hepatic or renal function. The study included no assessment of treatment on vital signs or ECG findings. There were a number of TEAEs associated with ABI-007/carboplatin that occurred more notably commonly in patients aged ≥ 65 years compared with patients aged < 65 years (particularly haematological toxicities), females compared with males, and Asians compared with Whites.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The pivotal Phase III study (CA031) showed that the benefits of ABI-007/carboplatin for the treatment of advanced NSCLC are comparable with those for Taxol/carboplatin. However, Taxol/carboplatin is not a TGA approved combination for the treatment of advanced NSCLC, although the combination is included in Australian clinical oncology guidelines as an accepted treatment for the condition.

In the pivotal Phase III study, all efficacy evaluations were based on the ITT population (n=1052): 521 patients in ABI-007 arm and 531 patients in the Taxol/carboplatin arm. The ORR in patients with advanced NSCLC was statistically significantly higher in the ABI-007/carboplatin arm (33%) than in the Taxol/carboplatin arm (25%), p=0.005; pA/pT = 1.313 (95.1% CI: 1.082, 1.593). However, the clinical significance of the absolute difference between the two treatment arms of 8% in favour of ABI-007/carboplatin is unlikely to be clinically meaningful in the absence of statistically significant differences between the two arms in PFS and OS. The primary superiority analysis of the PFS (blinded radiological assessment) showed that the difference between the median duration of PFS in the two treatment arms was not statistically significant. Consequently, the primary analysis of OS (which also showed no statistically significant difference between the two treatment arms) was considered to be exploratory rather than confirmatory due to the pre-specified hierarchical statistical analysis (i.e., superiority analysis of OS to proceed only if superiority of ABI-007/carboplatin over Taxol/carboplatin had been initially established).

The non-inferiority analysis of the PFS and OS (key secondary efficacy endpoints) showed that the ABI-007/carboplatin arm was non-inferior to the Taxol/carboplatin for both parameters. In the PFS (blinded radiological assessment) non-inferiority analysis, median PFS was 6.8 months in the ABI-007/carboplatin arm and 6.5 months in the Taxol/carboplatin arm; $HR_{A/T}$ = 0.949 (95% CI: 0.830, 1.086). In the OS non-inferiority analysis, median OS was 12.1 months in the ABI-007/carboplatin arm and 11.2 months in the Taxol/carboplatin arm; $HR_{A/T}$ = 0.922 (95% CI: 0.797, 1.066). In the non-inferiority analyses of both the PFS and the OS, the upper bound of the 95% CI of the $HR_{A/T}$ was less than the pre-specified non-inferiority margin of 1.176 (i.e., non-inferiority margin of 15%).

The results for the secondary efficacy endpoints of investigator assessed ORR and PFS were consistent with the primary analysis of these endpoint based on blinded assessment. In addition, there was no statistically significant difference between the two treatment arms as regards the secondary efficacy endpoints of disease control rate (53% and 49% in the ABI-007/carboplatin and Taxol/carboplatin arms, respectively) and median duration of response (9.6 and 9.5 months in the ABI-007/carboplatin and Taxol/carboplatin arms, respectively).

The pre-specified exploratory analysis of the effect of baseline stratification factors on the ORR showed that ORR was statistically significantly higher in the ABI-007/carboplatin arm compared with the Taxol/carboplatin arm in patients with squamous cell carcinoma (41% vs

24%, p < 0.001), patients with stage IV disease (31% vs 23%, p=0.015), male patients (33% vs 24%, p=0.011), patients aged < 70 years (32% vs 25%, p=0.013), and patients from Eastern Europe (34% vs 27%, p=0.014). The corresponding exploratory unplanned analysis for OS showed that median survival was longer in the ABI-007/carboplatin arm compared with the Taxol/carboplatin in North American patients (12.7 vs 9.8 months, p=0.008), and patients aged ≥ 70 years (19.9 vs 10.4 months, p=0.009). The corresponding exploratory unplanned analysis for PFS showed no statistically significant differences between the two treatment arms for any of the stratification factors. Overall, the exploratory analyses (planned and unplanned) of the effect of baseline stratification factors and other baseline prognostic factors on ORR, PFS and OS showed consistent benefits for patients in the ABI-007/carboplatin arm compared with the Taxol/carboplatin arm.

