CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-449/S-018

Clinical Pharmacology and Biopharmaceutics Review

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA:	20-449/SE1-018
Submission Date:	February 1, 2002
Submission Type:	NDA (Supplement)
Drug Name:	TAXOTERE (Docetaxel)
Formulation:	20 mg and 80 mg Docetaxel Concentrate for Intravenous Injection
Applicant:	Aventis Pharmaceuticals, Inc. Bridgewater, NJ
Reviewer:	Sophia Abraham, Ph.D.
Team Leader:	Atiqur Rahman, Ph.D.

I. Executive Summary

The Applicant seeks approval for the use of TAXOTERE (docetaxel) plus cisplatin as first-line combination therapy for the treatment of patients with unresectable locally advanced or metastatic non-small cell lung cancer (NSCLC) who have not previously received chemotherapy for this condition. The proposed dosing regimen is TAXOTERE 75 mg/m^2 administered intravenously over one hour immediately followed by cisplatin 75 mg/m^2 administered over 30-60 minutes, every three weeks.

A. Recommendations

Supplemental NDA 20-449 submitted for the use of TAXOTERE plus cisplatin as first-line combination therapy in patients with unresectable locally advanced or metastatic non-small cell lung cancer is acceptable to OCPB. The Statement

"Clearance of docetaxel in combination therapy with cisplatin was similar to that previously observed following monotherapy with docetaxel. The pharmacokinetic profile of cisplatin in combination therapy with docetaxel was similar to that observed with cisplatin alone. "

that was added to the **CLINICAL PHARMACOLOGY/ HUMAN PHARMACO-KINETICS** section of the current package insert for TAXOTERE is also acceptable to OCPB. No action is indicated.

/S/

Team Leader: Atiqur Rahman, Ph.D.
Division of Pharmaceutical Evaluation I

/S/

Reviewer: Sophia Abraham, Ph.D.
Division of Pharmaceutical Evaluation I

cc: NDA 20-449
HFD-150/Division file
HFD-150/Staten, Griebel, Dagher
HFD-860/Mehta, Marroum, Rahman, Abraham
CDR/Biopharm

II. Background

TAXOTERE (docetaxel) is a semisynthetic member of the taxoid family originally synthesized from 10-deacetyl baccatin III, a noncytotoxic precursor extracted from the needles of Taxus baccata and esterified with a chemically synthesized side chain. Docetaxel promotes assembly and stabilization of microtubules, altering the physiologic equilibrium between free tubulin dimers and tubulin microtubules. Docetaxel (Taxotere®) for Injection Concentrate was approved in May 1996 for the treatment of patients with advanced or metastatic breast cancer and on December 23, 1999 for the treatment of patients with advanced or metastatic non-small cell lung cancer. The recommended dose of TAXOTERE is 60-100 mg/m^2 and 75 mg/m^2 administered intravenously over one hour every three weeks for breast cancer and NSCLC, respectively. The pharmacokinetic profile of docetaxel follows a three-compartment pharmacokinetic model, with half-lives for the (alpha), (beta), and (gamma) phases of 4 min, 36 min, and 11 hours, respectively. Docetaxel was eliminated in both the urine and feces following oxidative metabolism of the *tert* -butyl ester group, but fecal excretion was the main elimination route. Within seven days, urinary and fecal excretion accounted for approximately 6% and 75% of the administered radioactivity, respectively. About 80% of the radioactivity recovered in feces is excreted during the first 48 hours as one major and three minor metabolites with less than 8% of unchanged drug.

Cisplatin and its analogue carboplatin are platinum derivatives used in the treatment of various cancers. Both compounds are composed of a platinum atom surrounded in a plane by two ammonia groups and two other ligands in the cis position. Intracellularly, cisplatin and carboplatin are activated by an aquation reaction in which the non-ammonia ligands are displaced by water. In a cell-cycle nonspecific manner, the positively charged platinum complexes that are formed react with nucleophilic sites on DNA. This produces intrastrand and interstrand cross-links, forming DNA-platinum adducts that ultimately lead to cell death. The drugs are not orally bioavailable and are therefore administered intravenously as an injection or infusion. Recommended cisplatin doses range from 75-100 mg/m^2 per cycle for combination or monotherapy in metastatic testicular and ovarian cancer. In advanced bladder cancer cisplatin is used alone at a dose of 50-70 mg/m^2 per cycle. Carboplatin clinical doses are 360 mg/m^2 per cycle as a single agent for recurrent ovarian cancer or 300 mg/m^2 per cycle as combination therapy for previously untreated ovarian cancer. The reported pharmacokinetics of total and free platinum following administration of carboplatin and cisplatin as single agents are shown in the attached table [*Van der Vijgh, Clinical pharmacokinetics of carboplatin, Clin Pharmacokin 21:242-261, 1991*].

