CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-065

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA	22-065
Submission Date:	16 April 2007
Brand Name:	Ixempra®
Generic Name:	ixabepilone
Formulation:	injection
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OCP Division:	Division of Clinical Pharmacology 5
ORM Division:	Division of Drug Oncology Products
Sponsor:	Bristol Myers Squibb
Submission Type; Code:	Original NDA; 000
Dosing regimen:	40 mg/m^2 IV over 3 hours once every 3 weeks
Indication:	metastatic or locally advanced breast cancer

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1 EXECUTIVE SUMMARY

Ixabepilone is a semi-synthetic analog of epothilone B and acts as a stabilizer of microtubules. The current submission is the original NDA for ixabepilone for the treatment of metastatic breast cancer as monotherapy or in combination with capecitabine.

To support the approval of the combination with capecitabine, the sponsor conducted one primary efficacy and safety phase 3 study and one supportive phase 1/2 study. In the phase 1/2 dose-escalation study patients received Ixabepilone (40 mg/m^2 as a 3-hour IV infusion on Day 1) plus Capecitabine (1650 mg orally QD Days 1-14) every 21 days. A dose escalation up to 2000 mg QD of capecitabine was allowed if no dose limiting toxicities were seen at the lower dose. The primary objective was to determine the recommended Phase 3 dose of the ixabepilone plus capecitabine combination based on safety and best response to therapy. The results of the trial indicated that the combination of 40 mg/m^2 ixabepilone plus 2000 mg/m^2 capecitabine would provide a durable response for further evaluation.

Patients in the primary efficacy phase 3 study were randomized to either ixabepilone (40 mg/m^2 as a 3-hour IV infusion on Day 1) plus capecitabine (1000 mg/m^2 orally BID Days 1-14) or capecitabine alone (1250 mg/m^2 orally BID Days 1-14) every 21 days. Progression free survival (PFS) was the primary endpoint and the median PFS (5.85 months) in the combination arm was statistically significant compared to the median in the capecitabine alone arm (4.17 months).

To support the approval of ixabepilone as monotherapy, the sponsor conducted one primary safety and efficacy phase 2 study and two supportive phase 2 studies. The supportive studies were both monotherapy studies in different patient populations with breast cancer (taxane resistant metastatic breast cancer & first line metastatic breast cancer). All studies used the 40 mg/m^2 once every 3 weeks regimen of ixabepilone and collectively they provided data on the efficacy of ixabepilone across the spectrum of breast cancer. The primary efficacy study was in patients who had received multiple prior therapeutic regimens and who had exhausted existing treatment options. All patients received ixabepilone 40 mg/m^2 and the primary endpoint was objective tumor response. Of the 113 evaluable patients, objective tumor responses were seen in thirteen patients who had extensive metastatic disease involvement.

Based on the results from the drug-drug interaction study with ketoconazole, labeling changes were made to reflect dose adjustments for concomitant administration of strong CYP3A4 inhibitors. A dose decrease of 50% for co-administration with potent inhibitors such as ketoconazole will be clarified in the Dosage and Administration section of the label.

Dose modifications for use in patients with hepatic impairment are warranted based on the dedicated hepatic study. The sponsor proposed dosage adjustments based on AST/ALT and bilirubin levels using data from the population PK analysis and the dedicated hepatic study. The addition of the population PK data to support hepatic dosing was not considered to be robust, therefore, dose recommendations were based on the dedicated hepatic study and will be added to the Dosage and Administration section of the label for moderate and mild hepatic impairment. Ixabepilone is not indicated in patients with severe hepatic impairment.

A rifampin DDI study is ongoing and *in-vitro* p-glycoprotein screens were not conducted therefore the completion of such studies plus a QT assessment will be phase 4 commitments.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 5 has reviewed the information contained in NDA 22-065. This NDA is considered acceptable from a clinical pharmacology perspective.

Phase IV commitments

1. Submit the completed report for the rifampin drug-drug interaction evaluation and datasets for study CA163102.
2. An *in-vitro* assessment to determine if ixabepilone is a P-glycoprotein substrate or inhibitor needs to be conducted.
3. The potential for ixabepilone to affect the QT interval needs to be investigated.

Labeling Recommendations

Please see Section 3 Detailed Labeling recommendations

1. Hepatic impairment dose modifications
2. Modifications to Section 7 - Drug Interactions
3. Adjustment to Use in Special Populations Section 8.7 - Renal Impairment

Signatures:

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OCP Briefing held on Sept 17, 2007 and attended by: Raj Madabushi, Yaning Wang, Brian Booth, Atik Rahman, Shiew-Mei Huang, Larry Lesko, Art Atkinson, Leslie Kenna, Ting Ong, Mehul Mehta, Dennis Bashaw, Joga Gobburu, Chandrahas Sahajwalla, Lei Zhang, Robert Lechleider, Ed Kaminskas, Ramzi Dagher,

1.2 CLINICAL PHARMACOLOGY SUMMARY

Ixabepilone is a microtubule stabilizer being developed for intravenous use in the treatment of metastatic breast cancer (MBC) as monotherapy or in combination with capecitabine.

The applicant has conducted several phase 1 studies in patients with cancer to evaluate the safety and pharmacokinetics of ixabepilone. The Tmax of ixabepilone typically occurs at the end of infusion, and following administration the concentrations of ixabepilone decreased in a multi-exponential manner with a half-life of approximately 52 hours after a 40 mg/m^2 IV dose infused over 3 hours. The pharmacokinetics of ixabepilone are dose proportional in the dosage range of 15 to 57 mg/m^2. After administration of radio-labeled ixabepilone, 65% of the total radioactivity was eliminated in the feces with 1.6% recovered as unchanged drug. Ixabepilone is metabolized by CYP3A4/5 to form several oxidative metabolites. None of the metabolites were present in human plasma in significant amounts. The known chemical degradants of ixabepilone (BMS-249798, BMS-326412 [redacted] were detected in the plasma of humans but their exposures were <4% that of ixabepilone. In addition their cytotoxicities were 174 to 312 fold less than that of ixabepilone and therefore their plasma concentrations were only characterized in the initial first-in-man trial.

Coadministration of ixabepilone with ketoconazole increased the exposure (AUC) of ixabepilone by 79% (Cmax increased by 7%). The interaction potential with the potent CYP3A4 inducer, rifampin, is on-going. *In-vitro*, ixabepilone was not an inhibitor or inducer of CYP enzymes therefore ixabepilone is not expected to alter the plasma concentrations of other drugs. *In-vitro* P-glycoprotein screens were not completed.

Results from one phase 1 study in patients with advanced solid tumors suggested that 50 mg/m^2 administered IV over 1-hour was a feasible phase 2 dose. However, peripheral neuropathy was reported with this dose and schedule early during the initial supportive phase 2 studies for monotherapy. Based on these reports the infusion duration was extended to 3-hours and the dose was reduced to 40 mg/m^2 after the observation of gastrointestinal events in a phase 1 trial. A dose escalation trial in combination with capecitabine (1650 mg/m^2 & 2000 mg/m^2) was conducted with fixed dose ixabepilone (40 mg/m^2). The 2000 mg/m^2 dose of capecitabine when co-administered with ixabepilone had a acceptable safety and efficacy profile and this dose was chosen for investigation in further trials. To support the combination therapy, a phase 1 study was conducted to investigate the pharmacokinetics of ixabepilone and capecitabine co-administration. Results suggest that that capecitabine does not have any clinically relevant effects on the PK of ixabepilone, and ixabepilone does not effect the PK of capecitabine or 5-flurouracil.

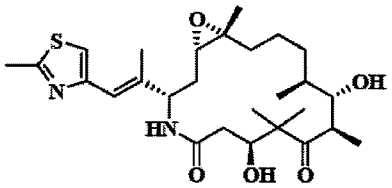
2 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Physico-chemical properties

1. Structural formula:



2. Established name: ixabepilone, BMS-247550
3. Molecular Weight: 506.7
4. Molecular Formula: $C_{27}H_{42}N_2O_5S$
5. Chemical Name: (1*S*,3*S*,7*S*,10*R*,11*S*,12*S*,16*R*)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[(1*E*)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-17-oxa-4-azabicyclo[14.1.0]heptadecane-5,9-dione

2.1.2 What are the proposed mechanisms of action and therapeutic indications?

Ixabepilone is a semi-synthetic analog of epothilone. Epothilones are a novel class of cytotoxic agents which are similar to the taxanes in that they target tubulin and are potent tubulin-stabilizing agents causing G2/M cell mitotic arrest and cell death. Ixabepilone is being developed for the treatment of metastatic breast cancer as monotherapy and in combination with capecitabine.

2.1.3 What are the proposed dosage and route of administration?

The recommended dosing regimen for ixabepilone as monotherapy and in combination with capecitabine is 40 mg/m^2 IV over three hours, once every three weeks.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Nine studies in patients with advanced cancer were completed to support the clinical pharmacology and biopharmaceutics portion of the NDA (see Table 1). In addition to the clinical pharmacology studies, the sponsor performed a population PK analysis which included pharmacokinetic data from two of the phase 2 trials for monotherapy (CA163010 and CA163009), the two ascending dose trials (CA163001 and CA163002) as well as many phase 2 trials for various other cancers (see Table 2)

TABLE 1. Studies supporting the clinical pharmacology and biopharmaceutics of ixabepilone

Study Number	Study Description	Number Enrolled	IV Dose Range
CA163001	Phase 1 ascending dose Q3W study with 1 hour and 3 hour infusions	61	7.4 - 65 mg/m^2
CA163002	Phase 1 ascending dose study given QW or on Days 1, 8, and 15 every 4 weeks. 0.5 and 1 hour infusions were used.	86	1-30 mg/m^2
CA163007	Phase 1 ascending dose study in combination with carboplatin. Ixabepilone doses given as 1 hour infusion Q3W or 1 hour infusion Days 1 and 8 Q3W.	52	20-40 mg/m^2
CA163008	Phase 1 ascending dose study in combination with doxorubicin. Ixabepilone doses given as 1 hour infusion Q3W.	12	30-35 mg/m^2
CA163025	Phase 1 ascending dose study in combination with irinotecan. Ixabepilone doses given as 3 hour infusion Q3W.	42	15-30 mg/m^2
CA163038	Phase 1 capecitabine interaction study. Ixabepilone given as a 3-hour infusion.	22	40 mg/m^2
CA163039	ADME study	8	70 mg
CA163042	Ketoconazole interaction study. Ixabepilone given as a 3-hour infusion.	27	10-40 mg/m^2
S0355	Hepatic impairment study	74	10-40 mg/m^2

TABLE 2. Studies contributing to Population Pharmacokinetics

Study Number	Study Description	Number evaluated for PopPK/number enrolled
CA163009	Open-label, multicenter; Patients with taxane-resistant metastatic breast cancer	41/66
CA163010	Open-label, multicenter, multinational; Metastatic breast cancer previously treated with an anthracycline	73/93
CA163011	Open-label, multicenter, multinational; amended to two-arm, randomized, non-comparative; Non-small cell lung cancer that failed first-line platinum-based chemotherapy	152/195
CA163012	Open-label, multicenter, multinational; Metastatic colorectal cancer previously treated with a fluoropyrimidine and irinotecan	41/51
CA163013	Open-label, multicenter, multinational, Metastatic gastric adenocarcinoma previously treated with a fluoropyrimidine and/or a platinum	13/21
CA163014	Open-label, multicenter, multinational, Metastatic gastric adenocarcinoma previously treated with a taxane	33/47
CA163015	Open-label, multicenter, multinational, Metastatic melanoma that failed previous interleukin-2 therapy	22/22
CA163036	Open-label, multicenter, multinational, Metastatic small-cell lung cancer, sensitive to first-line chemotherapy	30/38
CA163051	Open-label, multicenter, multinational, Metastatic small-cell lung cancer, refractory to first-line chemotherapy	16/30
CA163080	Open label, multicenter, multinational, Neoadjuvant treatment for breast cancer	125/161

To support the efficacy claims for the combination treatment with capecitabine the sponsor submitted two studies, one phase 1/2 study and a confirmatory phase 3 study. To support the monotherapy indication three studies were completed. Descriptions of these studies are below.

Combination therapy

Study CA163031 was a phase 1/2 study of ixabepilone in combination with capecitabine in

patients with metastatic breast cancer previously treated with a taxane and an anthracycline. The objective was to determine the recommended phase 2 dose, describe the safety profile, and any preliminary evidence of anti-tumor activity. Patients were enrolled into either schedule A or B.

- Schedule A: Ixabepilone 3-hr IV D1 Q3 week plus capecitabine D1-14 QD
- Schedule B: Ixabepilone 1-h IV D1-3 Q3week plus capecitabine D1-14 QD

Schedule B was closed to enrollment because the dosing schedule was less convenient than Schedule A and data from ongoing studies supported Schedule A administration. The ixabepilone dose in Schedule A was 40 mg/m^2. The capecitabine dose was started at 1650 mg/m^2/day, with subsequent escalation to 2000 mg/m^2/day. A total of 106 patients were enrolled in the study, 64 of whom received the recommended phase 2 dose of 40/2000 mg/m^2 of ixabepilone/capecitabine.

Study CA163046 was a phase 3 randomized, open-label, 2-arm study in patients with advanced breast cancer previously treated with or resistant to an anthracycline and taxane-resistant. In the combination arm, ixabepilone was administered as 40 mg/m^2 IV over 3 hours on Day 1 of a 21-day cycle along with capecitabine at 1000 mg/m^2 by mouth BID on Days 1-14. The capecitabine monotherapy arm received 1250 mg/m^2 of capecitabine BID for 14 days. Three-hundred sixty nine (369) women received ixabepilone plus capecitabine and 368 received capecitabine as monotherapy for a minimum of 18 cycles. The primary endpoint of this study was to compare progression-free survival (PFS) with ixabepilone plus capecitabine versus capecitabine alone. Sparse PK sampling was obtained in this study in Chinese patients.

Monotherapy

Study CA163081 was the primary efficacy study. It was a single-arm, phase 2 study in patients with advanced breast cancer who were anthracycline, taxane or capecitabine resistant. One hundred twenty six (126) patients were treated with ixabepilone 40 mg/m^2 infused over 3 hours. The primary efficacy endpoint was objective response rate (ORR). The secondary efficacy endpoints included overall response, time to response, duration of stable disease, PFS and OS. Tumor responses were durable with a median duration of response of 5.3 months. The ORR as assessed by the investigator was 18.3% for all treated patients with 23% achieving a partial response and 55% with stable disease.

Supportive studies CA163009 and CA163010 were open-label Phase 2 studies of ixabepilone in patients with metastatic or locally advanced breast cancer. CA163009 was conducted in patients with advanced breast cancer that was taxane resistant. CA163010 was conducted in patients with advanced breast cancer, who were previously treated with an anthracycline in the adjuvant setting, had relapsed with metastatic disease, and had not been treated for metastatic disease. In both studies, ixabepilone was initially administered at a higher dose and shorter infusion and was amended as toxicity data became available. The majority of the subjects received the 40 mg/m^2 dose infused over 3 hours. Only data from the recommended dose (40 mg/m^2 infused over 3 hours) are presented in this summary. The primary efficacy endpoint for both studies was overall response rate with duration of response, PFS and OS as secondary endpoints. For study CA163009, among the 49 treated with 40 mg/m^2, 6 achieved a PR to ixabepilone therapy. The six responders received a median of 10.5 cycles of ixabepilone therapy and had a median duration of response of 10.4 months. Among the 65 patients treated in CA163010, 27 achieved a

PR to ixabepilone therapy with a median duration of response of 8.2 months. Of the 27 patients who responded to ixabepilone in this study, six patients were without progression for more than 12 months. Sparse drug concentration samples were obtained in both studies.

Another supportive study (CA163080) was completed where ixabepilone was administered as neoadjuvant therapy. The study population consisted of women who had histologic confirmation of invasive breast adenocarcinoma not amenable to primary breast conservation surgery. Efficacy endpoints included pathologic response and best overall response, based on the review of clinical, radiographic, and histopathologic evidence at the primary tumor site at the end of treatment and prior to surgery. Among all treated patients, 61% were responders (ie, had a best overall response of CR or PR), and 35% were non-responders (ie, SD or PD). Of 161 treated patients, 18% achieved pathological complete response in the breast (pCRB) and 11% achieved pathological complete response in both breast and lymph nodes (pCRBL).

2.2.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

Combination therapy

Progression-free-survival (PFS) was the primary endpoint for the phase 3 study CA163046. PFS was measured from the time of randomization to progressive disease (PD) per Independent Radiology Review Committee (IRRC) using modified RECIST criteria. Secondary efficacy analyses based on IRRC assessments included ORR, time to response, and duration of response. The ORR was defined as the number of patients in each group whose best IRRC response was complete response (CR) or partial response (PR), divided by the number of randomized patients in that group. Time to response was defined as the time from first dose of study treatment until measurement criteria were first met for PR or CR. Duration of response was computed for all patients in each group with a best response of PR or CR and was measured from the time when measurement criteria were first met for PR or CR until the first date of documented progression or death.