It is considered that limited support for the benefits of the proposed ABI-007/carboplatin combination for the treatment of advanced NSCLC is provided from study CA028 in which 25 patients were treated with combination. However, no meaningful clinical data relating to the proposed ABI-007/carboplatin combination for the treatment of advanced NSCLC can be derived from studies CA015 and CA018 nominated by the sponsor as supportive as in neither study were patients exposed to the proposed combination dose regimen.

9.2. First round assessment of risks

Overall, it is considered that the risks of treatment with ABI-007/carboplatin for advanced NSCLC are satisfactory and generally comparable with those of Taxol/carboplatin, although the risk profiles of the two treatment regimens differ. The sponsor (Clinical Overview) states that "ABI-007 carboplatin is better tolerated than Taxol/carboplatin, with a marked reduction in Grade 3/4 peripheral neuropathy, neutropenia, arthralgia, and myalgia". However, the sponsor's contention that ABI-007/carboplatin is better tolerated than Taxol/carboplatin is unconvincing. Overall, it is considered that tolerability is comparable between the two treatment arms.

The pivotal Phase III study showed that the major risks of treatment with ABI-007/carboplatin at the proposed dose for the proposed indication relate to anaemia, thrombocytopenia, neutropenia, and peripheral neuropathy. While both anaemia and thrombocytopenia occurred notably more commonly in patients in the ABI-007/carboplatin arm, peripheral neuropathy occurred notably more commonly in the Taxol/carboplatin arm as did severe neutropenia. Arthralgia and myalgia also occurred commonly in patients in the ABI-007/carboplatin arm, but both of these events were reported notably more frequently in patients in the Taxol/carboplatin arm. In the ABI-007/carboplatin arm, both taxane and carboplatin dose reductions and dose delays/doses not given occurred in a greater proportion of patients than in the Taxol/carboplatin arm. However, the proportion of patients discontinuing the taxane component of the combination due to AEs was identical in both treatments, while the proportion of patients discontinuing the carboplatin component was similar. SAEs (fatal and non-fatal) were reported marginally more frequently in patients in the ABI-007/carboplatin arm than in the Taxol/carboplatin arm, but adverse events with a fatal outcome were reported in an identical proportion of patients in both treatment arms. A notably higher proportion of patients used concomitant pre-dosing medications of corticosteroids, antihistamines, drugs for acid-related disorders, and antiemetics/antinauseants in the Taxol/carboplatin arm compared with the ABI-007/carboplatin arm.

The pivotal Phase III study showed that the most commonly occurring risks (≥ 20% of patients) associated with treatment with ABI-007/carboplatin (vs Taxol/carboplatin) were alopecia (56% vs 60%), neutropenia (51% vs 48%), anaemia (44% vs 21%), thrombocytopenia (40% vs 23%), nausea (27% vs 25%), peripheral sensory neuropathy (26% vs 40%), fatigue (25% vs 23%), and peripheral neuropathy (20% vs 23%).

More TEAEs (all grades) occurred statistically significantly more commonly in patients in the AB1-007/carboplatin arm than in the Taxol/carboplatin arm (8 vs 4 events, respectively). TEAEs (all grades) reported statistically significantly (p≤0.05) more commonly in patients in the ABI-007/carboplatin arm compared with the Taxol/carboplatin arm were anaemia (44% vs 21%), thrombocytopenia (40% vs 23%), peripheral oedema (10% vs 4%), epistaxis (7% vs 2%), haemoglobin decreased (11% vs 6%), upper abdominal pain (3% vs 1%), haemorrhoids (2% vs < 1%), and nail disorder (2% vs <1%). TEAEs (all grades) reported statistically significantly (p≤ 0.05) more commonly in patients in the Taxol/carboplatin arm compared with the ABI-007/carboplatin arm were peripheral sensory neuropathy (40% vs 26%), arthralgia (25% vs 13%), myalgia (19% vs 10%), and pruritus (4% vs 2%).