In support of the docetaxel/cisplatin combination indication (Viz., NSCLC), the sponsor submitted two randomized, controlled, Phase III trials (TAX 326 ——— The main pivotal trial is Study TAX 326 which compared the safety and efficacy of docetaxel plus cisplatin and docetaxel plus carboplatin with an active

control, vinorelbine plus cisplatin, in chemotherapy-naïve patients with unresectable locally advanced and/or recurrent or metastaic NSCLC. As a supportive trial, Study TAX compared the docetaxel effect on survival as a single agent versus best supportive care in chemotherapy naïve patients with locally advanced, recurrent or metastatic NSCLC and good performance status. In Study TAX 326, 1218 patients with unresectable NSCLC and no prior chemotherapy were randomized to receive either TAXOTERE 75 mg/m^2 as a 1- hour infusion immediately followed by cisplatin 75 mg/m^2 over 30-60 minutes every three weeks, TAXOTERE 75 mg/m^2 as a 1 hour infusion immediately followed by carboplatin (AUC 6 mg/mL•min) over 30-60 minutes every 3 weeks, or vinorelbine 25 mg/m^2 administered over 6-10 minutes on days 1, 8, 15, 22 followed by cisplatin 100 mg/m^2 administered on day 1 of cycles repeated every 4 weeks. Median survival in the TAXOTERE + cisplatin group was 11.3 months compared to 10.1 months in the vinorelbine + cisplatin group; the 2-year survival rate was 21% and 14% respectively. The overall response rate was higher in the TAXOTERE + cisplatin group compared with the vinorelbine + cisplatin group (31.6% versus 24.5%). The median duration of response was comparable between the 2 groups (32 weeks versus 34 weeks), as was the median time to progression (22 weeks versus 23 weeks).

Clinical pharmacology and biopharmaceutics information submitted in this supplemental NDA was obtained from two Phase I trials, TAX 012 and TAX049, and one Phase I/II trial, TAX 018. Trials TAX 012 and TAX 018 assessed the pharmacokinetics (PK) of the combination of docetaxel and cisplatin given intravenously to patients with solid tumors and patients with NSCLC, respectively. Trial TAX 049 assessed the PK of the combination of docetaxel and carboplatin given intravenously to patients with advanced non-hematological cancers. A summary of these studies is shown below:

III. A Summary of the Submitted Studies

1. TAX 012, entitled "*A Phase I Study of Docetaxel and Cisplatin Combination Chemotherapy in Patients with Advanced Solid Tumors*", was an open-label, single-center, non-randomized, dose-escalation, Phase I study in 64 patients ranging in age from 21 to 74 years (33 males and 31 females). The primary objective of this study was to determine the Maximum Tolerated Dose (MTD) of docetaxel and cisplatin combination when administered as a 1-hour infusion and 3-hour infusion, respectively, every three weeks to minimally pretreated or untreated patients with solid tumors. As a secondary objective, the pharmacokinetic (PK) profiles of docetaxel and cisplatin and protein-binding of docetaxel were determined. Two dosing schemas were used. **Schema 1** involved a 3-hour interval between the end of docetaxel infusion and the beginning of cisplatin infusion. **Schema 2** involved an 18-hour interval between the end of cisplatin infusion and the beginning of docetaxel infusion. Docetaxel was administered intravenously over 1-hour infusion and cisplatin intravenously over 3-hour infusion every three weeks.

Schema 1:

Level	Docetaxel Dose mg/m^2	Cisplatin Dose mg/m^2
1	55	50
2	70	50
3	85	50
4	100	50
5	55	75
6	70	75
7	85	75
8	100	75
9	75	100
10	85	100
11	100	100

Schema 2:

Level	Cisplatin Dose mg/m^2	Docetaxel Dose mg/m^2
6	75	70
7	75	85
8	75	100
9	100	85
10	100	100

Three patients were enrolled at each dosing combination. Six patients were studied at the MTDs. Plasma samples were collected from 61 patients during first Cycle at each dose level up to 48 hours post docetaxel infusion and up to 21 hours post cisplatin infusion (47 patients on Schema 1 and 14 patients on Schema 2). Docetaxel concentrations in plasma samples were measured using an HPLC method with ultraviolet detection at 227 nm *[Vergnol et al, Determination of Taxotere in human plasma by a semiautomated high-performance liquid chromatographic method. J Chromatog 582:273-278, 1992]*. The assay was adequately validated. Plasma calibration curves for docetaxel were linear over the concentration range of μg/ml (r=). Intra- and inter-day precision was less than 5% at plasma concentrations of 0.01, 0.05, 0.5, and 2.5 μg/ml. Docetaxel % recovery was μg/ml and μg/ml. Plasma protein binding of docetaxel was determined by ultrafiltration of blood samples collected before infusion, at the end of infusion, and at 20 minutes, 1, 2, and 6 hours post infusion. Free platinum concentrations in plasma ultrafiltrates were measured using a flameless atomic absorption spectrometric method *[Ma et al. Comparison of ethanol plasma protein precipitation with ultrafilration for the measurement of unbound platinum concentration. Cancer Chemother Pharmacol38:391-394, 1996]*. Pharmacokinetic evaluation was performed on plasma data from 51 patients using model-dependent methods; three patients were excluded due to some experimental problems. Another seven patients were not evaluable due to either unreliable estimation of t½ or lack of documentation of the end of infusion time.