For study CA163931 an efficacy data set was defined for the 40/2000 mg/m^2 dose cohort. The primary efficacy endpoint was the tumor response rate. The response rate was defined as the number of responders, CRs and PRs, divided by the number of response-evaluable patients. The secondary efficacy endpoints included duration of response, time to response, and progression-free survival (PFS).

Monotherapy

For the primary phase 2 study (CA163081), the primary efficacy endpoint was objective response rate (ORR), defined as the number of patients with a best response of complete response (CR) or partial response (PR), as assessed by the IRRC, divided by the total number of response-evaluable patients. Secondary efficacy analyses based on IRRC assessments included duration of response, progression-free survival, and time to response. In addition, the overall survival was calculated for all patients.

For the two supportive studies (CA163090 & CA163010) the primary efficacy endpoint was response rate (RR). The RR was equal to the number of responders (patients with a tumor assessment of CR or PR) divided by the number of response-evaluable patients. Response was assessed according to modified World Health Organization (WHO) criteria. The secondary

efficacy endpoints included duration of response, time to progression, and survival.

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Plasma and urine samples were assayed for ixabepilone and its chemical degradation products, BMS-249798 and/or BMS-326412, by validated liquid chromatography tandem mass spectrometry methods (LC/MS/MS) for all studies.

2.2.4 Exposure-response

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

No specific exposure-response analyses were performed for efficacy. Doses for ixabepilone were selected on the basis of safety and tolerability. The efficacy of the selected dose of 40 mg/m^2 was tested in the phase 3 trials either as monotherapy or in combination with capecitabine.

2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

Exposure-response analyses were performed for neutropenia and neuropathy. Concentration dependent inhibition of absolute neutrophil count (ANC) with a time delay in the effect was observed. A semi-mechanistic non-linear mixed effects model for inhibition of neutrophil progenitor formation in the bone marrow by ixabepilone was developed. The model provided adequate description of the ANC-time profiles as shown in Figure 1. The parameters of the final model are shown in Table 3.

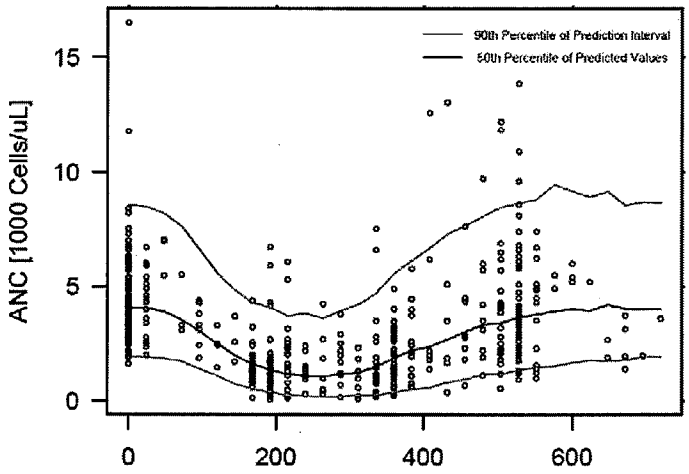


FIGURE 1: Visual predictive check for the final base model.

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TABLE 3. Parameter estimates for the final base model.

Parameter [Units]		Estimate[a]	Std. Error (SE%)	95% Conf. Interval
		Fixed Effects		
MTT [hr]	θ_1	105	3.78 (3.60)	97.6 - 112
E_{max}[-][b]	θ_2	1.00		
γ [-]	θ_3	0.132	0.0102 (7.73)	0.112 - 0.152
$C_{N,0}$ [1000/μL]	θ_4	4.08	0.154 (3.77)	3.78 - 4.38
EC_{50} [μg/mL]	θ_5	0.0141	0.00222 (15.7)	0.00975 - 0.0185

The estimated EC_{50} is 14 ng/mL. The highest peak concentrations of ixabepilone in the patient population is about 100-fold higher than the EC50 value, suggesting a strong suppression of bone marrow function immediately after ixabepilone administration. Even 2 days after dosing, approximately 50% of plasma concentration values observed in the patients were still higher than the EC_{50}, indicating a sufficient suppression of bone marrow function. Ixabepilone-associated neutropenia is not dependent on age, baseline ANC value, ECOG performance score, or study (taxane-refractory or anthracycline pre-treated subjects). Model based simulations suggest that risk of neutropenia does not change dramatically over 30 – 50 mg/m^2 despite dose-dependent increase in neutropenia.

Analyses to predict time-to-first neuropathy did not show any exposure-response relationship.

2.2.4.3 Does this drug prolong the QT or QTc interval?

No information regarding the potential to prolong the QT or QTc interval was submitted.

2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The dose and the dosing regimen proposed by the sponsor for monotherapy and in combination with capecitabine are reasonable.

The dose and dosing regimen for ixabepilone monotherapy was predominantly selected based on tolerability. Ixabepilone 50 mg/m^2 administered intravenously over 1 hour was initially proposed as the recommended Phase 2 dose based on results from the Phase 1 dose escalation study (CA163001) conducted with this schedule in patients with advanced solid tumors. Owing to early neuropathy and observation of frequent serious gastrointestinal events, the dosing schedule was amended to 40 mg/m^2 infused over 3 hours. This dose was tolerable and active and was used in phase 3 studies.

The proposed treatment schedule of 40 mg/m^2 ixabepilone plus 2000 mg/m^2 capecitabine is based on results of CA163031 and data from the Phase 2 ixabepilone monotherapy program in metastatic breast cancer. Study CA163031 established that the proposed doing regime was convenient and had acceptable adverse event profile, while the efficacy and safety of the ixabepilone regimen was established in the Phase 3 monotherapy study in metastatic breast cancer.

2.2.5 Pharmacokinetic characteristics of the drug and its major metabolites

2.2.5.1 What are the single dose and multiple dose PK parameters?

The initial patient tolerability studies (CA163001 and CA163002) investigated different infusion lengths (0.5, 1 hour and 3 hours) and various dose ranges of ixabepilone (1-65 mg/m^2). The majority of the dose-escalation data is for a 1-hour IV infusion. Only data for 40 mg/m^2 and 50 mg/m^2 is available for the indicated 3-hour IV infusion length.

The pharmacokinetics of ixabepilone are consistent over the infusion times studied with the Cmax of shorter infusions typically higher than the Cmax of a similar dose infused over 3-hours (see Table 4).

TABLE 4. Pooled summary of single-dose ixabepilone pharmacokinetic parameters following various doses and infusion times in patients with cancer.

Dose (mg/m^2)	Cmax (ng/mL) Geom. Mean (CV%)	AUC(INF) (ng h/mL) Geom. Mean (CV%)	T-Half (h) Mean (SD)	Tmax (h) Median (Min, Max)
30 min infusion Study CA163002				
20 (n = 3)	231.4 (43)	1013.7 (90)	53.0 (42)	0.27 (0.25, 0.27)
25 (n = 12)	432.6 (41)	1200.7 (51)	42.7 (28)	0.48 (0.25, 0.57)
30 (n = 4)	589.8 (74)	1457.5 (26)	36.0 (29)	0.48 (0.25, 0.52)
1-hour infusion Studies CA163001 and CA163002				
15 (n = 9)	165.50 (52)	751.8 (48)	38.0 (29)	0.93 (0.5, 1)
20 (n = 7)	218.1 (50)	1437.4 (80)	42.4 (33)	0.97 (0.95, 0.97)
25 (n = 27)	242.0 (37.3)	1344.6 (53)	42.3 (37)	0.93 (0.47, 1.3)
30 (n = 3)	403.0 (80)	1383.3 (22)	36.4 (20)	0.5 (0.5, 0.5)
50 (n = 20)	674.4 (43)	2485.4 (42)	28.4 (27)	0.97 (0.5, 1.17)
57 (n = 3)	1149.8 (19)	3480.8 (25)	31.6 (17)	0.97 (0.5, 0.97)
3-hour infusion Studies CA163001, CA1630038, CA1630040, CA1630042[a]				
40 (n = 73)	251.9 (56)	2142.5 (48)	52.1 (61)	2.98 (0.97, 3.25)
50 (n = 8)	280.7 (46)	2384.6 (47)	33.3 (32)	2.97 (1.5, 2.97)

a: results for Tmax are from study CA163001 and CA163038 only

Plasma concentration data from studies CA163001 and CA163002 were combined for the 1-hour infusion of doses with pharmacokinetic data for at least 3 patients. Figure 2 shows the mean concentration time profiles up to 8 hours of ixabepilone obtained from patients with cancer following single IV doses of ixabepilone at 15 mg/m^2 (n = 9), 20 mg/m^2 (n = 7), 25 mg/m^2 (n = 27), 30 mg/m^2 (n = 3), 50 mg/m^2 (n = 20) and 57 mg/m^2 (n = 3).

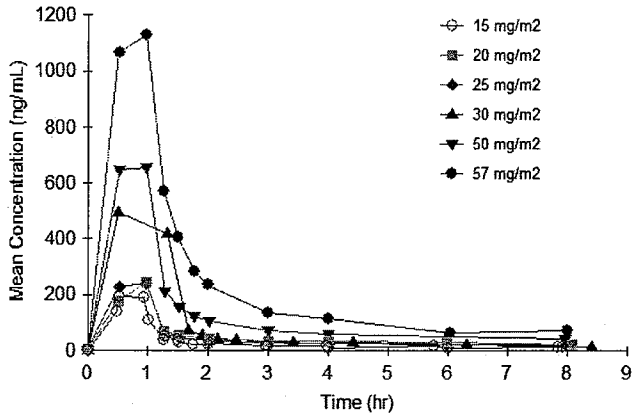

FIGURE 2: Mean ixabepilone concentration vs. time profiles after 1-hour IV infusions of ixabepilone 15, 20, 25, 30, 50 or 57 mg/m^2 in patients with cancer (Studies CA163001 & CA163002).

After a single 40 mg/m^2 3-hour IV infusion of ixabepilone (n = 14) , concentrations in blood decreased in a multi-exponential fashion with an average half-life of 52 hours in patients with advanced cancer (see Figure 3). BMS-249798, the oxazine chemical degradant of ixabepilone, was assessed in study CA163001 (n = 4). The exposure of patients to BMS-249798 was only 4% (see Table 5) of the ixabepilone exposure and therefore was not assessed in future clinical pharmacology studies. The PK of BMS-326412, the diol chemical degradant of ixabepilone was only assessed for the 3-hour IV infusion 50 mg/m^2 dose. No data on the 3-hour IV infusion at 40 mg/m^2 is available. At the 50 mg/m^2 dose, the exposure of BMS-326412 was less than 0.5% of ixabepilone exposures at the same dose. Similar to BMS-249798, the pharmacokinetics of BMS-326412 was not assessed in other trials.

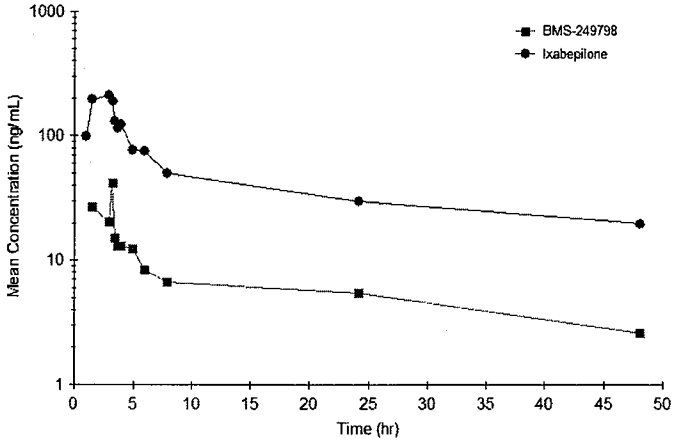

FIGURE 3: Mean ixabepilone and BMS-249798 concentration vs. time profiles after ixabepilone 40-mg single 3-hour IV infusion in cancer patients (Study CA163001).

TABLE 5. Single-dose ixabepilone and BMS-249798 pharmacokinetic parameters following a 3-hour IV infusion of 40 mg/m^2 ixabepilone in patients with cancer.

	N	Cmax (ng/mL) Geo. Mean (CV%)	AUC(0-T) (ng h/mL) Geo. Mean (CV%)	AUC(INF) (ng h/mL) Geo. Mean (CV%)	Tmax (h) Median (Min, Max)	T-Half (h) Mean (SD)
Ixabepilone	14	247 (72)	1847 (54)	2406 [a] (56)	2.97 (1.47,3.25)	35 [a] (12)
BMS-249798	4	24.6 (110)	86.1 (85)	-	2.46 (1.50, 3.50)	-

a: n = 13

Table 6 summarizes the single (Cycle 1) and multiple dose (Cycle 2) PK parameters in patients with cancer who received a 1-hour IV infusion of 50 mg/m^2 once every 3 weeks in study CA163001. Values of the ixabepilone AUC ratio (SD:MD) were near unity and indicate little or no accumulation with after 2 cycles of ixabepilone administered once every 3 weeks.

TABLE 6. Single- and multiple-dose pharmacokinetic parameters after a 1-hour IV infusion of 50 mg/m^2 ixabepilone dose in patients with cancer.

Pharmacokinetic Parameter	Cycle 1 (n = 20)	Cycle 2 (n = 18)
Cmax (ng/mL) Geo. Mean(CV%)	674 (43)	657 (47)
AUC(INF) (ng•h/mL) Geo. Mean(CV%)	2485 (42)	2145 (55) [b]
Tmax (h) Median (Min, Max)	0.97 (0.50,1.17)	0.97 (0.50,1.47)
T-Half (h) Mean (SD)	29 (8)	36 (14) [b]

b: n = 17

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

Not applicable. All studies with ixabepilone were done in patients with cancer.

2.2.5.3 What are the characteristics of drug absorption?

Following a 3-hour IV infusion of 40 mg/m^2 the Cmax of ixabepilone was typically observed by the end of infusion.

2.2.5.4 What are the characteristics of drug distribution?

Protein Binding

The serum protein binding of ixabepilone in humans was determined *in vitro* by ultrafiltration. Based on the concentrations observed in clinical pharmacokinetic studies concentrations of 50, 500, and 5000 ng/mL of ixabepilone were studied. The percentages ixabepilone bound to proteins at concentrations of 50, 500 and 5000 ng/mL were 76.6%, 72.0% and 67.1%, respectively. The protein binding of ixabepilone was not concentration dependent from 50 ng/mL to 5000 ng/mL.

Blood/Plasma Ratio (C_{rbc}/C_p)

Blood cell distribution of ixabepilone was determined in human blood (rpt 930011862). Samples

were incubated for 1 hour at 37°C at ixabepilone concentrations of 50, 500 and 5000 ng/mL. The blood to plasma concentration ratio (C_{blood}/C_{plasma}) for ixabepilone was 0.65 ± 0.03, 0.72 ± 0.03, 0.85 ± 0.05 at nominal concentrations of 50, 500 and 5000 ng/mL indicating that ixabepilone distributes freely in human red blood cells. The C_{blood}/C_{plasma} ratios of ixabepilone were dependant on concentration within the drug concentration range of 50 to 5000 ng/mL.

Volume of Distribution

The mean volume of distribution at steady-state (Vss) of ixabepilone in clinical studies at the proposed therapeutic dose of 40 mg/m^2 administered as a 3 hour infusion was 1844 L. Compared to the human total body water (42 L), the Vss in humans is approximately 44-fold greater than total body water, indicating that ixabepilone undergoes extensive extravascular distribution in humans.

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

Eight subjects with cancer received 70-mg [^{14}C]-ixabepilone containing 80 μCi of total radioactivity by IV infusion over 3 hours (Study CA163039). Approximately 86.2% of total radioactivity was recovered over the 7 days of the study with 64% recovered in the feces and 21% recovered in the urine. The results from this ADME study suggest that ixabepilone is excreted by both renal and biliary routes in humans, with the main route of elimination via the bile into the feces.

2.2.5.6 What are the characteristics of drug metabolism?

The human plasma, urine and fecal samples from the ADME study (Study CA163039) in eight cancer patients were analyzed for metabolic characterization (RPT 930012339).

Unchanged ixabepilone was the major component in the urine and plasma while BMS-249798, BMS-326412 and [redacted], known degradants of ixabepilone, were also detected in plasma, urine and/or feces in smaller amounts (see Table 7). The identified metabolites in human plasma, urine and feces were oxidized metabolites.

In plasma unchanged ixabepilone represented 26% and 20% of total radioactivity at 4 and 8 hours respectively. All other metabolites identified in plasma were minor and compromised <10% of total radioactivity (TRA) at 4 and 8 hours. Approximately 5.6% and 1.6% of the administered dose was excreted unchanged in the urine and feces, respectively.