The most commonly reported TEAEs (grade 3 or higher) occurring in ≥ 10% of patients in the ABI-007/carboplatin arm vs the Taxol/carboplatin arm were neutropenia (36% vs 40%), anaemia (25% vs 6%), and thrombocytopenia (17% vs 6%). The number of statistically significant TEAEs (grade 3 or higher) was similar in the ABI-007/carboplatin and Taxol/carboplatin arms (5 vs 4, respectively). TEAEs (grade 3 or higher) reported statistically significantly (p≤0.05) more commonly in patients in the ABI-007/carboplatin arm compared with the Taxol/carboplatin arm were anaemia (25% vs 6%), thrombocytopenia (17% vs 6%), haemoglobin decreased (4% vs < 1%), ALT increased (2% vs < 1%), and platelet count decreased (2% vs < 1%). TEAEs (grade 3 or higher) reported statistically significantly (p≤0.05) more commonly in patients in the Taxol/carboplatin arm compared with the ABI-007/carboplatin arm were peripheral neuropathy (5% vs 2%), peripheral sensory neuropathy (7% vs < 1%), arthralgia (2% vs < 1%), and myalgia (2% vs < 1%).

Anaemia (broadly defined to include anaemia, haemoglobin decreased, haematocrit decreased, and red blood cell count decreased), occurred more commonly in the ABI-007/carboplatin arm than in the Taxol/carboplatin arm for all grade adverse events (54% vs 24%, respectively) and for grade 3 or higher adverse events (28% vs 7%, respectively). Anti-anaemic preparations were administered to a higher proportion of patients in the ABI-007/carboplatin arm (35%) than in the Taxol/carboplatin arm (20%). In both treatment arms, a minority of patients with anaemia required blood transfusion (16%, ABI-007 vs 4%, Taxol/carboplatin). However, the majority of transfused patients in both treatment arms required only 1 transfusion. In the ABI-007/carboplatin arm, greater percentages of patients discontinued, had dose reductions, or dose delay/dose not given due to anaemia (preferred term) than patients in the Taxol/carboplatin arm. The incidence of haemorrhagic AEs was similar in the ABI-007/carboplatin and the Taxol/carboplatin arms (13% vs 10%, respectively), suggesting that the observed anaemia in both treatment arms is due to a direct toxic effect on red blood cell formation.

Thrombocytopenia (including MedDRA preferred terms of thrombocytopenia and platelet count decreased) occurred more commonly in the ABI-007/carboplatin arm than in the Taxol/carboplatin arm for all grade adverse events (45% vs 27%, respectively) and for grade 3 or higher adverse events (18% vs 7%, respectively). The majority of thrombocytopenic events (preferred term) resulted in taxane dose delays in both treatment arms, with a minority resulting in taxane dose reductions and small number in taxane discontinuation. Thrombocytopenia did not result in platelet transfusions in either treatment arm. The increased risk of thrombocytopenia observed in patients in the ABI-007/carboplatin arm appeared to result in a small increased risk of haemorrhagic adverse events (13%, ABI-007/carboplatin vs 10%, Taxol/carboplatin), predominantly due to an increased risk of epistaxis in the ABI/carboplatin arm compared with the Taxol/carboplatin arm (7% vs 2%, respectively).

Neutropenia (NCI CTCAE) showed a statistically significant reduction in severity across all grades in patients in the ABI-007/carboplatin arm relative to the Taxol/carboplatin arm (p=0.007), as did grade 3 or 4 neutropenia (p < 0.001). The incidence of neutropenia (NCI CTCAE grades 1-4) including MedDRA preferred terms neutropenia, granulocytopenia,

neutrophil count decreased, and granulocyte count decreased was higher in patients in the ABI-007/carboplatin arm compared with the Taxol/carboplatin arm (59% vs 56%, respectively), but neutropenia (NCI CTCAE) grade 3 or higher occurred more frequently in patients in the Taxol/carboplatin arm compared with the ABI-007/carboplatin arm (48% vs 42%, respectively). Febrile neutropenia was reported in 1% and 2% of the ABI-007/carboplatin and Taxol/carboplatin arms, respectively. Infection and infestation (MedDRA SOC) treatment emergent SAEs occurred in a similar proportion of patients in the ABI-007/carboplatin and Taxol/carboplatin arms (4% vs 3%, respectively).