Results:

Table I. Mean±SD (%CV) PK Parameters for Docetaxel (Schema 1)

Dose (mg/m^2)		n	C_{max} ($\mu g/ml$)	$AUC_{0-\infty}$ ($\mu g.h/ml$)	CL ($L/h/m^2$)	V_{ss} (L/m^2)	$t_{1/2}\lambda_3$ (h)	PB (%)
Doce	CisPt							
55	50	2	2.58, 1.13	3.59,1.51	15.3,36.5	8.0,28	1.1,1.0	–
55	75	3	1.89±0.32 (17%)	2.26±0.75 (33%)	26.7±10.7 (40%)	27±12 (45%)	3.8,6.0 (n=2)	–
70	50	2	1.2,4.17	3.76,7.7	9.0,18.6	49,110	11,20.6	–
70	75	4	3.03±1.2 (38%)	4.02±1.9 (48%)	21.2±11.4 (54%)	40±15 (37%)	8.3±3.2 (38%)(n=3)	98.5% (n=1)
75	100	5	2.36±1.02 (43%)(n=6)	3.97±1.8 (47%)	22.3±9.3 (42%)	106±93 (88%)	12.1±5.1 (42%)	96.5% (n=3)
85	50	2	2.0±1.7 (86%)(n=3)	2.91,6.38	29.2,13.3	22,88	23.7 (n=1)	–
85	75	4	2.58±0.62 (24%)	3.65±1.3 (38%)	25.3±7.0 (28%)	75±36 (9%)	10.4±1.5 (15%)	–
85	100	7	3.0±0.55 (18%)(n=8)	4.2±0.72 (17%)	20.5±4.1 (20%)	85±40 (47%)	11.8±4.3 (37%)	97.3% (n=3)
100	50	4	2.9±0.64 (22%)	4.53±1.3 (29%)	23.4±6.3 (27%)	124±103 (83%)	16.2±11.2 (69%)	95.6% (n=1)
100	75	4	3.0±0.9 (30%)(n=9)	5.8±1.8 (31%)	18.5±5.2 (28%)	92±47 (51%)	15.6±8.9 (57%)	97.7%, (n=2)
100	100	1	3.57	4.18	23.9	21	4.1	97.5%

Doce [Docetaxel] CisPt [cisplatin] PB [Protein bound]
Schema 1 [3-hour interval between the end of docetaxel infusion and the beginning of cisplatin infusion]

Table II. Mean±SD (%CV) PK Parameters for Docetaxel (Schema 2)

Dose (mg/m^2)		n	C_{max} ($\mu g/ml$)	$AUC_{0-\infty}$ ($\mu g.h/ml$)	CL ($L/h/m^2$)	V_{ss} (L/m^2)	$t_{1/2}\lambda_3$ (h)	PB (%)
CisPt	Doce							
75	70	3	1.65±0.28 (17%)(n=4)	2.26±0.57 (25%)	32.4±8.8 (27%)	39±20 (50%)	3.6, 6.0 (n=2)	–
75	85	4	2.15±0.76 (36%)	3.43±1.06 (31%)	27.0±9.9 (37%)	116±94 (81%)	16.1±10.3 (64%)(n=2)	96.9% (n=1)
75	100	6	3.5±1.0 (29%)	5.85±2.7 (46%)	19.7±7.1 (36%)	94±45 (47%)	14.2±4.1 (29%)(n=5)	98.1% (n=5)

CisPt [cisplatin] Doce [Docetaxel] PB [Protein bound]
Schema 2 [18-hour interval between the end of cisplatin infusion and the beginning of docetaxel infusion]