TABLE 7. Distribution of Radioactivity in Plasma, Urine and Fecal samples from ADME Study CA163039

Compound	Plasma (%) 4 h	Plasma (%) 8 h	Urine (%)	Feces (%)
Ixabepilone	26.79	20.57	22.47	3.10
BMS-249798	2.74	-	8.12	6.7
BMS-326412 & M8	8.57	2.77	5.37	5.98
M19	2.86	2.58	0.64	1.32
M41	0.86	2.58	3.01	3.39
[redacted]	-	-	7.24	4.52
Others	58.18	71.50	44.58	69.59

Numerous other minor drug related components in the plasma extracts, including metabolites

M19 (M-2 metabolite) and M41 (a hydroxylated metabolite) which each corresponded to <5.4% of plasma radioactivity. The known degradants of ixabepilone, BMS-249798, BMS-326412 were detected in plasma extracts in small amounts (2.7-8.6% of the plasma radioactivity).

The biotransformation pathway of ixabepilone is shown below in Figure 4. CYP3A4/5 is responsible for the oxidative metabolism of ixabepilone.

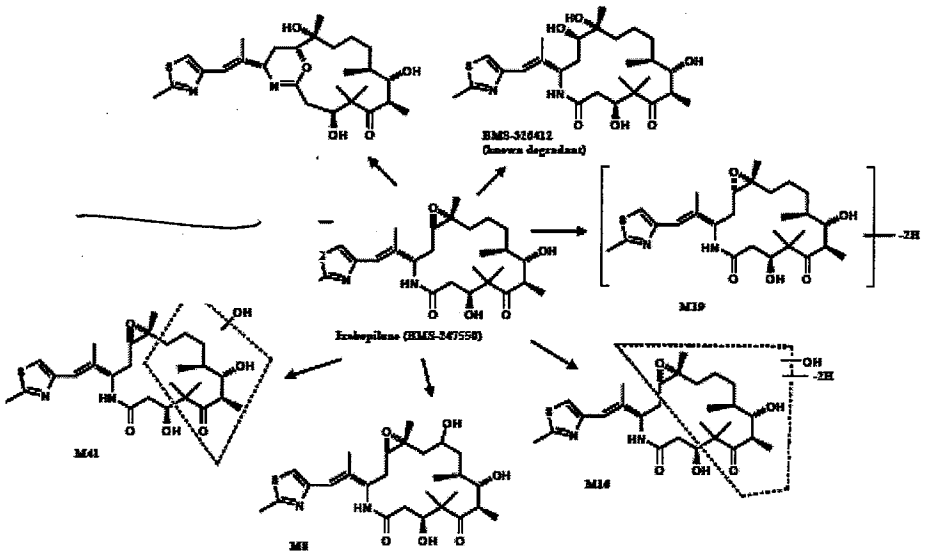

FIGURE 4: Proposed biotransformation of [^{14}C]-ixabepilone in humans

In order to assess whether the oxidative metabolites of ixabepilone possess cytotoxicity sufficient to cause biologically meaningful effects, ixabepilone (10 μM) was incubated in HLM in the presence of NADPH for 0, 10, 30 and 60 min. The resultant incubation mixtures were then tested for cytotoxicity by a clonogenic cell survival assay in the HCT116 human colon carcinoma cell line. It was demonstrated that the cytotoxicity of the incubation mixtures decreased rapidly with increasing incubation time and the degree of cytotoxicity reduction correlates directly with the disappearance of ixabepilone from the incubation mixtures. In conclusion, the oxidative metabolites formed from the liver microsomal metabolism of ixabepilone are unlikely to contribute to the overall cytotoxicity of ixabepilone.

2.2.5.7 What are the characteristics of drug excretion?

Route of Elimination

Ixabepilone is excreted by renal and biliary routes in humans with the major route of elimination likely via the bile into the feces. Over 7-days post a 70 mg IV [^{14}C]-ixabepilone dose in the human ADME study, 64% of total radioactivity was recovered in the feces and 21% of total radioactivity was recovered in the urine. Approximately 5.6% and 1.6% of the administered dose was excreted unchanged in the urine and feces, respectively.

Clearance

The mean (SD) clearance of ixabepilone following a 40 mg/m^2 dose infused over 3-hours in patients with cancer was 35.3 (15.2) L/h. Ixabepilone clearance ranged from 25 to 50.9 L/h across studies with varying IV doses and infusion times,

Half-life

The ixabepilone half-life in cancer patients receiving a 3-hour IV infusion of 40 mg/m^2 was approximately 52 hours.

2.2.5.8 Based on PK parameters, what is the degree of linearity or non-linearity based in the dose-concentration relationship?

The dose proportionality and PK linearity for ixabepilone administration as a 1-hour infusion can be extrapolated from studies CA163001 and CA163002. Combining these two studies the following dose levels had PK parameters for at least 3 patients: 15, 20, 25, 30, 50 and 57 mg/m^2. The pharmacokinetic results indicate that AUCinf increases in a dose related manner across the dose range of 15 to 57 mg/m^2 (see Figure 5). Cmax did not show the proportional increases between the dosing range of 15 to 25 mg/m^2 but dose proportional increases were seen between 30 and 57 mg/m^2.

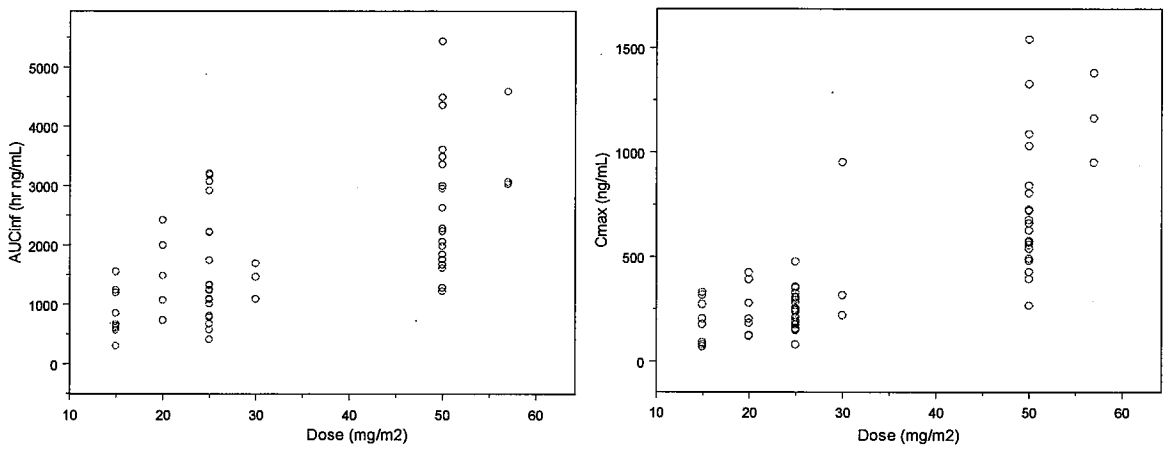

FIGURE 5: Ixabepilone AUCinf and Cmax versus dose in patients with cancer receiving at 1-hour IV infusion.

2.2.5.9 How do the PK parameters change with time following chronic dosing?

The pharmacokinetics of chronic dosing for the 3-hour IV infusion once every three weeks was not addressed. Given that the half-life of for a 3-hour IV infusion of 40 mg/m^2 ixabepilone is 52 hours no accumulation in plasma is expected when dosing is once every 3 weeks.

2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

The variability between patients with cancer ranged between 47-55% for pharmacokinetic measures of exposure. The variability seen in patients may include variability in treatment practices across the large number of clinical sites including; concomitant medications, variability in dosing and sampling times and increased variability in subjects underlying disease status.

2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Based on population pharmacokinetic analysis, no clinically significant differences in exposure were observed by age, gender, race, weight, height, disease. The clearance of ixabepilone was similar between mild/moderate renally impaired patients and patients with normal renal function. Markers for hepatic function such as AST, ALT and total bilirubin were not significant predictors of ixabepilone clearance. It should be noted that the range of total bilirubin in the population pharmacokinetic database was less than 1.5 ULN. For more information please see the pharmacometric review.

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

2.3.2.1 Pediatric patients

There were no pediatric studies included in the current submission.

2.3.2.2 Renal impairment

The population pharmacokinetic analysis revealed a trend for an increase in clearance with increase in creatinine clearance (see Figure 6). However, the clearance among normal, mild impairment (50 – 80 mL/min) and moderate impairment (30 – 50 mL/min including 4 patients less than 30 mL/min) patients were similar.

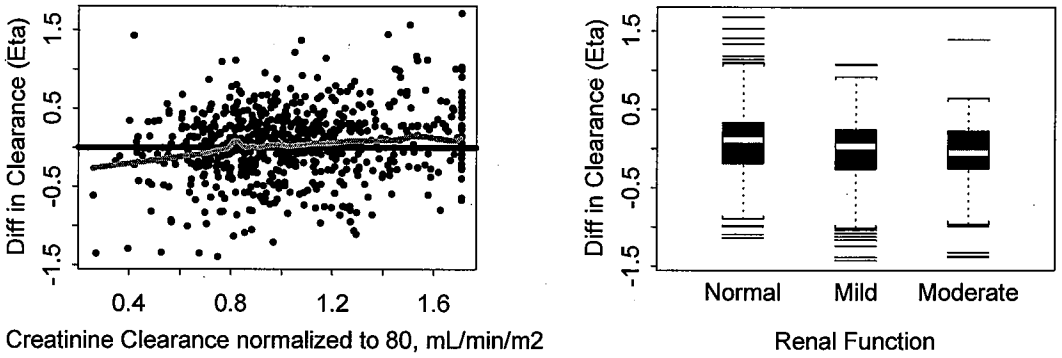

FIGURE 6: No clinically significant effect of creatinine clearance on Ixabepilone clearance

No specific study was conducted in patients with renal impairment. Given that 5.49% of the administered dose of ixabepilone is eliminated renally, adjustments for renal impairment do not appear necessary.

2.3.2.3 Hepatic impairment

To investigate the ideal dosing strategy for patients with hepatic impairment the sponsor

combined data from the dedicated hepatic study S0355, the population PK analysis, and clinical safety data from 240 patients treated with monotherapy ixabepilone at 40 mg/m^2 and from 431 patients with 40 mg/m^2 ixabepilone plus 2000 mg capecitabine.

Dedicated Hepatic Study S0355

A study investigating the effect of hepatic impairment on the PK of ixabepilone was completed ——————————Study S0355). Patients were stratified based on their degree of hepatic dysfunction using the NCI Cancer Therapy Evaluation Program criteria:

	Group A	Group B		Group C	Group D
	Normal Hepatic Function	Group B1 Mild	Group B2 Mild	Moderate	Severe
Bilirubin	≤ ULN	≤ ULN	> 1.0 x ≤ 1.5 x ULN	> 1.5 x ≤ 3 x ULN	> 3 x ULN
AST	≤ ULN	> ULN	Any	Any	Any

AST: aspartate aminotransferase; ULN: upper limit of normal

In addition, a dose-escalation study design was used in order to evaluate the MTD of single dose ixabepilone within each hepatic dysfunction group based on prospectively defined dose-limiting toxicities. The following dose escalation schema was employed:

Dose Level	Group A Normal Hepatic Function	Group B Mild Hepatic Dysfunction	Group C Moderate Hepatic Dysfunction	Group D Severe Hepatic Dysfunction
Level 1	40	30	20	10
Level 2	--	40	30	20
Level 3	--	--	40	30
Level 4	--	--	--	40

Note: doses are expressed in mg/m^2

Pharmacokinetic sampling was performed in Cycle 1 for all patients for up to 144 hours following the start of the ixabepilone infusion. Of the seventy-four patients who where treated, 73 had pharmacokinetic results. The PK for 5 patients in the 10-mg/m^2 dose level of the severe dysfunction group could not be adequately characterized due to lack of quantifiable plasma concentrations after 24 hours. Therefore, all patients (n=9) at the 10-mg/m^2 dose level of the severe dysfunction group (Group D) were excluded from the statistical analysis of dose-normalized AUC(INF).

Below in Table 8 is the breakdown of the doses studied in each group and the summary pharmacokinetic parameters at those doses.

TABLE 8: Ixabepilone pharmacokinetic parameters by group and dose level.

Group	Dose (mg/m^2)	Cmax (ng/mL)	AUC(INF) (ng·h/mL)	AUC(0-T) (ng·h/mL)	Thalf (h)
	N	Geo.Mean (CV%)	Geo.Mean (CV%)	Geo.Mean (CV%)	Mean (SD)
A	40 (N = 17)	255 (52)	2155 (53)	1698 (65)	64.3 (50.0)
B	30 (N = 12)	178 (45)	1812 (58)	1464 (59)	62.0 (51.6)
	40 (N = 14)	340 (48)	2833 (60)	2447 (55)	56.7 (35.2)
C	20 (N = 10)	90 (75)	1464 (69)	1079 (72)	65.0 (35.6)
	30 (N = 3)	143 (68)	1829 (24)	1542 (22)	50.7 (11.0)
D	10 (N = 9)	54 (201)	424[a] (128)	305 (142)	35.1[a] (31.1)
	20 (N = 8)	149 (52)	1951 (86)	1535 (82)	73.0 (20.9)

A: n=8, AUC(INF), T-Half, could not be determined for Patient 187126.
Group A: Normal, bilirubin <= ULN and AST <= ULN
Group B: Mild, ULN < bilirubin <= 1.5 x ULN and any AST or bilirubin <= ULN and AST > ULN
Group C: Moderate, 1.5 x ULN < bilirubin <= 3.0 x ULN and any AST
Group D: Severe, bilirubin > 3.0 x ULN and any AST

Results from the dose-normalized data indicated that ixabepilone exposure, as measured by the dose-normalized AUC(INF), increased in patients with hepatic dysfunction relative to control patients (see Fig. 7 and Table 9). Increases in exposure of 22% for patients with mild dysfunction, 30% for patients with moderate dysfunction and 81% for patients with severe dysfunction were observed. The ixabepilone half life and Vss were not affected by hepatic dysfunction, while mean clearance values showed a slight decrease for the mild, moderate, and severe groups (see Fig. 8).

TABLE 9: Dose normalized Summary Statistics for Ixabepilone pharmacokinetic parameters by group.

Group	Pharmacokinetic Parameter				
	Cmax (ng/mL) Geo.Mean (CV%)	**AUC(INF) (ng·h/mL)** Geom. Mean (CV %)	**MRT (h)** Mean (SD)	**VSS (L)** Mean (SD)	**Clearance (L/h)** Mean (SD)
Normal (N = 17)	254 (52)	2155 (53)	65.7 (64.7)	2149 (1444)	37.1 (19.6)
Mild (N = 26)	287 (50)	2633 (59)	60.7 (48.6)	1574 (938)	30.2 (13.1)
Moderate (N =13)	182 (70)	2807 (66)	77.0 (38.1)	2339 (1458)	30.3 (14.3)
Severe[a] (N = 8)	298 (51)	3901 (86)	84.0 (24.5)	1925 (1117)	23.7 (12.1)

a - All subjects in the severe group receiving 10 mg/m^2 were excluded from these summary statistics
Normal - bilirubin <= ULN and AST <= ULN
Mild - ULN < bilirubin <= 1.5 x ULN and any AST or bilirubin <= ULN and AST > ULN
Moderate - 1.5 x ULN < bilirubin <= 3.0 x ULN and any AST
Severe - bilirubin > 3.0 x ULN and any AST

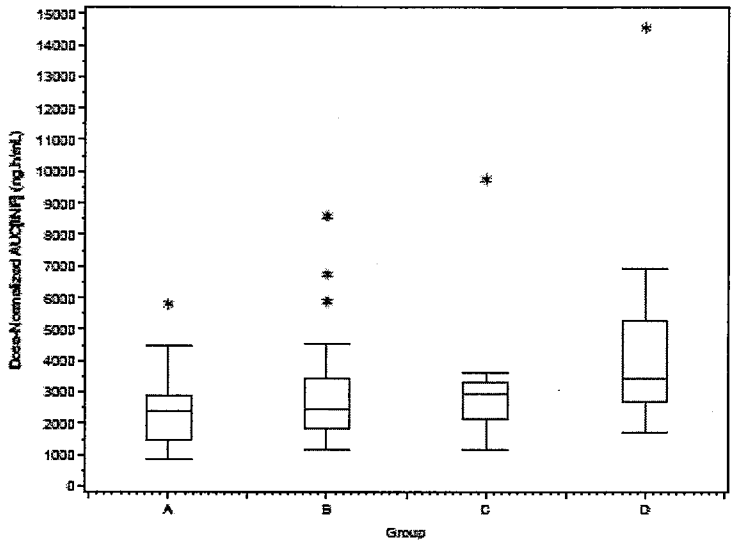

FIGURE 7: Ixabepilone Dose-Normalized AUC(INF) (40 mg/m^2) by degree of hepatic dysfunction (A = normal, B = mild, C = moderate, D = severe).