Peripheral neuropathy (broadly defined) occurred statistically significantly ($p \leq 0.05$) more commonly in patients in the Taxol/carboplatin arm than in the ABI-007 arm (64% vs 48%), as did arthralgia (25% vs 13%) and myalgia (19% vs 10%).

Drug hypersensitivity/hypersensitivity events occurred infrequently in both the ABI-007/carboplatin and Taxol/carboplatin arms, although these events were more common in the Taxol/carboplatin arm than in the ABI-007/carboplatin arm.

There were no marked differences between the two treatment arms as regards gastrointestinal disorders or skin and subcutaneous tissue disorders (no cases of Stevens-Johnson syndrome or toxic epidermal necrolysis were reported). The ABI-007/carboplatin combination did not appear to notably impair renal, hepatic or cardiac function. However, patients were required to have adequate hepatic and renal function in order to be included in the study, and patients with clinically significant hepatic or renal function were excluded as were patients with any significant concurrent illness. No cranial nerve palsies were reported in the pivotal Phase III study.

Cardiac disorders occurred in a similar proportion of patients in both treatment arms (6%, ABI-007/carboplatin vs 5%, Taxol/carboplatin). Hepatobiliary disorders also occurred in a similar proportion of patients in the ABI-007/carboplatin and Taxol/carboplatin arms (3% vs 2%, respectively) with the majority of TEAEs (preferred terms) in both arms being hyperbilirubinaemia (2% vs 1%, respectively). Similarly, renal and urinary disorders occurred in a similar proportion of patients in both the ABI-007/carboplatin and Taxol/carboplatin arms (3% vs 2%, respectively), with no TEAE (preferred term) occurring in more than 1% of patients in either treatment arm.

TEAEs with an outcome of death occurred in 4% of patients in both treatment arms, and SAEs (fatal or non-fatal) were reported in 18% of patients in the ABI-007/carboplatin arm and 16% of patients in the Taxol/carboplatin arm. The main difference between the two treatment arms as regards treatment-emergent SAEs (fatal and non-fatal) was the higher percentage of patients with anaemia in the ABI-007/carboplatin arm (4%) compared with the Taxol/carboplatin arm (<1%).

The risks of treatment with ABI-007/carboplatin were notably increased in patients aged ≥ 65 years compared with patients aged < 65 years (particularly haematological toxicities), and in Asian patients compared with White patients. In addition, females appear to be at an increased risk of experiencing adverse events with the combination compared with males.

9.3. First round assessment of benefit-risk balance

The benefit-risk balance of Abraxane/carboplatin at the proposed dosage regimen for the proposed usage is considered to be favourable. In the pivotal Phase III study, the clinical benefits relating to PFS and OS were similar for the ABI-007/carboplatin and Taxol/carboplatin arms, and tolerability of the two treatment arms was comparable although the risk profiles differed.

10. First round recommendation regarding authorisation

It is recommended that Abraxane at a dose of 100 mg/m^2 administered IV over 30 minutes on days 1, 8, and 15 of each 21-day cycle combined with carboplatin AUC = 6 mg.min/mL on day 1 of each 21-day cycle be approved for the first-line treatment of non-small cell cancer in patients who are not candidates for potentially curative surgery or radiotherapy.

11. Clinical questions

11.1. Pharmacokinetics

No questions.

11.2. Pharmacodynamics

No questions.

11.3. Efficacy

No questions.

11.4. Safety

No questions.

12. Second round evaluation of clinical data submitted in response to questions

Not applicable.

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