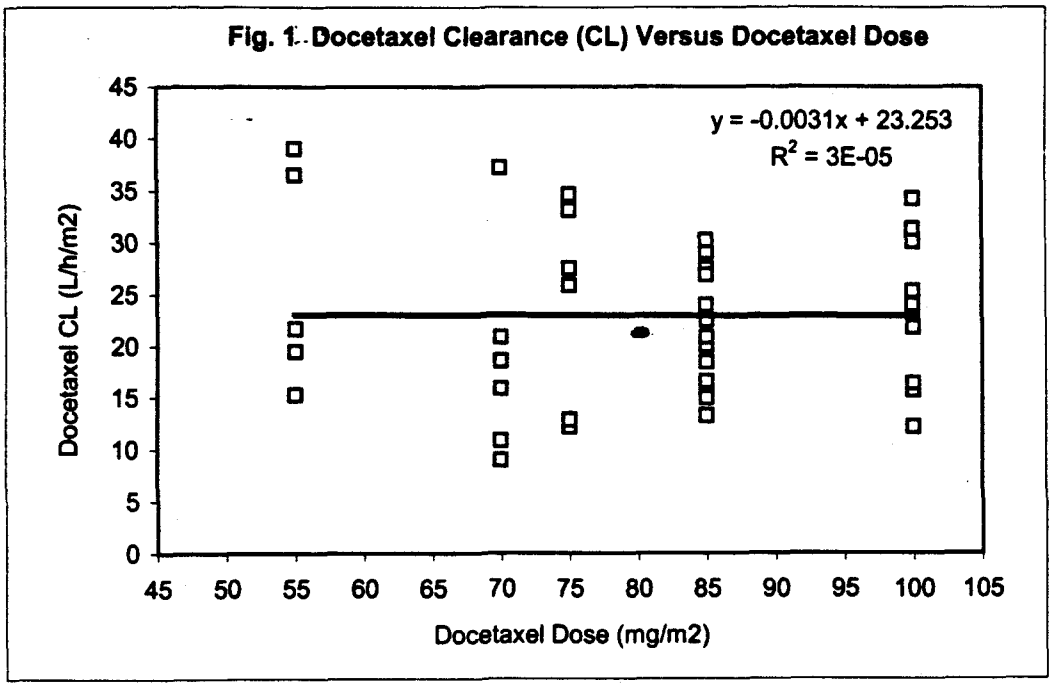


Fig. 1 Docetaxel Clearance (CL) Versus Docetaxel Dose
y = -0.0031x + 23.253
R2 = 3E-05
Docetaxel CL (L/h/m2)
Docetaxel Dose (mg/m2)
0
5
10
15
20
25
30
35
40
45
45
50
55
60
65
70
75
80
85
90
95
100
105

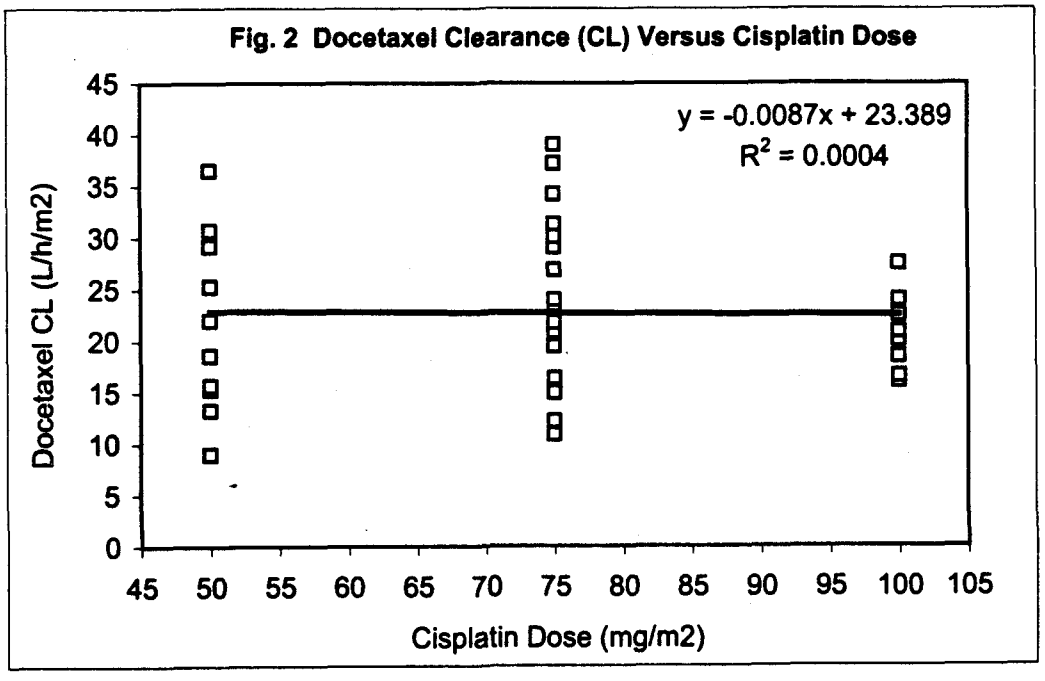
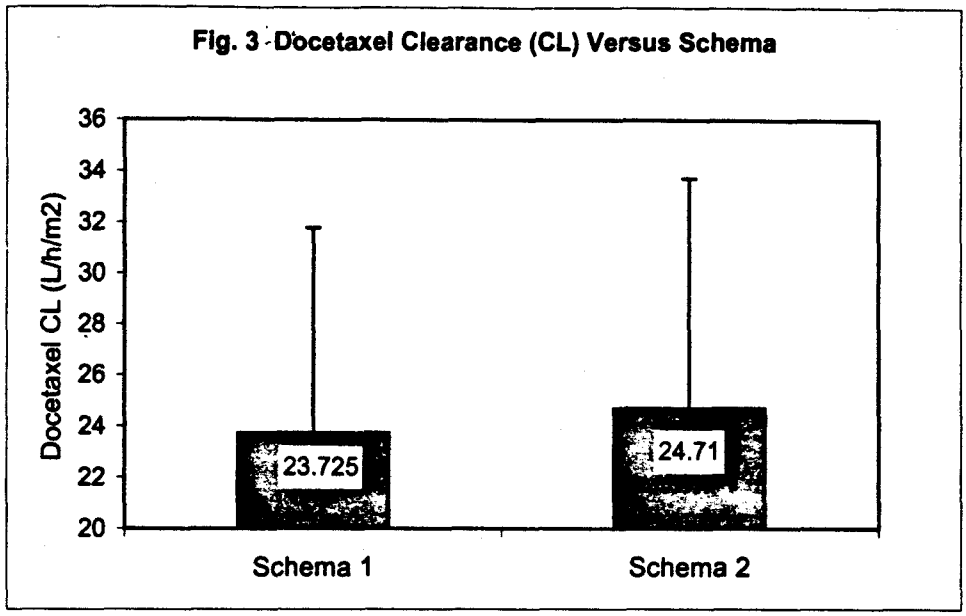