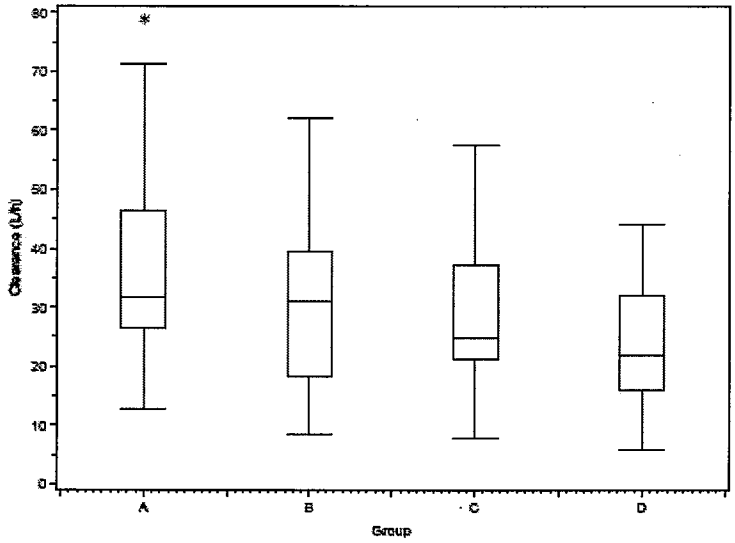

FIGURE 8: Ixabepilone clearance by degree of hepatic dysfunction (A = normal, B = mild, C = moderate, D = severe).

The conclusion based on the sponsors analysis from the dedicated hepatic impairment study suggests that for patients with mild hepatic dysfunction the tolerable ixabepilone dose based on protocol defined DLT criteria and pharmacokinetics is 40 mg/m^2. For patients with moderate or severe hepatic dysfunction the dose of ixabepilone would be 20 mg/m^2.

Population PK Analysis

The population PK analysis showed no trends between clearance of ixabepilone (ηCL) and total bilirubin and AST (see Figure 9).

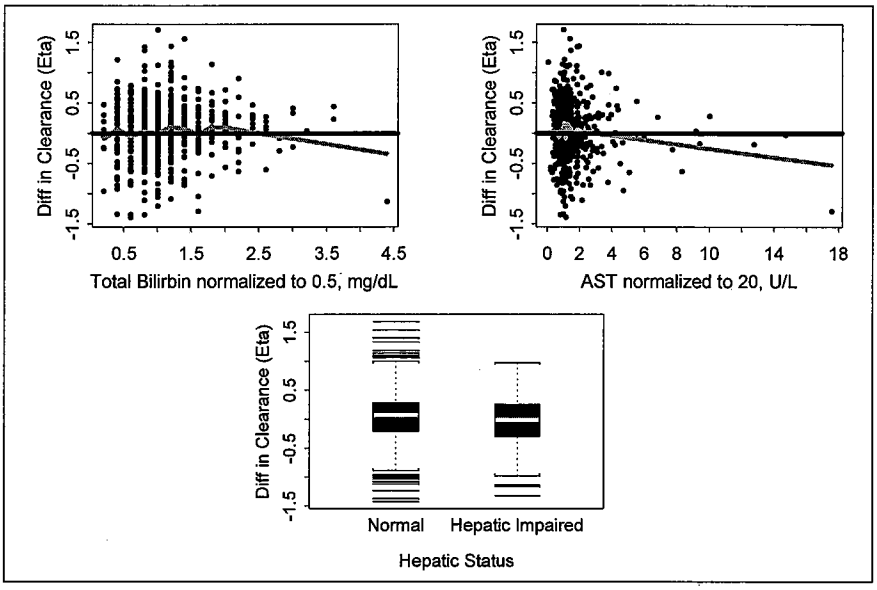

FIGURE 9: Effect of hepatic function on the clearance of Ixabepilone

Patients with a total bilirubin greater than the upper limits of normal were excluded from the efficacy trials and therefore it is not surprising that population analysis did not show any trends of decreasing clearance with increasing total bilirubin (bilirubin range: 0.1 to 2.2 mg/dL).

Clinical Safety Data

Clinical safety data from 240 patients treated with monotherapy ixabepilone at 40 mg/m^2 and from 431 patients with 40 mg/m^2 ixabepilone plus 2000 mg capecitabine was analyzed for AE's in patients with and without baseline liver function test abnormalities.

Seven subsets were defined based on different levels for baseline AST or ALT and total bilirubin ranges per NCI CTC criteria. One subset served as a reference group with normal hepatic function and one subset corresponded with the criteria for moderate and severe dysfunction used in the dedicated hepatic study. Five subsets fit within the criteria for mild dysfunction used in the dedicated hepatic study.

The analyses of safety in patients with hepatic impairment included evaluation of AEs (all, treatment-related, treatment-related Grade 3/4 AEs, SAEs, and AEs leading to discontinuation, and deaths) and on treatment absolute neutrophil count (ANC) and platelet values in patients with and without baseline LFT abnormalities (AST, ALT, or bilirubin). The breakdown of significant AE findings associated with AST/ALT and total bilirubin grade are below in Table 10. Most of the patients fell within the subset of patients with normal levels at baseline. The next largest groups fell within the 'mild category' with patients having Grade 1 AST or ALT and normal bilirubin or those having $\geq$ Grade 2 AST or ALT and normal bilirubin. The number of patients in each of the remaining subsets was ≤ 5 and therefore clinical interpretation was limited.

TABLE 10: Clinical safety data summary and hepatic impairment breakdown from monotherapy and combination therapy studies.

	AST or ALT	Total Bilirubin	Monotherapy Findings (Studies CA1630811, 009 & 010)	Combination therapy Findings (Studies CA163046 & 031)
Normal	**Grade 0 (≤ ULN)**	**Grade 0 (≤ ULN)**	(n = 153)	(n = 295)
Subsets corresponding with mild / hepatic dysfunction criteria	**Grade 1 (> ULN to ≤ 2.5x ULN)**	**Grade 0 (≤ ULN)**	(n = 58) No consistent and clinically meaningful differences in AEs were observed	(n = 107) No consistent and clinically meaningful differences in AEs were observed
	Grade 0 (≤ ULN)	**Grade 1 (> ULN to ≤ 1.5x ULN)**	(n = 3)	(n = 4)
	Grade 1 (> ULN to ≤ 2.5x ULN)	**Grade 1 (> ULN to ≤ 1.5x ULN)**	(n = 2)	(n = 8)
	≥ Grade 2 (> 2.5x ULN)	**Grade 0 (≤ ULN)**	(n = 17) Higher Grade 4 neutropenia rate, febrile neutropenia rate (12% vs 2%). Higher rates of treatment-related SAEs (29% vs 16%) and treatment-related AEs leading to discontinuation (24% vs 18%).	(n = 14) higher rates of Grade 3/4 neutropenia, Grade 3/4 thrombocytopenia, overall Grade 3/4 AEs, treatment-related febrile neutropenia, treatment-related SAEs, treatment-related AEs leading to discontinuation, and toxicity-related deaths
	≥ Grade 2 (> 2.5x ULN)	**Grade 1 (> ULN to ≤ 1.5x ULN)**	(n = 4)	(n = 2)
Moderate/ Severe based on Bilirubin	**Any Level**	**Grade 2 (> 1.5x ULN to ≤ 3x ULN)**	(n = 3)	(n = 1)

In conclusion, based on safety findings it appears that patients with AST/ALT >2.5x ULN and may require dose adjustments. There was not sufficient numbers of patients with moderate or severe hepatic impairment in the efficacy trials to elucidate dosing recommendations from the safety data.

Reviewers Analysis

The following criteria was proposed for dosing adjustment by the sponsor for patients receiving monotherapy:

	Degree of Hepatic Impairment			Recommended Dose[a]
	Transaminase Levels		Bilirubin Levels	Ixabepilone (mg/m^2)
mild	AST and ALT ≤ 2.5x ULN	and	≤ 1x ULN	40
mild	AST or ALT > 2.5x ULN - ≤ 10x ULN[b]	and	≤ 1x ULN	32
mild	AST and ALT ≤ 10x ULN	and	> 1x ULN - ≤ 1.5x ULN	32
moderate →	AST and ALT ≤ 10x ULN	and	> 1.5x ULN - ≤ 3x ULN	20

Using data from the dedicated hepatic study, the sponsors dosing proposal for hepatic impairment was investigated. For each patient, the upper limit of normal (ULN) was calculated for AST (Stratification in this study was not done by ALT therefore no results for ALT were provided in the study report) and bilirubin and data sets for each of the sponsors limits above were created and are individually discussed below.

Mild 1: AST and ALT ≤ 2.5 × ULN and Total Bilirubin ≤ 1 × ULN

Reviewers note: The sponsor based their recommendation for this group on the similar safety profile demonstrated in the 58 patients with Grade 1 AST or ALT and normal

bilirubin at baseline. This group best correlates with Group "B1 mild" from study ——

Twenty-eight patients from the dedicated hepatic study —— met the above criteria for AST and bilirubin. Seventeen of these patients were considered to have 'normal' hepatic function and received 40 mg/m^2 of ixabepilone. The remaining subjects (n = 11) were in the 'mild' group and received either 30 mg/m^2 (n = 6) or 40 mg/m^2 (n = 5).

As seen below in Table 11, a dose reduction to for the 'mild' patient group to 30 mg/m^2 decreased Cmax and AUC by 32% and 25%, respectively. The five subjects with mild hepatic impairment who received the standard 40 mg/m^2 dosage had similar exposure results compared to the patients with normal hepatic function.

TABLE 11: Summary statistics for Cmax and AUC from patients with AST/ALT ≤ 2.5 × ULN and Total Bilirubin ≤ 1 × ULN from study ——.

	Dose (mg/m^2)	Cmax (ng/mL) Mean (CV)	AUC (ng hr/mL) Mean (CV)
Normal	40 (n =17)	284 (51)	2445 (52)
Mild	30 (n = 6)	193 (37)	1818 (35)
	40 (n = 5)	307 (22)	3451 (85)

In conclusion, in agreement with the sponsors proposal patients that have AST/ALT ≤ 2.5 × ULN and Total Bilirubin ≤ 1 × ULN do not need a dose reduction.

Mild 2: AST or ALT >2.5× ULN ≤ 10 × ULN and Total Bilirubin ≤ 1 × ULN

Reviewers note: The sponsor based their recommendation for this group on the clinical safety data in 17 patients with ≥ Grade 2 AST/ALT and normal bilirubin at baseline. The recommendation was supported by the results of ——. *This group does not correlate with any specific criteria from study* ——.

For our analysis ten patients from the dedicated hepatic study —— met the above criteria for AST and bilirubin. All of the patients were in the 'mild' group and received either 30 mg/m^2 (n = 5) or 40 mg/m^2 (n = 5).

A dose reduction to 30 mg/m^2 decreased Cmax and AUC by 48% and 28%, respectively when compared to patients receiving 40 mg/m^2 who had normal hepatic function. The 40 mg/m^2 dosage resulted in a 49% increase in Cmax and a 30% increase in AUC. The sponsors proposal is to dose these patients with 32 mg/m^2. When AUC and Cmax was dose normalized to 32 mg/m^2 the Cmax and AUC were 248 ng/mL and 2206 ng hr/mL, respectively, which is similar to the Cmax and AUC achieved with the patients with normal hepatic function receiving 40 mg/m^2.

TABLE 12: Summary statistics for Cmax and AUC from patients with AST or ALT >2.5× ULN ≤ 10 × ULN and Total Bilirubin ≤ 1 × ULN from study ——.

	Dose (mg/m^2)	Cmax (ng/mL) Mean (CV)	AUC (ng hr/mL) Mean (CV)
Mild	30 (n = 5)	147 (10)	1742 (55)
	40 (n = 5)	424 (67)	3193 (51)

In conclusion, a dose of 32 mg/m^2 for patients with AST or ALT >2.5× ULN ≤ 10 × ULN and Total Bilirubin ≤ 1 × ULN will adjust the Cmax and AUC to values seen in patients

with normal hepatic function receiving 40 mg/m^2. In addition the safety data from the monotherapy/combination therapy studies indicated that patients with AST/ALT > 2.5 may need dose adjustments. This supports the need for two dosing strategies for the 'mild' impaired patients.

Mild 3: AST and ALT ≤ 10 × ULN and Total Bilirubin >1 × ULN ≤ 1.5 × ULN

Reviewers note: The sponsor based their recommendation on the results of ——. *This group correlates with Group "B2 Mild" from study* ——.

Only two patients from the dedicated hepatic study —— met the above criteria for AST and bilirubin. Both subjects were in the mild treatment group and both received 40 mg/m^2 of ixabepilone.

TABLE 13: Patients with AST and ALT ≤ 10 × ULN and Total Bilirubin >1 × ULN ≤ 1.5 × ULN from study ——.

Subject	Dose (mg/m^2)	AST	Total Bilirubin	Cmax (ng/mL)	AUC (ng hr/mL)
195628	40	5.7 × ULN	1.1 × ULN	441	3658
198214	40	3.6 × ULN	1.3 × ULN	265	2209

Subject 195628 with the higher AST value had an increased Cmax and AUC compared to the subject with AST only 3.6 x ULN. No firm conclusion can be drawn from these two patients. The sponsor is proposing a 32 mg/m^2 dose for this group.

In conclusion, the only difference between this AST/ALT/Bilirubin stratification and the one prior are the limits for bilirubin. When all the mild classified subjects from study —— were grouped together and data was dose normalized, a dose of 32 mg/m^2 appropriately adjusted Cmax and AUC to levels within the normal range. There does not appear to be a need for two stratifications, therefore these groups will be combined and a recommended dose of 32 mg/m^2 will be retained:

AST or ALT > 2.5x ULN - ≤ 10x ULN[b]	and	≤ 1x ULN	32
AST and ALT ≤ 10x ULN	and	> 1x ULN - ≤ 1.5x ULN	32

Moderate: AST and ALT ≤ 10 × ULN and Total Bilirubin >1.5 × ULN ≤ 3 × ULN

Reviewers note: The sponsor based their recommendation on the tolerable dose and the increase in AUC for the group with moderate hepatic impairment as defined in ——. *This group correlates with Group "moderate" from study* ——.

Four patients from the dedicated hepatic study —— met the above criteria for AST and bilirubin. All of the patients were in the 'moderate' group and received either 20 mg/m^2 (n = 3) or 30 mg/m^2 (n = 1).

TABLE 14: Patients with AST and ALT ≤ 10 × ULN and Total Bilirubin >1.5 × ULN ≤ 3 × ULN from study ——.

Subject	Dose (mg/m^2)	AST	Total Bilirubin	Cmax (ng/mL)	AUC (ng hr/mL)
185878	20	5.1 × ULN	2.3 × ULN	58	873
186690	20	3.5 × ULN	2.9 × ULN	230	1808
187127	20	3.5 × ULN	2.7 × ULN	66	1738
189190	30	5.1 × ULN	2.1 × ULN	71	1628

The results are inconclusive to support a solid dosing recommendation based on the sponsors defined AST/bilirubin criteria. None of the patients who received either dose were close the exposure seen in normal patients receiving 40 mg/m^2 (AUC 2445 ng h/mL, Cmax 284 ng/mL). The sponsor is proposing a 20 mg/m^2 dose for this group.

However, when all the patients in the moderate group as defined by —— were dose normalized to 30 mg/m^2 the AUC was 2394 ng hr/mL which is comparable to the AUC for normal hepatic function at 40 mg/m^2 (2445 mg hr/mL). However, of the 3 patients who received 30 mg/m^2 in study —— two had dose limiting toxicities. Therefore, this group will be redefined as what was used for the moderate group in study —— and a dosing recommendation of 20-30 mg/m^2 will be proposed with the caveat that doses will start at 20 mg/m^2 and titrated up to 30 mg/m^2 if tolerated by the patient.

Overall Conclusions

Taking the data from study ——, the safety data, and the sponsors proposed dose adjustments into consideration, the following will be proposed for dose recommendations for patients with hepatic impairment:

TABLE 15: Proposed mild and moderate hepatic impairment dose adjustments for monotherapy ixabepilone

	Degree of Hepatic Impairment			Recommended Dose	
	AST and/or ALT		Bilirubin	MonoTx	ComboTx
Mild	≤ 2.5 x ULN	and	≤ ULN	40	40
	> 2.5 x ULN - ≤ 10 x ULN	and	≤ 1.5 x ULN	32	CI
Moderate	> 2.5 x ULN - ≤ 10 x ULN	and	> 1.5 x ULN - ≤ 3 x ULN	20 - 30	CI

CI = Contraindicated

These recommendations stratify mild hepatic impairment into two groups instead of three, based on results from the safety analysis that supported lower doses due to drug related AE's in patients with AST/ALT > 2.5 x ULN. Patients who have AST/ALT < 2.5 x ULN may continue to receive the normal dose of ixabepilone based on the results from Study —— .