Fig. 2 Docetaxel Clearance (CL) Versus Cisplatin Dose
y = -0.0087x + 23.389
R2 = 0.0004
Docetaxel CL (L/h/m2)
Cisplatin Dose (mg/m2)
0
5
10
15
20
25
30
35
40
45
45
50
55
60
65
70
75
80
85
90
95
100
105



In this study,

- Docetaxel dose and cisplatin dose did not affect docetaxel clearance (CL); the overall mean docetaxel CL in combination with cisplatin is 22.7±7.6 L/h/m^2.
- The overall mean docetaxel CL in combination with cisplatin in this study (22.7±7.6 L/h/m^2) is comparable to that reported for docetaxel as a single agent (21±6.6 L/h/m^2) [PDR®].
- No difference was observed in docetaxel CL between Schema 1 and 2 (p= 0.753), mean CL=23.7±8.04 L/h/m^2versus 24.7±9.02 L/h/m^2, respectively.
- No difference was observed in docetaxel protein binding between Schema 1 and 2, %PB ranged from 95.6-98.5%.

Table III. Mean±SD (%CV) PK Parameters for Free Platinum (Schema 1) Following 3-hour Cisplatin infusion

Dose (mg/m^2)		n	$AUC_{0-\infty}$ ($\mu g.h/ml$)	CL ($L/h/m^2$)	V_{ss} (L/m^2)	t½ (h)	Pt_{ur} (%)
Doce	CisPt						
55	50	2	2.04, 1.72	15.9, 18.9	19.13.7	0.83, 0.51	27, 25
55	75	3	2.77±0.33 (12%)	17.8±2.3 (13%)	12.2±0.8 (6%)	0.48±0.08 (17%)	29±2.0 (7%)
70	50	3	2.46±0.02 (1.0%)	15.6±4.1 (26%)	14.5±6.4 (44%)	0.63±0.15 (23%)	35±1.0 (2%)
70	75	4	3.17±0.61 (19%)	15.9±3.8 (24%)	13.4±1.6 (12%)	0.60±0.13 (22%)	28±4.0 (14%)
75	100	3	2.52±0.14 (6%)	26.6±2.2 (8%)	24.9±7.2 (29%)	0.67±0.18 (26%)	24±3.0 (12%)
85	50	3	2.04±0.34 (17%)	16.3±3.0 (18%)	12.9±2.0 (16%)	0.62±0.16 (27%)	29±6.0 (23%)
85	75	4	1.97±0.37 (19%)	25.6±5.0 (19%)	20.3±3.8 (19%)	0.56±0.09 (16%)	22±1.0 (2%)
85	100	6	2.52±0.14 (6%)	26.6±2.2 (8%)	24.9±7.2 (29%)	0.67±0.18 (26%)	25±5.0 (20%)
100	50	4	1.7±0.38 (23%)	20.2±5.4 (27%)	12.6±1.8 (14%)	0.48±0.14 (29%)	29±5.0 (19%)
100	75	4	2.38±0.55 (23%)	21.4±4.8 (22%)	15.8±4.6 (29%)	0.52±0.17 (32%)	23±5.0 (5%)
100	100	1	3.22	20.2	17.9	0.62	25

Doce [Docetaxel] CisPt [cisplatin] Pt_{ur} [% platinum excreted in urine]
Schema 1 [3-hour interval between the end of docetaxel infusion and the beginning of cisplatin infusion]

Table IV. Mean±SD (%CV) PK Parameters for Free Platinum (Schema 2) Following 3-hour Cisplatin infusion

Dose (mg/m^2)		n	$AUC_{0-\infty}$ ($\mu g.h/ml$)	CL ($L/h/m^2$)	V_{ss} (L/m^2)	t½ (h)	Pt_{ur} (%)
CisPt	Doce						
75	70	4	2.20±0.59 (27%)	23.7±7.3 (31%)	16.1±5.5 (34%)	0.47±0.06 (13%)	24±7.0 (28%)
75	85	4	2.75±0.31 (11%)	17.9±2.2 (12%)	13.9±3.2 (23%)	0.54±0.14 (26%)	36 (n=1)
75	100	6	2.73±0.41 (15%)	18.2±2.5 (14%)	22.4±6.6 (30%)	0.47±0.11 (22%)	24±6.0 (26%)

CisPt [cisplatin] Doce [Docetaxel] Pt_{ur} [% platinum excreted in urine]
Schema 2 [18-hour interval between the end of cisplatin infusion and the beginning of docetaxel infusion]

- The mean platinum CL ranged from 15.6±4.1 $L/h/m^2$ to 26.6±2.2 $L/h/m^2$ at cisplatin doses of 50 to 100 mg/m^2; with an overall mean value of 19.7±4.8 $L/h/m^2$.

- The overall mean free platinum CL in this study (19.7±4.8 L/h/m^2) is comparable to that reported for free platinum following cisplatin administration as a single agent (21.2±1.9 L/h/m^2) (see attached table).

- No difference in platinum clearance was observed between Schema 1 and Schema 2 (p= 0.418), mean CL=20.5±5.3 L/h/m^{2}versus 19.0±4.7 L/h/m^2, respectively.

In conclusion, it does not appear that there is an interaction between docetaxel and cisplatin when they are administered in combination. The PK parameters of either drug in combination or as a single agent are comparable. Docetaxel protein binding was 96% and not influenced by cisplatin.

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2. TAX 018, entitled "*A Phase I/II Study of Docetaxel and Cisplatin Combination Chemotherapy in Patients with Unresectable Metastatic and/or Locally Advanced Non Small Cell Lung Carcinoma*", was an open-label, multi-center, non-randomized, dose-escalation, Phase I/II study in 71 patients with NSCLC. The primary objectives of this study were to determine the Maximum Tolerated Dose (MTD) of docetaxel/cisplatin combination (Phase I study) and to determine the efficacy of this combination as first-line treatment for metastatic and/or locally advanced unresectable non-small cell lung carcinoma (NSCLC) (Phase II study). As a secondary objective, the pharmacokinetic (PK) profiles of docetaxel and cisplatin and protein-binding of docetaxel were determined in the Phase I study. The Phase I dose-escalation study in 24 patients was followed by a Phase II efficacy study in 47 patients. Docetaxel was administered as a 1-hour infusion every three weeks (1 cycle). Cisplatin was given immediately after the end of docetaxel infusion also as a 1-hour infusion. The starting doses were docetaxel 50 mg/m^2 and cisplatin 75 mg/m^2. Doses were escalated as follows:

Dose-Escalation Schedule (Phase I Study)

Docetaxel (mg/m^2)	Cisplatin (mg/m^2)	Number of Patients (n)
50	75	3
75	75	13
75	100	6
100	75	2
100	100	0
75 or 100	120	0

In the Phase II study, docetaxel 75 mg/m^2 and cisplatin 75 mg/m^2 doses were given every three weeks based on the safety results of the Phase I study.

The PK of both docetaxel and cisplatin were performed during the first cycle of the Phase I study. Blood samples were collected up to 48 hours post docetaxel infusion and up to 23 hours post cisplatin infusion. Plasma protein binding of docetaxel was determined by ultrafiltration of blood samples collected before

infusion, at the end of infusion, and at 20 and 60 minutes, 2, and 6 hours post docetaxel infusion. Docetaxel concentrations in plasma samples were measured by [redacted] Platinum concentrations in plasma (total) and ultrafiltrates (free) were measured using [redacted] Pharmacokinetic evaluation was performed on plasma data from 22 patients for docetaxel and from 16 patients for cisplatin using model-independent methods.

Results:

Table V. Mean±SD (%CV) PK Parameters for Docetaxel

Dose (mg/m^2)		n	C_{max} ($\mu g/ml$)	$AUC_{0-\infty}$ ($\mu g.h/ml$)	CL ($L/h/m^2$)	V_{ss} (L/m^2)	$t_{1/2}$ (h)
Doce	CisPt						
50	75	3	1.5±0.57 (38%)	2.4±1.4 (57%)	25±11 (46%)	138±89 (64%)	16.2±13.9 (86%)
75	75	11	2.4±0.49 (20%)	3.8±1.9 (49%)	23±7.6 (34%)	139±125 (90%)	17.3±12.8 (74%)
75	100	6	2.4±0.42 (18%)	3.4±0.95 (28%)	23±6.5 (27%)	65±49 (76%)	9.0±5.2 (58%)
100	75	2	2.6, 5.1	5.6, 8.2	17.6, 12.1	75, 61	12.8, 10.5

Doce [Docetaxel] CisPt [cisplatin]

The overall mean docetaxel CL in combination with cisplatin in this study (22.4±7.6 $L/h/m^2$) is comparable to that reported for docetaxel as a single agent (21±6.6 $L/h/m^2$) [PDR®].

Table VI. Mean±SD (%CV) PK Parameters for Total Platinum Following 1-hour Cisplatin Infusion

Dose (mg/m^2)		n	C_{max} ($\mu g/ml$)	AUC_{0-24h} ($\mu g.h/ml$)
Doce	CisPt			
50	75	3	2.7±0.94 (35%)	28±8.2 (28%)
75	75	5	2.4±0.84 (35%)	27±6.2 (23%)
75	100	6	3.6±0.80 (22%)	42±12 (30%)
100	75	2	1.9, 3.7	25, 43

Doce [Docetaxel] CisPt [cisplatin]

Table VII. Mean±SD (%CV) PK Parameters for Free Platinum Following 1-Hour Cisplatin Infusion

Dose (mg/m^2)		n	C_{max} (μg/ml)	$AUC_{0-\infty}$ (μg.h/ml)	CL (L/h/m^2)	V_{ss} (L/m^2)	t½ (h)
Doce	CisPt						
50	75	3	1.75±0.37 (21%)	2.3±0.47 (20%)	22±4.8 (22%)	13±2.4 (18%)	0.42±0.08 (19%)
75	75	5	1.3±0.18 (14%)	1.8±0.17 (9%)	27±2.6 (9.6%)	17±1.1 (6%)	0.45±0.07 (15%)
75	100	6	1.9±0.52 (27%)	2.6±0.60 (23%)	26±6.2 (24%)	18±4.6 (25%)	0.48±0.03 (7%)
100	75	2	1.2, 1.5	1.6, 1.9	29, 25	–	0.50, 0.42

Doce [Docetaxel] CisPt [cisplatin]

The overall mean free platinum CL in this study (25.9±4.8 L/h/m^2) is comparable to that reported for free platinum following cisplatin administration as a single agent (21.2±1.9 L/h/m^2) (see the table attached).