For patients with moderate hepatic a 30 mg/m^2 dose would adjust the AUC to exposures seen in the normal group (see Table 16). However since 2 out of 3 patients in the moderate arm at 30 mg/m^2 had dose limiting toxicities, the range of 20 - 30 mg/m^2 will be proposed with the caveat that dose may be titrated up in subsequent cycles to 30 mg/m^2 if tolerated by the patient.

In addition, the sponsor did not propose a dose reduction for patients

tolerated by the patient.

TABLE 16: Monotherapy sponsor, agency and PK based dosing recommendations for hepatic impairment

Group	Pharmacokinetic Parameter		Percent change		Dose Recommendations (mg/m^2)		
	Clearance (L/h) Mean (CV%)	AUC(INF) (ng·h/mL) Geom. Mean (CV %)	CL	AUC	Sponsor	PK Based AUC	Agency
Normal (N = 17)	37.1 (52)	2155 (53)	-	-	-	-	
Mild (N = 26)	30.2 (43)	2633 (59)	18.6%	22%	40/32/32 [b]	31	40/32 [b]
Moderate (N =13)	30.3 (47)	2807 (66)	18.3%	30%	20	28	20 - 30 [c]

Normal - bilirubin <= ULN and AST <= ULN
Mild - ULN < bilirubin <= 1.5 x ULN and any AST or bilirubin <= ULN and AST > ULN
Moderate - 1.5 x ULN < bilirubin <= 3.0 x ULN and any AST

CI = contraindicated
a - All subjects in the severe group receiving 10 mg/m^2 were excluded from these summary statistics
b - different recommendations based on varying levels for AST/ALT and Bilirubin
c - Doses will start at the lower range and may be titrated up in subsequent cycles if tolerated

Although a patient with 'any' upper limit of normal AST could be enrolled in the dedicated hepatic study, data is limited for those who had AST/ALT > 10 x ULN which is why our recommendations include specific ranges for AST/ALT.

Dosing recommendations for patients receiving the combination therapy with capecitabine are driven by the safety analysis from studies CA163045 and CA163031. Of the 17 patients with Grade 2 AST, ALT, or bilirubin at baseline, 5 (29%) patients died on study from study drug toxicity. Based on these finding, ixabepilone plus capecitabine is contraindicated in patients with AST or ALT > 2.5 x ULN or Bilirubin > 1 x ULN.

2.3.2.4 What pregnancy and lactation use information is there in the application?

No data regarding the excretion of ixabepilone in the milk of humans or animals was provided. Embryo-fetal reproductive toxicology studies showed embryo-fetal toxicities at high-doses in rats and rabbits and therefore ixabepilone is pregnancy category D.

2.4 EXTRINSIC FACTORS

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

There were no specific studies or analyses designed to evaluate the effects of factors such as herbal products, diet, smoking or alcohol use on the PK or PD of ixabepilone.

2.4.2 Drug-drug interactions

2.4.2.1 Is there an in vitro basis to suspect *in-vivo* drug-drug interactions?

Since CYP3A4/5 is the major CYP isozyme responsible for the metabolism of ixabepilone, inhibitors and inducers of CYP3A4 could affect the pharmacokinetics of ixabepilone.

In-vitro studies suggested that ixabepilone was not an inducer or inhibitor of CYP450 isozymes.

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

The *in vitro* metabolism of ixabepilone was investigated by incubating the compound with human cDNA-expressed CYP enzymes, CYP1A2, CYP2B6, CYP2D6, CYP2E1, CYP3A4, CYP3A5, CYP2C8, CYP2C9 and CYP2C19 (rpt 930012647, 930018090). Ixabepilone undergoes oxidative metabolism mainly by CYP3A4 and CYP3A5 to form multiple metabolites:

- Mono-oxygenation of ixabepilone to form several M+16 metabolites (M2, M3, M8, M9, M10, M11) and M+14 metabolites (M4, M5, M14, M15, M16 and M17)
- Dehydrogenation of the parent molecule to form M-2 metabolites (M19 and M20)

CYP2D6 and CYP2C19 also metabolized ixabepilone, forming M9 (M+16 metabolite), a minor metabolite detected in the incubations of ixabepilone with human liver microsomes (HLM).

Ixabepilone was also incubated in human liver microsomes in the presence of CYP inhibitors (rpt 930012647, 930018090) to evaluate the inhibition effects on the oxidative metabolism of ixabepilone (Table 17). When ixabepilone was incubated in the presence of ketoconazole or troleandomycin, inhibitors of CYP3A4, formation of M+16, M+14 and M-2 metabolites was inhibited. Montelukast, a selective inhibitor of CYP2C8 did not show any inhibition for the formation of M+16, M+14 and M-2 metabolites. 1-Aminobenzotriazole, a non-selective metabolism-dependent CYP inhibitor, inhibited the formation of all metabolites.

TABLE 17. Metabolite formation of ixabepilone in HLM in the presence of CYP inhibitors

CYP Inhibitors	Percent of total peak area[a]					Overall % inhibition
	BMS-249798	BMS-326412 and M8	M19	M20	Ixabepilone	
No NADPH (negative control)	8.13	0.92	ND	ND	90.95	-
No Inhibitor (positive control)	11.26	4.93[b]	2.43	0.77	80.60	-
Montelukast (3 µM, 2C8)	9.67	5.07[b]	2.88	1.51	80.87	2.6
Troleandomycin (20 µM, 3A4)	9.23	1.73	0.25	0.23	88.55	76.8
Ketoconazole (1µM, 3A4)	8.10	1.58	0.27	0.47	89.59	86.8
1-Aminobenzotriazole (1000µM, general inhibitor)	9.01	1.41[b]	ND	ND	89.58	86.7

a: UV chromatograms were acquired at the wavelength of 250 nm. The peaks of interest listed in the table were integrated in the UV chromatograms (shown in Figure 23). The total peak area is the sum of all areas under the peaks of interest including BMS-249798, BMS-326412, M8, M19, M20 and ixabepilone. Data is obtained from the incubations of ixabepilone at the final concentration of 50 µM. The percent of total peak area were calculated by HPLC software.
b: M8 was co-eluted with BMS-326412 and it was detected by LC/MS.
c: % Inhibition = (% IXA peak area with inhibitor - % IXA peak area in positive control)/(%IXA peak area in negative control - %IXA peak area in positive control)
ND: Not Detected

In conclusion, CYP3A4 is the major CYP450 isozyme responsible for the formation of ixabepilone and metabolites analyzed.

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

***In-vitro* induction**

The potential for ixabepilone to induce hepatic CYP enzymes (CYP1A2, CYP2B6, CYP2C9,

and CYP3A4) was investigated in primary cultures of hepatocytes from three human donors (rpt 930012012). Ixabepilone did not cause any statistically significant increases in the enzyme activity or the mRNA expression of any of the enzymes tested at concentrations up to 20 μM. The positive controls omeprazole (100 μM), phenobarbital (750 μM), and rifampin (10 μM) caused anticipated increases in enzyme activities and levels of CYP mRNA expression.

The results from these induction experiments demonstrate that ixabepilone is not likely to be an inducer of CYP1A2, CYP2B6, CYP2C9, or CYP3A4 at concentrations up to 20 μM (10134 ng/mL) which is significantly higher than the mean Cmax seen after an 3-hour infusion of 40 mg/m^2 ixabepilone (285 ng/mL).

***In-vitro* inhibition**

The potential of ixabepilone to act as a direct or metabolism-dependent inhibitor of CYP enzymes was investigated using human liver microsomes (rpt 930012272).

Ixabepilone inhibited CYP3A4/5 activity as measured by midazolam 1'-hydroxylation, with an IC_{50} value of 15 μM. However, ixabepilone did not significantly inhibit another marker substrate of CYP3A4/5 activity (testosterone 6β-hydroxylation). Ixabepilone did not directly inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1, or CYP2D6, with IC_{50} values greater than the highest concentration of ixabepilone studied (30 μM). Ixabepilone did not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP2E1 at concentrations up to 30 μM.

TABLE 18. IC_{50} values of ixabepilone for CYP450 isoforms.

		Zero-minute pre-incubation		30-minute pre-incubation		Potential for metabolism-dependent inhibition[b]
Enzyme	CYP reaction	IC50 (μM)	Maximum inhibition at 30 μM (%)[a]	IC50 (μM)	Maximum inhibition at 30 μM (%)[a]	
CYP1A2	Phenacetin *O*-deethylation	> 30	NA	> 30	NA	little or no
CYP2A6	Coumarin 7-hydroxylation	> 30	14	> 30	NA	little or no
CYP2B6	Bupropion hydroxylation	> 30	3.8	> 30	19	little or no
CYP2C8	Paclitaxel 6α-hydroxylation	> 30	8.3	> 30	11	little or no
CYP2C9	Diclofenac 4′-hydroxylation	> 30	18	> 30	17	little or no
CYP2C19	*S*-Mephenytoin 4′-hydroxylation	> 30	17	> 30	7.6	little or no
CYP2D6	Dextromethorphan *O*-demethylation	> 30	6.7	> 30	0.90	little or no
CYP2E1	Chlorzoxazone 6-hydroxylation	> 30	NA	> 30	NA	little or no
CYP3A4/5	Testosterone 6β-hydroxylation	> 30	12	9.0 ± 0.6	73	yes
CYP3A4/5	Midazolam 1′-hydroxylation	15 ± 1	66	3.0 ± 0.2	91	yes

Notes Values were calculated using the average data obtained from duplicates for each incubation condition. The IC50 values were calculated using XLFit.

a Maximum inhibition (%) is calculated using the following formula and data for the highest concentration of BMS-247550 for which usable data were collected (results are rounded to two significant figures): Maximum inhibition (%) = 100% – Percent of solvent control activity (see **Appendix 8**)

b Metabolism-dependent inhibition was determined by comparison of IC50 values with and without pre-incubation and by visual inspection of IC50 plots.

NA Inhibition was not observed at the highest concentration of BMS-247550 studied (30 μM) as indicated by a "percent of solvent control activity" greater than 100%.

The ability for ixabepilone to act as a time-dependent inhibitor of CYP3A4/5 was evaluated using midazolam 1′-hydroxylation. Ixabepilone concentrations of zero (solvent control) and 30 μM, were pre-incubated at 37 ± 1°C for 30-minutes with pooled human liver microsomes. After the pre-incubation period was complete, the marker substrate (midazolam, at a concentration approximately equal to its Km (3 μM)) were added and incubated to measure the residual CYP3A4/5 activity. The results indicated that CYP3A4/5 inhibition by ixabepilone was

metabolism-dependent with a K_i = 7.5 μM and k_{inact} = 0.043 min^{-1}.

The inhibition of CYP3A4/5 by ixabepilone would be predicted to be weak based on the *in-vitro* inhibition parameters and the *in-vivo* plasma concentrations. Using geometric mean Cmax of 268 ng/mL (0.5 μM) for the 40 mg/m^2 infusion of ixabepilone over 3 hours, the Cmax/K_i ratios for CYP3A4 inhibition is 0.07 which is less than the 0.1 benchmark for *in-vivo* investigation.

In conclusion, ixabepilone is not likely to be an inhibitor of CYP450 enzymes or cause drug-drug interactions via CYP450 inhibition with coadministered drugs that are metabolized by CYP450 enzymes *in-vivo*.

2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

No evaluation of P-glycoprotein transport systems was conducted.

2.4.2.5 Are there other metabolic/transporter pathways that may be important?

None have been identified.

2.4.2.6 Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?

Pre-Medication

It is recommended that an antihistamine (diphenhydramine), and an H_2 antagonist (ranitidine) be administered before the ixabepilone infusion to avoid hypersensitivity reactions with the administration of ixabepilone. Patients who experienced a hypersensitivity reaction to ixabepilone in prior cycles are to be dosed with corticosteroids in addition to the H_1 and H_2 antagonists. Early in the phase 1 program, a decision was made to pre-treat all patients receiving ixabepilone IV with diphenhydramine and ranitidine. The interaction potential between these agents has not been formally studied in the clinical setting. Based on metabolism pathways no interaction is predicted with diphenhydramine or ranitidine.

Capecitabine

Ixabepilone will be co-administered with capecitabine in patients with metastatic or locally advanced breast cancer after failure of an anthracycline and a taxane. The sponsor conducted an interaction study (CA163038) investigating the effect of co-administration on the pharmacokinetics of each agent.

The study was an open-label, sequential design which enrolled twenty-two advanced cancer patients. All patients received the following treatments:

- Ixabepilone alone: A single 3-hour IV infusion of 40 mg/m^2 of ixabepilone was administered on Day 1 of Cycle 1
- Capecitabine alone: A single PO dose of 1000 mg/m^2 of capecitabine was administered on Day 15 of Cycle 1
- Ixabepilone plus Capecitabine: A 3-hour IV infusion of 40 mg/m^2 of ixabepilone was administered on Day 1 and 1000 mg/m^2 PO q12h of capecitabine was administered on Days 1-5 during Cycle 2

Blood samples were collected for PK evaluation after each dose of ixabepilone up to 120 hours

post-dose and after capecitabine dosing up to 12 hours post-dose for Cycles 1 and 2. Statistical analysis of the comparison between Cmax and AUC(INF) for ixabepilone, capecitabine and 5-FU when ixabepilone and capecitabine were dosed separately or together was performed on all patients with complete PK data for Cycles 1 and 2 (n=20). Point estimates and 90% confidence intervals for the effect of capecitabine on ixabepilone and for the effect of ixabepilone on capecitabine and 5-FU were calculated.

In patients with advanced cancer receiving ixabepilone plus capecitabine in combination, Cmax and AUC decreased for both ixabepilone (19% and 6%, respectively) and capecitabine (27% and 5%, respectively), relative to there values when administered separately. The Cmax and AUC increased for 5-FU (1% and 14%, respectively). The differences in ixabepilone exposures was not significant, however the changes in Capecitabine Cmax did effect the lower bound of the 90% CI (see Table 19).

TABLE 19. Results of Statistical Analysis for Ixabepilone, Capecitabine and 5-FU.

Pharmacokinetic Variable	Geo. Mean		Point Estimate	90% CI
	Reference	Test		
Ixabepilone				
Cmax (ng/mL)	309	250	0.809	(0.662, 0.989)
AUC(INF) (ng hr/mL)	2219	2078	0.936	(0.840, 1.043)
Capecitabine				
Cmax (ng/mL)	4280	3132	0.732	(0.549, 0.975)
AUC(TAU) (ng hr /mL)	5613	4313	0.946	(0.771, 1.163)
5-Fluorouracil				
Cmax (ng/mL)	208	210	1.008	(0.760, 1.338)
AUC(TAU) (ng hr /mL)	377	429	1.139	(0.966, 1.342)

Reference: Cycle 1; ixabepilone 40 mg/m^2 alone or capecitabine 1000 mg/m^2 alone
Test: Cycle 2; ixabepilone + capecitabine

These PK differences are not expected to change the safety or efficacy of either ixabepilone or capecitabine. In addition the pivotal efficacy trial (CA163043) used the same doses of ixabepilone/capecitabine for the combination treatment arm which demonstrated that the combination of ixabepilone plus capecitabine is an efficacious treatment option for patients with taxane-resistant and anthracycline-pretreated or resistant, metastatic or locally advanced breast cancer.

2.4.2.7 Are there any *in-vivo* drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

Co-administration of Ixabepilone with CYP3A4 Inhibitors

The effect of ketoconazole, a potent inhibitor of CYP3A4 on the PK of ixabepilone was investigated in Study CA163042. Twenty-seven subjects received the following treatments:

- Ketoconazole 400 mg was administered daily in the morning from Day -1 to Day 5 of Cycle 1.
- A single IV dose of 10-30 mg/m^2 of ixabepilone was administered on Day 1 of Cycle 1.
- A single IV dose of 40 mg/m^2 of ixabepilone was administered on Day 1 of Cycle 2 (1 patient erroneously received 25 mg/m2 and 1 patient received a reduced dose of 32 mg/m^2)

Pretreatment with diphenhydramine (50 mg) and ranitidine (150-300 mg) was administered

approximately 1 hour before start of ixabepilone infusions. For safety reasons, the administration of ixabepilone with ketoconazole in Cycle 1 was conducted in the style of a dose-escalation study. The starting dose for the first cohort of patients was 10 mg/m^2. Blood samples were collected for PK evaluation after each dose of ixabepilone up to 120 hours post-dose during Cycle 1 and Cycle 2.

According to the FDA drug-drug interaction guidance, the study design and choice of CYP3A4 inhibitor are appropriate.

To assess the effect of ketoconazole on the PK of ixabepilone, a two-way analyses of variance was performed on dose-normalized log(Cmax) and log(AUC(INF)) for all subjects who had values for Cycle 1 (ixabepilone plus ketoconazole) and Cycle 2 (ixabepilone alone). The Cmax and AUC(INF) from Cycle 1 (ixabepilone plus ketoconazole) were dose normalized to a 40 mg/m^2 dose.

There were two subjects who received doses less than 40 mg/m^2 in Cycle 2 (ixabepilone alone). Once subject received 25 mg/m^2 in error and one subject received a reduced dose of 32 mg/m^2 based on their toxicity profile from Cycle 1. The Cmax and AUC(INF) from these two subjects were dose normalized to 40 mg/m^2 for the two-way analyses of variance.

The 90% confidence intervals (CI) for dose-normalized ratios of geometric means of Cmax for ixabepilone were within the range of 80 to 125%. For AUC(INF), respective dose-normalized ratios of geometric means were higher than the upper confidence limit of 125%. The mean pharmacokinetic parameters can be found in Appendix 4.1.8 - Study CA163042 and the results of the statistical analysis is below in Table 20.

TABLE 20. Statistical analysis of dose normalized 40 mg/m^2 IV ixabepilone Cmax and AUC following treatment with or without ketoconazole 400 mg.

	Ratio of Geometric Means	Lower 90% CI	Upper 90% CI
Cmax	1.067	93.1	122.3
AUC (INF)	1.791	154.7	207.4

Reference: dose normalized ixabepilone IV 40 mg/m^2 mg alone
Test: dose normalized ixabepilone IV 40 mg/m^2 + ketoconazole oral 400 mg QD

In the 22 subjects that received ixabepilone both with ketoconazole (Cycle 1) and without ketoconazole (Cycle 2), a significant 1.8 fold increase in normalized AUC(INF) was observed when co-administered with ketoconazole. There was no significant difference in the dose-normalized Cmax values with or without ketoconazole. Based on this increase in AUC(INF), the 20 mg/m^2, 25 mg/m^2 and 30 mg/m^2 doses of ixabepilone with ketoconazole correspond to 36 mg/m^2, 45 mg/m^2, and 54 mg/m^2 doses of ixabepilone alone, respectively. Based on DLT criteria, the MTD of ixabepilone is 25 mg/m^2 when co-administered with ketoconazole in this study. The results of this study indicate that CYP3A4 inhibitors should be used with caution in patients taking ixabepilone. If the use of a strong inhibitor is unavoidable the dose of ixabepilone should be decreased by half to 20 mg/m^2 when administered with the inhibitor, and the ixabepilone dose should return to 40 mg/m^2 once treatment with the inhibitor has ceased.

Co-administration of Ixabepilone with CYP3A4 Inducers

The effect of potent inducers of CYP3A4 on the PK of ixabepilone is ongoing. Based on

ixabepilone metabolism such compounds would be expected to decrease ixabepilone exposure. The sponsor recommends that alternative therapeutic agents with low enzyme induction potential should be considered for co-administration with ixabepilone.

2.5 GENERAL BIOPHARMACEUTICS

2.5.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

Not applicable

2.5.2 What is the composition of the to-be-marketed formulation?

Ixabepilone for injection was supplied as a lyophilized, white to off-white, whole or fragmented cake in 10, 15, 20, 30 and 45 mg vials for the clinical trials (Table 21). The diluent was comprised of an ethanol plus Cremophor®EL mixture (1:1 by volume) that was clear to slightly hazy and was colorless to pale yellow in color.

For the clinical-trial formulations, [redacted] was used to manufacture the 10 mg/vial and 20 mg/vial strengths, and [redacted] was used to manufacture the 15 mg/vial, 30 mg/vial and 45 mg/vial strengths. There are no differences, except for the potency and overfill amounts, in the products used for clinical development since the [redacted] are removed during the lyophilization process.

TABLE 21. Composition of ixabepilone for injection used during clinical development.

Product Identification Number (PIN)	247550-P010-001	247550-P015-032[a] 247550-P015-033[a] 247550-P015-040[a]	247550-P020-007	247550-P030-021	247550-P045-047[h]
Labeled Potency	[redacted]				45 mg/Vial
Component	Amount per Vial (mg)				
Ixabepilone[b]	11.0[c]	16.0[c]	22.0[d]	33.0[e]	47.0[d]
[redacted]					

a
b
c
d
e
f
g
h The 45 mg/vial product has not yet been used in clinical studies

Two different presentations, 15 mg/vial and 45 mg/vial, have been developed for marketing (see Table 22). These formulations are identical to those used in the clinical trials.

Appears This Way
On Original

TABLE 22. To-be-marketed composition of ixabepilone for injection.

		Label Potency		
		15 mg/Vial	45 mg/Vial	
Component	Quality Standard	Amount per Vial (mg)		Function
Ixabepilone	BMS[a] Specification	16.0[b]	47.0[c]	Active Ingredient

[redacted]

[a] Bristol-Myers Squibb
[b] [redacted]
[c] [redacted]
[d] [redacted]
[e] [redacted]

The final marketed product will be co-packaged with the vehicle for constitution to obtain a solution with an ixabepilone concentration of 2 mg/mL. The 15 mg/vial is constituted with 8 mL of vehicle and the 45 mg/vial is constituted with 23.5 mL of vehicle. Prior to IV administration, the constituted solution is further diluted with Lactated Ringer's to final ixabepilone concentrations ranging from 0.2 mg/mL to 0.6 mg/mL.

2.5.3 What moieties should be assessed in bioequivalence studies?

Ixabepilone should be assessed in human whole blood.

The pharmacokinetics of the oxazine and diol chemical degradants, (BMS-249798 and BMS-326412, respectively) was assessed in the phase 1 first-in-human trial (CA163001). The exposure of patients with advanced cancer to BMS-249798 and BMS-326412 was less than 4% and 0.5% respectively, to that of ixabepilone over the dose range of 7.4 mg/m^2 to 50 mg/m^2.

In addition, *in-vitro*, BMS-249798 and BMS-326412 were 174 and 312 fold less cytotoxic than ixabepilone against a human tumor cell line panel, respectively. Due to these findings, the remaining studies for ixabepilone did not assess BMS-249798 or BMS-326412 concentrations.

2.5.4 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Ixabepilone is administered intravenously therefore an evaluation of food effect is not necessary.

2.5.5 Has the applicant developed an appropriate dissolution method and specification that will assure *in-vivo* performance and quality of the product?

Not applicable.

2.6 ANALYTICAL SECTION

2.6.1 Were relevant metabolite concentrations measured in the clinical pharmacology and biopharmaceutics studies?

Plasma and urine samples were assayed for ixabepilone and its chemical degradation products, BMS-249798 and/or BMS-326412, by validated liquid chromatography tandem mass spectrometry methods (LC/MS/MS).

2.6.2 Were the analytical procedures used to determine drug concentrations in this NDA acceptable?

Plasma and urine samples were assayed for ixabepilone and its chemical degradation products, BMS-249798 and/or BMS-326412, by a validated LC/MS/MS method. A structural analogue was used as internal standard.

The accuracy and precision of the analytical methods were < 15%. The freeze thaw stability for ixabepilone in plasma was 3 cycles, and long term stability at -20°C was 3.9 years. Short term stability for ixabepilone was 24 hours at room temperature for plasma.

Please see appendix 4.3 for the bioanalytical methods that were used at each of the analytical sites, the quantitative range of the assays and the accuracy (% bias) and the precision (% coefficient of variation) of the assay quality control (QC) samples included for each study for ixabepilone, BMS-326412 and BMS-249798.

7 Page(s) Withheld

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_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Clin Pharm/Bio-_____

4 APPENDICES

4.1 INDIVIDUAL STUDY REVIEWS

4.1.1 CA163001: Ascending Q3week dose monotherapy study

Title: Phase I study of BMS-247550 given every three weeks in patients with advanced malignancies

Investigators: David R. Spriggs, MD
Memorial Sloan-Kettering Cancer Center, New York, NY;

Study Period: Date first subject enrolled: 26-Oct-99
Date last subject completed: 07-Oct-02

Clinical Phase: 1

Objectives: The primary objectives were to: (1) Establish the maximum tolerated dose (MTD), dose-limiting toxicity (DLT), safety and a recommended Phase 2 dose. (2) Assess safety and preliminary evidence of response in patients with pretreated, non-Hodgkin's lymphoma. (3) Evaluate the safety of ixabepilone when administered as a 3-hour infusion at 50 mg/m^2 once every 3 weeks to patients with advanced solid tumors or relapsed/refractory non-Hodgkin's lymphoma (NHL). The secondary objectives were to: (1) Evaluate the plasma pharmacokinetics (PK) of ixabepilone in patients when administered as a 1-hour and as a 3-hour intravenous infusion (2) Explore the pharmacodynamics of ixabepilone using an assay that measures the amount of endogenous tubulin in peripheral blood mononuclear cells (PBMCs) that exists in the polymerized versus the unpolymerized state (3) Describe any preliminary evidence of anti tumor activity

Design: This was an open-label, single arm, dose escalation study. The starting dose level was 7.4 mg/m^2 administered once every 3 weeks (Q3w). The following doses were studied:

Table 1: Accrual per Dose Cohort - All Treated Patients

Dose Cohort	Number of Patients N = 61
7.4 mg/m^2 1 hr	3
15 mg/m^2 1 hr	3
30 mg/m^2 1 hr	3
40 mg/m^2 3 hr	16
50 mg/m^2 1 hr	22
50 mg/m^2 3 hr	8
57 mg/m^2 1 hr	3
65 mg/m^2 1 hr	3

Pharmacokinetics: Blood samples for the pharmacokinetics of ixabepilone and two degradation products of ixabepilone (ie, the oxazine derivative BMS-249798 and the diol derivative BMS-326412) were collected as follows:

- For patients receiving a one-hour infusion: Predose, 00:30, 1:00 (end-of infusion), 1:15, 1:30, 1:45, 2:00, 3:00, 4:00, 6:00, 8:00, 24:00, 48:00 and 72:00 post start of infusion.

- For patients receiving a 3-hour infusion: Predose, 1:30, 2:58 (end of infusion), 3:15, 3:30, 3:45, 4:00, 5:00, 6:00, 8:00, 24:00, 48:00 and 72:00 post start of infusion.

Analytical: Plasma samples were shipped frozen to Bristol-Myers Squibb Pharmaceutical Research Institute, New Brunswick, NJ for the assay of ixabepilone, BMS-249798 and BMS-326412. Plasma samples were assayed by a validated LC/MS/MS method for the measurement of ixabepilone, BMS-249798 and BMS-326412 concentrations.

Plasma samples from study CA163001 [illegible]

[redacted]

PK Results: Following a 1-hour infusion mean Cmax and AUC appear to increase less than proportionally to dose. The sample size for this conclusion was small (n = 3) for most of the doses except 50 mg/m^2. For the 1-hour infusion data from Cycle 1 and Cycle 2 was available. Tmax occurred around 0.5-0.9 hours post start of infusion. The half-life was approximately 30 hours and ranged from 25-48 hours. There was no hint of accumulation after the second dose which is consistent with the half-life of the drug. On average exposures (Cmax and AUC) tended to be less for Cycle 2 than what was seen in Cycle 1 for the 1-hour infusions. PK data from the 3-hour infusions is below:

Table 11.2.1C: Summary of Ixabepilone Pharmacokinetics, 3-hour Infusion, Cycle 1		
Pharmacokinetic Parameter	Ixabepilone Dose (mg/m^2) (n) for Cycle 1	
	40 (14)	50 (8)
Cmax (ng/mL) Geom. Mean (CV%)	247 (72)	281 (46)
AUC(0-T) (ng•h/mL) Geom. Mean (CV%)	1847 (54)	1844 (46)
AUC(INF) (ng•h/mL) Geom. Mean (CV%)	2406 (56) [a]	2385 (47)
Tmax (h) Median (Min, Max)	2.97 (1.47,3.25)	2.97 (1.50,2.97)
T-Half (h) Mean (SD)	35 (12) [a]	35 (11)
MRT(INF) (h) Mean (SD)	41 (13)	36 (17)
CLT (L/h) Mean (SD)	35.3 (15.2)	46 (22.8)
VSS (L) Mean (SD)	1476 (836)	1511 (572)

Source: Supplemental Table S.11.2.1B

[a] n = 13

The systemic exposure of BMS-326412 and BMS-249798 were much less than the systemic exposure of ixabepilone indicating that these are not major circulating products.

Safety Results: Myelosuppression was dose dependent and manifested primarily as neutropenia and leukopenia. Of note, severe thrombocytopenia and anemia were rare. Sensory neuropathy, although generally mild to moderate, was the most common ixabepilone-related adverse event leading to dose reductions or discontinuations, both of which generally occurred at doses $\geq$ 50 mg/m^2. Additional toxicities included fatigue, myalgia, arthralgia, and nausea, all of which are common toxicities associated with the use of chemotherapeutic drugs. Discontinuations due to study drug related adverse events occurred in a minority of patients (9 [15%] patients).

4.1.2 CA163002: Ascending weekly or Q4 week monotherapy study

Title: Phase I Study of BMS-247550 Given Weekly in Patients with Advanced Malignancies.

Investigators: Martine Piccart, MD
Jules Bordet Institute, Brussels, Belgium;

Study Period: Date first subject enrolled: 27-Dec-1999
Date last subject completed: 11-Oct-2002

Clinical Phase: 1

Objectives: The primary objectives were to: (1) To establish the maximum tolerated dose (MTD), dose limiting toxicity (DLT), safety and a recommended Phase 2 dose of the investigational agent BMS-247550 when administered as a weekly infusion to patients with solid tumors who have failed standard therapy or for whom no standard therapy exists (2) To characterize the safety and tolerability of ixabepilone when given at 15, 20, and 25 mg/m^2 using a modified weekly schedule and infusion time.

Secondary objectives included: (1) To evaluate the plasma pharmacokinetics of ixabepilone in patients when administered as an intravenous infusion, as an oral solution and as an oral

suspension (2) To assess the absolute oral bioavailability of ixabepilone when given as an oral solution and as an oral suspension (3) To explore the pharmacodynamics of ixabepilone following oral and IV administration using an assay that measures the amount of endogenous tubulin in PBMCs that exists in the polymerized versus the unpolymerized state (4) To describe any preliminary evidence of antitumor activity

Design: At the start of the trial, Ixabepilone was administered weekly as a 30-minute infusion on a continuous 21-day schedule. Because of neurotoxicity on this regimen, the infusion time was increased from 30 minutes to 1 hour and the schedule was modified to allow for a 1 week break in therapy. For patients treated on the modified 28-day schedule, 1 cycle was defined as 4 weeks and consisted of 3 weekly IV administrations (on Days 1, 8 and 15) followed by a 1-week rest period (ie, the first administration of the next cycle was on Day 29). The starting dose level was 1 mg/m^2 administered as a 30-minute infusion weekly once every 3 weeks. Dosing continued as long as patients tolerated the treatment, unless there was evidence of progressive disease and/or the patient met discontinuation criteria.

This study also assessed the absolute oral bioavailability of ixabepilone when given as an oral *solution* or as an oral *suspension*. Starting at the 20 mg/m^2-dose level, patients received an additional single oral dose of ixabepilone, either as an oral *solution* or as an oral *suspension*, on Day -6 before Cycle 1. The oral *solution* dose was intended to be equivalent to the dose planned for the IV administration for that particular dose level. The oral *suspension* was given as either a micronized or non-micronized suspension at a fixed total dose of 50 mg.

The doses studied are below:

Table 1: Ixabepilone Dose Cohorts

Dose Cohort	Number of Treated Patients N = 86
21-Day Schedule[a]	
Oral solution only	1[b]
1 mg/m^2	4
2.5 mg/m^2	4
5 mg/m^2	3
10 mg/m^2	3
20 mg/m^2 + oral solution	3
25 mg/m^2 + oral solution	12
30 mg/m^2 + oral solution	4
28-Day Schedule[c]	
Oral Suspension only	1[d]
15 mg/m^2	9
20 mg/m^2	10
20 mg/m^2 + oral solution	2
20 mg/m^2 + oral suspension	3
25 mg/m^2	10
25 mg/m^2 + oral solution	4
25 mg/m^2 + oral suspension	13

[a] Ixabepilone administered as a 30-minute infusion on Days 1, 8, and 15 every 3 weeks (1 cycle = 3 weeks)

[b] Patient CA163002-2-209 received a single 50 mg/m^2 oral dose of ixabepilone only.

[c] Ixabepilone administered as a 1-hour infusion on Days 1, 8, and 15 every 3 weeks followed by a 1-week break (1 cycle = 4 weeks)

[d] Patient CA163002-2-231 received a single 50 mg/m^2 oral dose of ixabepilone only.

Pharmacokinetics: Approximately 7 ml blood samples were collected for ixabepilone analysis.