In conclusion, it does not appear that there is an interaction between docetaxel and cisplatin when they are administered in combination.

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3. TAX 049, entitled "*A Phase I Study of Docetaxel and Carboplatin Combination Chemotherapy in Patients with Advanced Non-Hematological Malignancy*", was an open-label, single-center, non-randomized, dose-escalation Phase I study in 22 patients with advanced non-hematological cancers. The primary objective of this study was to determine the Maximum Tolerated Dose (MTD) of docetaxel and carboplatin when administered in combination. As a secondary objective, the pharmcokinetics of docetaxel and carboplatin combination were determined. Docetaxel was administered as a 1-hour infusion on day 1 of each three-week cycle. Carboplatin was administered as a 0.5-hour infusion immediately after docetaxel infusion at a dose targeted to an AUC value of 6 mg.min/ml depending on patients' creatinine clearance values.

Dose-Escalation Schedule

Docetaxel (mg/m^2)	Carboplatin (mg)	Number of Patients (n)
65	[6 mg.min/ml x CrCl*]+ 25	3
80		10
90		6
100		3

*CrCL [patient's creatinine clearance values in ml/min)

The pharmacokinetics of docetaxel and carboplatin were assessed during the first cycle in 20 patients for docetaxel and 21 patients for carboplatin. Two patients and one patient could not be analyzed due to unreliable plasma levels for docetaxel and carboplatin, respectively. Plasma samples were collected up to 24 hours post-dosing. Docetaxel plasma concentrations were measured by HPLC with UV detection at 225 nm *[Vergniol et al, Determination of Taxotere in human*

plasma by a semiautomated high-performance liquid chromatographic method. J Chromatog 582:273-278, 1992]. Platinum concentrations in plasma (total) and ultrafiltrates (free) were measured using [redacted]. Docetaxel PK parameters were estimated using the population (NONMEM) approach. Platinum PK parameters were calculated using non-compartmental methods.

Results:

Table VIII. Mean±SD (%CV) PK Parameters for Docetaxel

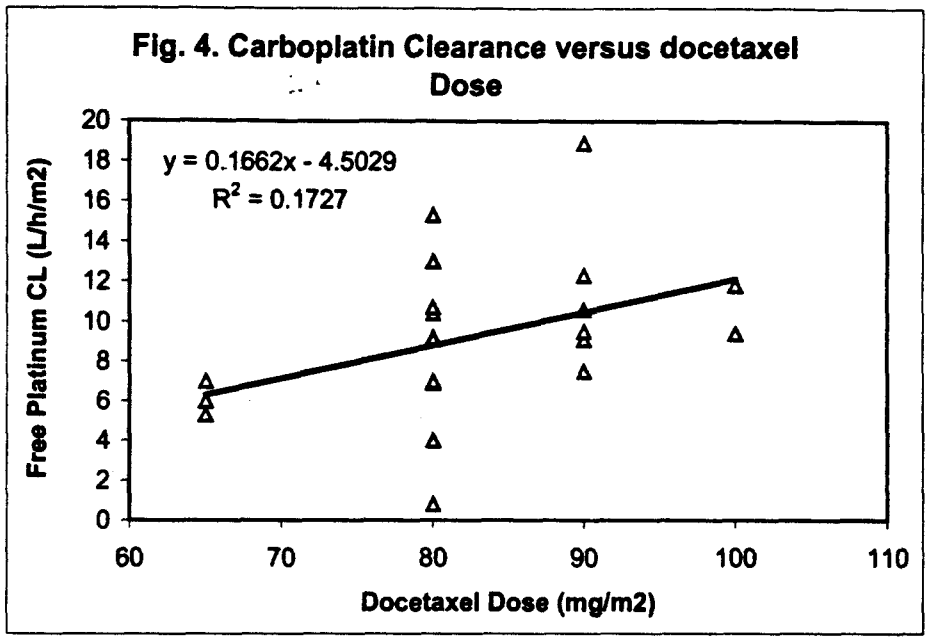
Dose (mg/m^2)	n	$AUC_{0-\infty}$ ($\mu g.h/ml$)	CL ($L/h/m^2$)
65	3	3.7±1.2 (33%)	18.8±6.1 (32%)
80	10	3.4±0.69 (20%)	24.7±6.0 (24%)
90	4	3.9±0.82 (21%)	23.7±5.9 (25%)
100	3	4.5±0.98 (22%)	26±6.2 (24%)

The overall population mean docetaxel CL (post-hoc) in combination with carboplatin in this study (23.4±5.7 $L/h/m^2$) is comparable to that reported for docetaxel as a single agent (21±6.6 $L/h/m^2$) [PDR®].