The collection schedule (from the start of the IV infusion) for patients receiving a 30-minute infusion was as follows: Predose, 00:15, 00:30 (end-of-infusion), 00:45, 1:00, 1:30, 2:00, 3:00, 4:00, 6:00, 8:00, 24:00, 48:00 and 72:00.

The collection schedule (from the start of the IV infusion) for patients receiving a one-hour infusion was as follows: Predose, 00:30, 0:58 (end-of-infusion), 1:15, 1:30, 2:00, 3:00, 4:00, 6:00, 8:00, 24:00, 48:00 and 72:00.

Analytical: Plasma samples were assayed by a validated LC/MS/MS method for the measurement of ixabepilone concentrations.

Plasma samples from study CA163002, after the 30-min infusion dose, were analyzed for ixabepilone in 14 analytical runs (Runs 2, 5-6, 11-13, 16, 18, 20-21 and 24-27), those after the oral dose were analyzed in 16 analytical runs (Runs 1-2, 4-10 and 12-18) and those after the 1-hr infusion dose were analyzed in 12 analytical runs (Runs 1-2, 4-6, 8, 10 and 12-16); all of these analytical runs met the previously established acceptance criteria.

Results for the standard curves for 30-min, oral and 1-hr doses, respectively, are summarized as follows: The standard curves were well fitted by a 1/x-weighted quadratic equation over the concentration range of 2.00 to 500 ng/mL, with r^2 values ≥ 0.9933, ≥ 0.9888 and ≥ 0.9888. Coefficient of variation (CV) for the between-run and within-run precision for analytical quality control samples were no greater than 9.4%, 8.5% and 11.7% with deviations from the nominal concentrations of no more than ±8.6%, ± 7.9% and 6.6%. The lower QC for the first run in CA163-002 exhibited a mean deviation of 19.7%. This was due to a preparation problem and the QC was re-prepared for subsequent analyses. The standard curve and QC data indicate that the ixabepilone plasma assay method is precise and accurate.

PK Results: The pharmacokinetics results showed that the exposure to ixabepilone appeared to increase in proportion to dose for the IV doses. The absolute bioavailability of ixabepilone was 41.3% when administered as an oral solution and 36.6% when administered as an oral suspension. However, the variability of the exposure resulting from administration of these oral formulations was greater than that for IV administration.

Table 11.2.1C: Summary of Ixabepilone Pharmacokinetics following Oral Solution Doses and an Oral Suspension Dose

	Ixabepilone Oral Treatments			
	Oral Solution Dose (mg/m^2) (n)			Oral Suspension Dose (mg/m^2) (n)
Pharmacokinetic Parameter	20 (3)	25 (17)	30 (4)	50 (20)
Cmax (ng/mL) Geom. Mean (CV%)	108 (75)	167 (61)	260 (38)	131 (89)
AUC(0-T) (ng•h/mL) Geom. Mean (CV%)	268 (94)	395 (92)	641 (41)	429 (81)
AUC(INF) (ng•h/mL) Geom. Mean (CV%)	354 (92)	510 (83)	782 (40)	545 (85)
F (%) Geom. Mean (CV%)	34.9 (48.0)	40.1 (46.7)	53.7 (28.0)	36.6 (45.6)
Tmax (h) Median (Min, Max)	1.03 (0.25,1.52)	0.50 (0.25,2.95)	0.54 (0.25,0.77)	0.90 (0.48,2.00)
T-Half (h) Mean (SD)	28 (20)	31 (23)	31 (3)	24 (14)

CA163002
Source: Supplemental Table S.11.2.1B

Table 11.2.1B:	Summary of Ixabepilone Pharmacokinetics following 1 hr IV Infusion		
PK Parameter	Ixabepilone Dose (mg/m^2) (n)		
	15 (6)	20 (6)[a]	25 (27)
Cmax (ng/mL)	166	218	242
Geom. Mean (CV%)	(52)	(50)	(37)
AUC(0-T) (ng•h/mL)	569	1032	964
Geom. Mean (CV%)	(57)	(72)	(52)
AUC(INF) (ng•h/mL)	735	1437	1345
Geom. Mean (CV%)	(54)	(80)	(53)
Tmax (h)	0.94	0.97	0.93
Median (Min, Max)	(0.90,0.97)	(0.95,0.97)	(0.47,1.30)
T-Half (h)	36	44	45
Mean (SD)	(11)	(15)	(16)
MRT(INF) (h)	43	56	54
Mean (SD)	(10)	(19)	(22)
CLT (L/h)	41.5	30.5	39.4
Mean (SD)	(23.5)	(19.3)	(23.5)
Vss (L)	1682	1655	1990
Mean (SD)	(756)	(1089)	(995)

CA163002
Source: Supplemental Table S.11.2.1B
a: n=7 for Cmax and Tmax.

Safety Results: Ixabepilone demonstrated an acceptable safety profile at 25 mg/m^2 administered as a 30-minute infusion on a continuous 21-day schedule and at 20 mg/m^2 administered as a 1-hour infusion on a modified 28-day schedule. On the 21-day schedule, myelosuppression of any type was uncommon. At the MTD of 25 mg/m^2, no patients developed Grade 3/4 neutropenia. At this dose, sensory neuropathy was mostly Grade 1/2 and was Grade 3 in 1/12 patients (8%). In those patients who had neuropathy, its severity typically increased with repeated exposure. Fatigue was dose-limiting at 30 mg/m^2 and was Grade 3 in 3/12 (25%) patients at the MTD.

On the 28-day schedule, myelosuppression of any type was uncommon. At 20 mg/m^2, 2/15 patients (13%) had Grade 3 neutropenia and no patients had Grade 4. Overall, toxicity was generally less at 20 mg/m^2 than at 25 mg/m^2, with the most notable being Grade 3/4 sensory neuropathy (7% vs 19%, respectively). Again, the neuropathy was cumulative, with the severity increasing with repeated exposure. Fatigue was generally Grade 1/2 at all doses, though Grade 3 fatigue occurred in 10 patients (20%).

All patient deaths were due to disease progression. No deaths in either schedule were attributed to ixabepilone.

4.1.3 CA163007: Ascending dose study with carboplatin

Title: Phase 1 Study of BMS-247550 in Combination With Carboplatin in Patients With Advanced Malignancies

Investigators: Mark Verrill MD
Newcastle General Hospital

Study Period: Date first subject enrolled: 03-Jan-2001
Date last subject completed: 18-June-2003

Clinical Phase: 1

Objectives: The primary objective is to establish the recommended Phase 2 dose based on the maximum tolerated dose (MTD) and to assess the dose-limiting toxicities (DLT) of two schedules of ixabepilone and carboplatin. Secondary Objectives included: (1) to describe the safety profile and adverse events (AEs) associated with the combination of ixabepilone and carboplatin, (2) to characterize the plasma pharmacokinetics of ixabepilone when administered as a 1-hour intravenous infusion followed by carboplatin infused over 30 minutes, (3) to describe any preliminary evidence of antitumor activity of the combination of the two agents administered as described, (4) to obtain exploratory determination of carboplatin pharmacokinetics.

Design: This was an open-label, single-arm Phase 1 dose escalation study where ixabepilone was administered with carboplatin administered using two different schedules to patients with advanced non-hematologic malignancies.

- Schedule A: ixabepilone 1- hour infusion on Day 1 of each 21-day cycle plus carboplatin infused over 30 minutes.
- In Schedule B: ixabepilone on Day 1 and Day 8 plus carboplatin infusion over 30 minutes on Day 1 only.

The starting dose of ixabepilone on Schedule A was 30 mg/m^2 and the initial dose of carboplatin corresponded to the target area under the curve (AUC) of 6 mg/ml min. For Schedule B, the starting dose of ixabepilone was 20 mg/m^2 given on Days 1 and 8 and the starting dose of carboplatin corresponded to the target AUC of 5 mg/ml min. For Schedule B, the dose of carboplatin was escalated to an AUC of 6 mg/ml min after ixabepilone had been explored to 20 mg/m^2. Cycles were repeated every 21 days. Patients were treated for a minimum of 2 cycles unless progression or unacceptable toxicity occurred. Blood samples for PK analysis were obtained during Day 1 of the first cycle for all patients and also 24 h after each carboplatin infusion for patients of Schedule B.

The following doses were studied for Schedule A:

Dose Level	Ixabepilone (mg/m^2)	Carboplatin ([mg/ml]•min)
-2	20	5
-1	30	5
1 (starting)	30	6
2	40	6
3	50	6
4	60	6

And for Schedule B:

Dose Level	Ixabepilone (mg/m^2) Day 1/Day 8	Carboplatin ([mg/ml]•min) Day 1
-1	15	5
1 (starting)	20	5
2	20	6
3	25	6

Pharmacokinetics: The collection schedule (expressed as hours:minutes from the start of the 1-

hour infusion of ixabepilone was as follows: predose, 0:15, 0:30, 0:45, 1:00 (end of the ixabepilone infusion), 1:30, 2:00, 3:00, 4:00, 6:00, 8:00, 24:00, 48:00 and 72:00 for the analysis of ixabepilone.

Analytical: Plasma samples were assayed by a validated LC/MS/MS method for the measurement of ixabepilone concentrations.

PK Results: The PK results for ixabepilone in this study are comparable to that of other studies. Carboplatin does not appear to affect the pharmacokinetics of ixabepilone. Exploratory determination of carboplatin PK indicated that the combination of ixabepilone with carboplatin does not appear to alter the AUC of carboplatin.

Table 11.2.1: Summary Statistics for Ixabepilone Pharmacokinetic Parameters

Pharmacokinetic Parameter	Dose Cohort [Ixabepilone (mg/m^2) / Carboplatin (mg/ml•min)[a]]						
	20/5 (n=7)[b]	20/6 (n=13)[c]	25/6 (n=3)	30/5 (n=3)	30/6 (n=5)	40/5 (n=13)[d]	40/6 (n=2)
Cmax (ng/mL) Geo. Mean (CV%)	391.24 (48.66)	446.14 (62.07)	757.65 (73.87)	376.16 (38.36)	488.87 (14.31)	635.08 (35.40)	542.82 (9.16)
Tmax (h) Median (Min, Max)	0.75 (0.75, 1.03)	0.98 (0.53, 1.00)	1.00 (0.50, 1.00)	0.75 (0.75, 0.75)	0.98 (0.75, 1.00)	0.80 (0.50, 1.33)	0.99 (0.98, 1.00)
AUC(INF)(ng·h/mL) Geo. Mean (CV%)	1416[b] (49)	1217[c] (35)	2373 (55)	1209 (27)	1604 (56)	2059[d] (32)	1641 (16)
T-HALF (h) Mean (SD)	33.68[b] (14.87)	27.03[c] (8.70)	31.62 (3.67)	40.62 (13.67)	28.69 (4.83)	23.52[d] (8.83)	25.45 (18.91)
MRT(INF) (h) Mean (SD)	32.35[b] (11.12)	24.70[c] (9.02)	34.77 (2.42)	32.40 (12.97)	25.69 (6.77)	19.79[d] (6.46)	22.14 (19.86)
CLT (L/h) Mean (S.D.)	28.15[b] (9.78)	28.39[c] (7.93)	23.14 (20.34)	41.92 (15.89)	35.98 (12.77)	36.64[d] (14.65)	45.09 (3.71)
Vss (L) Mean (SD)	880.95[b] (430.60)	673.05[c] (272.90)	818.29 (739.92)	1420 (980)	898.15 (340.89)	657.73[d] (148.66)	961.55 (813.38)

Source: Supplemental Table S.11.2.1B

[a] Carboplatin was administered 30 minutes after completion of ixabepilone infusion to patients at a dose corresponding to a target AUC of 5-6 mg/ml•min, as determined by a modified Calvert formula.

[b] n=6 for AUC(INF), T-HALF, MRT(INF), CLT and Vss.

[c] n=12 for AUC(INF), T-HALF, MRT(INF), CLT and Vss.

[d] n=10 for AUC(INF), T-HALF, MRT(INF), CLT and Vss.

Safety Results: The major toxicities encountered in this study were neutropenia and sensory/motor neuropathy, which were mostly reversible but could be dose-limiting at higher

doses. Arthralgia/myalgia was seen in many patients but was mostly Grade 1 or 2. Other adverse events (AEs) often seen with cytotoxic regimens such as stomatitis/mucositis, nausea/vomiting, and fatigue were mostly mild to moderate.

4.1.4 CA163008: Ascending dose study with doxorubicin

Title: A Phase I Study of BMS-247550 in Combination With Doxorubicin in Patients With Advanced Malignancies

Investigators: Howard A. Burris, III, MD

Study Period: Date first subject enrolled: 29-Aug-2000
Date last subject completed: 11-Sep-2001

Clinical Phase: 1

Objectives: The primary objective was to establish the maximum-tolerated dose (MTD), dose-limiting toxicity (DLT), and a recommend Phase 2 dose of ixabepilone plus doxorubicin. Secondary Objectives included: (1) to describe the safety profile and adverse events associated with the combination of ixabepilone and doxorubicin, (2) to characterize the plasma pharmacokinetics of the combination of ixabepilone and doxorubicin (3) to describe any preliminary evidence of antitumor activity of the combination.

Design: This was an open-label, single-arm, Phase I, dose-escalation study to establish the MTD, DLT, and a recommended Phase 2 dose of ixabepilone when administered with doxorubicin. The initial starting doses were 50 mg/m^2 of doxorubicin and 30 mg/m^2 of ixabepilone. Doxorubicin was administered as a bolus IV infusion over 10 to 15 minutes on Day 1 of each 21-day cycle. Ixabepilone was administered as a 1-hour IV infusion beginning 30 minutes after completion of the doxorubicin dose. Treatment was repeated every 21 days or after all toxicities had resolved to baseline severity or to National Cancer Institute (NCI) Common Toxicity Criteria (CTC) Grade $\leq$1, whichever occurred later. A minimum of 3 patients were to be treated at each dose level prior to dose escalation. When the MTD was reached with this combination, approximately 12 to 15 patients were to be studied at the MTD to determine its suitability as the recommended dose for Phase 2 combination studies.

Twelve patients were enrolled in this study. The following ixabepilone/doxorubicin doses were studies and the accrual of patients by cohort is summarized below.

Accrual Per Dose Cohort - All Enrolled Patients

Ixabepilone/Doxorubicin Dose Cohort	N (%)
30/50 mg/m^2	3 (25%)
30/40 mg/m^2	6 (50%)
35/40 mg/m^2	3 (25%)
All Cohorts	12

Pharmacokinetics: Blood samples for the analysis of doxorubicin and doxorubicinol were collected at (expressed as hours:minutes from the start of the 10-minute IV doxorubicin infusion) predose and 0:09, 0:30, 1:10, 1:38, 2:00, 2:15, 2:30, 3:00, 3:30, 4:00, 6:00, 8:00, 24:00, 48:00, and 72:00.

The collection schedule (expressed as hours:minutes from the start of the 1-hour infusion of ixabepilone) was as follows: predose and 0:30, 0:58 (prior to end of the ixabepilone infusion), 1:20, 1:35, 1:50, 2:20, 2:50, 3:20, 5:20, 7:20, 23:20, 47:20, and 71:20 for the analysis of ixabepilone.

Analytical: Ixabepilone plasma samples were assayed by a validated liquid chromatography (LC/MS/MS) method for the measurement of ixabepilone concentrations. Plasma samples were analyzed for ixabepilone in 4 analytical runs (Runs 1, 6. 7 and 9); all of these analytical runs met the previously established acceptance criteria.

PK Results: The pharmacokinetic results for ixabepilone in this study were comparable to those of study CA163001. The pharmacokinetic results for doxorubicin in this study were similar to those previously reported in the literature.