Table IX. Mean±SD (%CV) PK Parameters for Free Platinum Following 0.5-hour Infusion of Carboplatin

Dose		n	C_{max} ($\mu g/ml$)	$AUC_{0-\infty}$ ($\mu g.h/ml$)	CL ($L/h/m^2$)	V_{ss} (L/m^2)	$t_{1/2}$ (h)
Doce (mg/m^2)	Car (mg)						
65	444-780	3	21.6±10.2 (47%)	56.9±17.3 (30%)	6.1±0.9 (15%)	22.3±5.2 (23%)	4.6±0.6 (13%)
80	588-1020	10	20.2±7.0 (34%)	50.4±20.5 (41%)	8.6±4.2 (49%)	26.2±10.7 (41%)	3.9±0.5 (13%)
90	594-1236	6	20.0±4.7 (23%)	42.5±11.1 (26%)	11.3±4.0 (36%)	32.5±10.6 (33%)	4.1±1.7 (42%)
100	792, 966	2	26.9, 18.6	48.2, 42.3	9.4, 11.8	25.4, 41	3.7, 4.3

Doce [Docetaxel] car [carboplatin]



Free platinum clearance tends to increase as docetaxel dose increased when docetaxel and carboplatin are administered in combination. The overall mean CL of free platinum (9.2±3.9 L/h/m^2) is about 43% higher than that reported for free platinum after administration of carboplatin as a single agent (6.4±1.1 L/h/m^2) (see the table attached).

In conclusion, carboplatin has no effect on docetaxel clearance. There is a trend for free platinum clearance to increase as docetaxel dose increased; this may not clinically significant.

Table V Pharmacokinetic comparison of carboplatin with cisplatin, JM-40 and spiroplatin. Values are mean (± SD)

Parameter (units)	Carboplatin[a]	JM-40[b]	Cisplatin[c]	Spiroplatin[d]
Ultrafilterable platinum				
$t_{½α}$ (min)	23 ± 8	10 ± 6	6 ± 2	4.4 ± 0.7
$t_{½β}$ (min)	120 ± 11	44 ± 11	36 ± 1	
AUC/D (min · m²/L)	17 ± 4	7 ± 2	5.1 ± 0.5	0.9 ± 0.2
V_c[e] (L)	10 ± 3	11 ± 5	10 ± 2	
V_{ss}[e] (L)	17 ± 2	18 ± 5	19 ± 2	12 ± 2
CL[e] (ml/min)	107 ± 19	249 ± 54	354 ± 33	578 ± 64[f]
CL_R[e] (ml/min)	81 ± 17	73 ± 42	74 ± 29	86 ± 47[f]
CL_m[e] (ml/min)	26 ± 11	180 ± 56	281 ± 19	803 ± 52
k_m ($\times 10^{-3}$ min^{-1})	1.5 ± 0.6	10 ± 3	15 ± 1	67
k_p[g] ($\times 10^{-3}$ min^{-1})	0.24	2.0	6.8	23
$CUE_{(0-24)}$ (%D)	77 ± 5	42 ± 14	28 ± 4	30 ± 6
Total platinum				
$t_{½α}$ (min)	22 ± 10	12 ± 9	13 ± 9	2.3 ± 6
$t_{½β}$ (min)	116 ± 14	60 ± 24	43 ± 24	182
$t_{½γ}$[h] (days)	5.8 ± 1.6	4.1 ± 0.9	5.4 ± 1.0	4.0 ± 0.6
AUC/D (min · m²/L)	83 ± 32	210 ± 67	299 ± 28	548 ± 106
V_c[e] (L)	10 ± 2	12 ± 4	10 ± 3	4.9 ± 1.6
V_{ss}[e] (L)	176 ± 58	62 ± 14	52 ± 13	23 ± 6
CL[e] (L/h)	1.38 ± 0.36	0.54 ± 0.18	0.35 ± 0.03	0.20 ± 0.04
RBC (%D)	0.4 ± 0.1	0.24 ± 0.12	1.2 ± 0.2	2.4 ± 0.3

a Etterink et al (1987b)
b Etterink et al (1987c)
c Vermorken et al (1984)
d Van der Vijgh et al (1988)
e Normalised to 1.73m²
f During prolonged infusion
g Rate constant of protein binding *in vitro*; from Van der Vijgh et al (1988)
h Calculated by curve stripping over days 1-5

Abbreviations: $t_{½α}$ = distribution half-life; $t_{½β}$ = initial elimination half-life; $t_{½γ}$ = terminal elimination half-life; AUC/D = area under the plasma concentration-time curve normalised by the dose; V_c = volume of central compartment; V_{ss} = apparent volume of distribution at steady-state; CL = total body clearance; CL_R = renal clearance; CL = metabolic clearance; k_m = first-order rate constant of metabolic elimination; k_p = rate constant of *in vitro* protein binding; $CUE_{(0-24)}$ = cumulative urinary excretion over the first 24h; RBC (%D) = percentage of dose present in red blood cells at maximum concentration

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