Table 11.2.1: Summary Statistics for Ixabepilone Pharmacokinetic Parameters

Pharmacokinetic Parameter	Dose Cohort [Ixabepilone (mg/m^2) / Doxorubicin (mg/m^2)] 30/50 (n=3)	30/40 (n=6)	35/40 (n=3)
Cmax (ng/mL) Geometric Mean (CV %)	340.76 (27.84)	294.97 (42.74)	451.00 (36.84)
Tmax (h) Median (Min, Max)	0.97 (0.50, 0.98)	0.57 (0.42,0.97)	0.97 (0.88, 1.00)
C(INF)(ng·h/mL) Geometric Mean (CV %)	1287 (71)	1266 (27)	1706 (26)
T-HALF (h) Mean (SD)	36.13 (11.08)	43.80 (16.10)	21.98 (2.33)
MRT(INF) (h) Mean (SD)	37.64 (5.89)	45.49 (18.61)	26.42 (3.09)
CLT (L/h) Mean (SD)	49.53 (24.04)	47.28 (15.91)	41.71 (11.96)
Vss (L) Mean (SD)	1938 (1122)	2110 (975)	1081 (204)

Table 11.2.2: Summary Statistics for Doxorubicin Pharmacokinetic Parameters

Pharmacokinetic Parameter	Dose Cohort [Ixabepilone (mg/m^2) / Doxorubicin (mg/m^2)] 30/50 (n=3)	30/40 (n=6)
Cmax (ng/mL) Geometric Mean (CV %)	2999 (38)	2480 (42)
Tmax (h) Median (Min, Max)	0.15 (0.15,0.17)	0.15 (0.15,0.23)
AUC(INF)(ng·h/mL) Geometric Mean (CV %)	2197 (23)	1839 (35)
T-HALF (h) Mean (SD)	27.30 (11.01)	36.08 (6.20)
MRT(INF) (h) Mean (SD)	23.90 (4.33)	29.96 (4.29)
CLT (L/h) Mean (SD)	44.03 (9.57)	43.83 (15.62)
Vss (L) Mean (SD)	1025 (55)	1313 (503)

Table 11.2.3: Summary Statistics for Doxorubicinol Pharmacokinetic Parameters

Pharmacokinetic Parameter	Dose Cohort [Ixabepilone (mg/m^2) / Doxorubicin (mg/m^2)] 30/50 (n=3)	30/40 (n=6)
Cmax (ng/mL) Geometric Mean (CV %)	31.45 (48.71)	34.26 (50.23)
Tmax (h) Median (Min, Max)	3.05 (0.65,3.98)	3.42 (1.65,6.00)
AUC(INF) (ng·h/mL) Geometric Mean (CV %)	1265 (52)	1134 (52)
T-HALF (h) Mean (SD)	37.78 (4.54)	42.54 (19.82)
MRT(INF) (h) Mean (SD)	50.66 (6.60)	59.61 (25.16)

Safety Results: All 12 of the patients experienced at least one treatment-related adverse event. The most frequently reported treatment-related adverse events (reported in ≥50% of patients) associated with combination therapy with doxorubicin and ixabepilone were alopecia (92%; 11/12), fatigue (92%; 11/12), nausea (83%; 10/12), arthralgia (58%; 7/12), myalgia (58%; 7/12), vomiting (50%; 6/12), and sensory neuropathy (50%; 6/12). Most treatment-related adverse events were rated mild (Grade 1) to moderate (Grade 2) in intensity.

4.1.5 CA163038: Capecitabine Drug-Drug interaction

Title: Effect of Capecitabine on the Pharmacokinetics of Ixabepilone and Ixabepilone on the Pharmacokinetics of Capecitabine and its Metabolites in Patients with Advanced Malignancies

Investigators: Howard A. Burris III, MD (Site 1)
Sarah Cannon Cancer Center,
Nashville, TN, USA

Study Period: Date first subject enrolled: 01-Oct-2004
Date last subject completed: 23-Dec-2005

Clinical Phase: 1

Objectives: The primary objective was to assess the effect of capecitabine on the pharmacokinetics of ixabepilone and to assess the effect of ixabepilone on the pharmacokinetics of capecitabine and its metabolites in patients with advanced malignancies. Secondary objectives included: (1) to evaluate the safety of ixabepilone co-administered with capecitabine, (2) to evaluate the safety of ixabepilone and (3) to describe any preliminary evidence of antitumor activity.

Design: This was an open-label, sequential design study in subjects with advanced non-hematologic malignancies. During Cycle 1, subjects were administered a single intravenous (IV) dose of ixabepilone 40 mg/m^2 over 3 hours on Day 1 and a single oral (PO) dose of capecitabine 1000 mg/m^2 on Day 15. During Cycle 2, subjects were administered a 3-hour IV infusion of ixabepilone 40 mg/m^2 on Day 1 and capecitabine 1000 mg/m^2 PO every 12 hours (q12h) on Days 1-5. One cycle was defined as 21 days. Subjects who completed Cycle 2 continued in the study on a therapeutic regimen of ixabepilone mg/m^2 IV administered over 3 hours every 21 days until disease progression, unacceptable toxicity, or subject refusal.

Pharmacokinetics: Blood samples for ixabepilone, capecitabine and 5-FU were collected according to the following schedule.

Table 5.10.1: PK Sampling Schedule

Cycle, Day	Time Relative to Dosing (hour:minute)	Volume of Blood Sample for Plasma Pharmacokinetics
Cycle 1, Day 1	Pre-dose	5 mL
	1:00	5 mL
	3:00[a]	5 mL
	3:15	5 mL
	3:30	5 mL
	4:00	5 mL
	6:00	5 mL
	8:00	5 mL
	24:00	5 mL
	48:00	5 mL
	72:00	5 mL
	96:00	5 mL
	120:00	5 mL
Cycle 1, Day 15	Pre-dose	5 mL
	0:30	5 mL
	1:00	5 mL
	2:00	5 mL
	3:00	5 mL
	4:00	5 mL
	5:00	5 mL
	6:00	5 mL
	8:00	5 mL
	12:00	5 mL
Cycle 2, Day 1	Pre-dose[b]	10 mL
	0:30[c]	5 mL
	1:00[b]	10 mL
	2:00[c]	5 mL
	3:00[b,d]	10 mL
	3:15[e]	5 mL
	3:30[d]	5 mL
	4:00[b]	10 mL
	5:00[c]	5 mL
	6:00[b]	10 mL
	8:00[b]	10 mL
	12:00[c]	5 mL
	24:00[d]	5 mL
	48:00[d]	5 mL
	72:00[d]	5 mL
	96:00[d]	5 mL
	120:00[d]	5 mL

Source: Appendix 5.1A

[a] This sample was taken just prior to the end of the infusion even if the infusion lasted for less than or more than the planned 3 hours.

[b] 10 mL blood sample to measure ixabepilone, capecitabine and 5-FU

[c] 5 mL blood sample to analyze capecitabine and 5-FU

[d] This sample was taken just prior to the end of ixabepilone infusion even if the infusion lasts for less than or more than the planned 3 hours.

[e] 5 mL blood sample to assay ixabepilone

Analytical: The samples for ixabepilone were analyzed for using a validated liquid chromatography tandem mass spectrometry (LC/MS/MS) detection method.

Samples for capecitabine and 5-fluorouracil were analyzed for using liquid chromatography (LC/MS/MS) detection. Capecitabine-d_{11}, the stable isotope labeled

PK Results: Twenty-subjects completed the PK portion of the protocol as designed.

- Co-administration of capecitabine with ixabepilone resulted in a decrease in ixabepilone Cmax of approximately 19% while AUC(INF), remained constant. The 90% CI's remained within the similarity boundaries of .80-1.25 for both AUC and Cmax.
- Co-administration of ixabepilone with capecitabine resulted in a decrease in capecitabine Cmax of approximately 27% and a decrease of approximately 5% in capecitabine AUC(TAU). The 90% CI remained within the similarity boundaries of .80-1.25 for AUC but for Cmax the lower bound was below 0.8 (Cmax 90% CI: 0.549, 0.975)
- An increase of less than 1% in 5-FU Cmax and an increase of 14% in 5-FU AUC(TAU) were observed when administered with ixabepilone.

Summary Statistics for Ixabepilone Pharmacokinetic Parameters

Cycle (n=20)	Cmax (ng/mL) Geom. Mean (CV %)	AUC(INF) (ng•h/mL) Geom. Mean (CV%)	Tmax (h) Median (Min, Max)	T-HALF (h) Mean (SD)	VSS (L) Mean (SD)	CL (L/h) Mean (SD)
1	309 (51)	2219 (31)	3.00 (0.97, 3.05)	48.29 (15.09)	1456 (682)	34.79 (11.53)
2	250 (48)	2078 (23)	3.00 (1.00, 3.03)	44.39 (11.87)	1515 (674)	36.35 (9.47)

Cycle 1 = 40mg/m^2 ixabepilone IV
Cycle 2 = 40mg/m^2 ixabepilone IV with 1000mg/m^2 capecitabine PO

Summary Statistics for Capecitabine Pharmacokinetic Parameters

Cycle (n=20)	Cmax (ng/mL) Geom. Mean (CV%)	AUC(TAU) (ng•h/mL) Geom. Mean (CV %)	Tmax (h) Median (Min, Max)	T-HALF (h) Mean (SD)
1	4280 (69)	5613 (66)	1.00 (0.50, 4.10)	0.49 (0.20)
2	3132 (98)	5313 (61)	2.00 (0.50, 4.00)	0.66 (0.37)

Cycle 1 = 1000mg/m^2 capecitabine PO
Cycle 2 = 40mg/m^2 ixabepilone IV with 1000mg/m^2 capecitabine PO

Summary Statistics for 5-Fluorouracil Pharmacokinetic Parameters

Cycle (n=20)	Cmax (ng/mL) Geom. Mean (CV%)	AUC(TAU) (ng•h/mL) Geom. Mean (CV %)	Tmax (h) Median (Min, Max)	T-HALF (h) Mean (SD)
1	208 (69)	377 (39)	2.00 (0.50, 4.10)	0.71 (0.12)
2	210 (75)	429 (39)	2.00 (0.50, 5.00)	0.82 (0.25)

Cycle 1 = 1000mg/m^2 capecitabine PO
Cycle 2 = 40mg/m^2 ixabepilone IV with 1000mg/m^2 capecitabine PO

Safety Results: Four (18%) subjects had SAEs during Cycles 1 and 2. Among these, mucosal inflammation was reported in 2 (9%) subjects. Other SAEs included abdominal pain, constipation, diarrhea, chest pain and dehydration in 1 (4.5%) subject each. Most of the treatment-related AEs in Cycles 1 and 2 were either Grade 2 or Grade 3. There was 1 Grade 4 treatment-related AE in Cycle 1 and 2 (thrombocytopenia in 1 subject, 4.5%). The most common Grade 3 treatment-related AEs in Cycles 1 and 2 were neutropenia (7 subjects, 32%) and mucosal inflammation (2 subjects, 9%).

4.1.6 CA163039: ADME

Title: Pharmacokinetics and Metabolism of [^{14}C]BMS-247550 in Patients with Advanced Cancer

Investigators: Jan H.M. Schellens, MD, PhD
Netherlands Cancer Institute (NKI)
Amsterdam, Netherlands

Study Period: Date first subject enrolled: 06-Jan-2003
Date last subject completed: 18-May-2004

Clinical Phase: 1

Objectives: The primary objective was to assess the pharmacokinetics, metabolism, and routes and extent of elimination of a single IV dose of [^{14}C]ixabepilone in patients with advanced cancer. Secondary objectives included: (1) to evaluate the safety of a single IV dose of [^{14}C]ixabepilone followed by a therapeutic regimen of ixabepilone administered as a 3 hour infusion every 21 days, (2) to describe any preliminary evidence of anti-tumor activity.

Design: This was a 2-part, single site, open-label, non-randomized study. Part A of the study utilized a single dose to evaluate the safety, tolerability, pharmacokinetics and metabolism of ixabepilone in patients with advanced cancer. On Day 1, following collection of baseline assessments, all patients received a single intravenous (IV) dose of [^{14}C]ixabepilone as a 3 hour infusion at a fixed dose of 70 mg containing 80 nCi of total radioactivity (TRA).

Patients who completed Part A of the study were placed on a therapeutic continuation of the study (Part B) based on evaluation by the Investigator. Ixabepilone was administered as a 3 hour infusion at a dose of 40 mg/m^2 once every 3 weeks. Toxicity was evaluated continuously, hematology was evaluated weekly and serum chemistry was evaluated prior to each cycle. Dosing continued once every 3 weeks as long as patients tolerated the treatment, unless there was evidence of progressive disease or the patient met discontinuation criteria.

Pharmacokinetics: Blood samples for the measurement of ixabepilone and TRA were obtained predose and at 1.5, 3, 3.25, 3.5, 3.75, 4, 5, 6, 8, 10-12, 24, 48, 72, 120, and 168 hours post-dose. Blood samples for biotransformation analysis were obtained at predose, and 3, 4, 8, and 24 hours post-dose. Urine samples for determining total radioactivity were collected predose and continuously over 24-hour intervals throughout the study period (0-24, 24-48, 48-72, 72-96, 96-120, 120-144, and 144-168 hours). Fecal samples for determining total radioactivity were collected predose and continuously over 24-hour intervals throughout the study period (0-24, 24-48, 48-72, 72-96, 96-120, 120-144, and 144-168 hours).

Analytical: Human EDTA plasma samples were assayed for ixabepilone and human urine samples were assayed for ixabepilone, by validated LC/MS/MS methods. Total radioactivity in plasma, urine and feces was measured using liquid scintillation counting and accelerated mass spectrometry.

PK Results: Eight patients completed part A of the study. One subject (CA163039-1-8) was deemed unevaluable for statistical analysis of plasma pharmacokinetic parameters and mass balance because this subject had a blocked gastric stent which resulted in an altered disposition of ixabepilone. One subject (CA163039-1-4) was deemed unevaluable for the statistical analysis of mass balance because this subject excreted only 12.3 grams of feces after the first 24 h collection.

Radioactivity was detected in plasma up to at least 168 hours post dose. Concentrations of parent ixabepilone were lower than the corresponding concentrations of total radioactivity and the AUC(INF) of the parent ixabepilone was an average of 24% of the AUC for the total radioactivity. The mean (SD) cumulative percent of ixabepilone excreted in urine (CUE) was 5.49 (1.38). The recovery of TRA was 86.2% from the 6 evaluable subjects over the 7 days of the study. Approximately 3/4 of the recovered TRA was eliminated in feces and approximately 1/4 of the recovered TRA was eliminated in urine.

Table 11.2.1.1: Summary Statistics for Ixabepilone Pharmacokinetic Parameters

Group	Pharmacokinetic Parameter						
	Cmax (ng/mL) Geometric Mean (C.V. %)	AUC(INF) (ng·h/mL) Geometric Mean (C.V. %)	AUC(0-T) (ng·h/mL) Geometric Mean (C.V. %)	Tmax (h) Median (Min, Max)	T-HALF (h) Mean (S.D.)	Renal Clearance (L/h) Mean (S.D.)	Clearance (L/h) Mean (S.D.)
All Subjects (n = 7)	304.81 (32)	2929.13 (23)	2907.57 (21)	2.75 (1.55, 3.18)	50.78 (16.62)	1.47 (0.51)	24.35 (4.89)

Table 11.2.2.1: Summary Statistics for Total Radioactivity Pharmacokinetic Parameters

Group	Pharmacokinetic Parameter				
	Cmax (ng/mL) Geometric Mean (C.V. %)	AUC(INF) (ng·h/mL) Geometric Mean (C.V. %)	AUC(0-T) (ng·h/mL) Geometric Mean (C.V. %)	Tmax (h) Median (Min, Max)	T-HALF (h) Mean (S.D.)
All Subjects (n = 7)	539.29 (35)	12152.12 (81)	9894.49 (53)	2.80 (1.58, 2.95)	69.52 (57.95)

Table 11.2.2.2: Summary of Total Radioactivity Recovered

	Urine (% recovered)	Feces (% recovered)	Total (% recovered)
Mean (n=6)	21.35	64.85	86.20
S.D.	6.30	16.18	20.60

Mass balance Results: The major radioactive component in the pooled urine (22.5% of urine radioactivity) and plasma extracts (20.6-26.8% of plasma radioactivity) was unchanged [14C]ixabepilone. There were numerous radioactive drug related compounds in the urine sample and in the plasma extracts. Two of the radioactive peaks in urine and plasma samples were identified as known degradants BMS-249798 and BMS-326412 which corresponded to <10% of the total radioactivity. In the pooled feces, unchanged drug accounted for 3.1% of radioactivity (1.6% of the dose). There were at least 29 drug related compounds, including known degradants of ixabepilone (BMS-249798, BMS-326412 [redacted]), in the fecal extract, each accounting for <10.3% of the fecal radioactivity. Each of the drug related compounds in urine and feces accounted for only a small amount of the administered dose, <2.1% and <5.4% of the dose, respectively. The identified metabolites in human plasma, urine and/or feces were oxidized metabolites including 2 M+16 metabolites, an M+14 metabolite and an M-2 metabolite.

Safety Results: There were no Grade 4 adverse events. The most common Grade 3 adverse events were abdominal pain (37.5%), fatigue (25%) and vomiting (25%).

4.1.7 CA163042: Ketoconazole DDI

Title: Effect of Ketoconazole on the Pharmacokinetics of BMS-247550 in Patients with Advanced Cancer

Investigators: Sridhar Mani, MD
Montefiore Medical Center, Bronx, NY, USA

Study Period: Date first subject enrolled: 04-Nov-2003

Date last subject completed: 10-Nov-2005

Clinical Phase: 1

Objectives: To assess the effect of ketoconazole on the pharmacokinetics of ixabepilone in patients with advanced cancer. The secondary objectives are to (1) to evaluate the safety of ixabepilone co-administered with ketoconazole, (2) to evaluate the safety of ixabepilone, (3) to measure the change in the extent of microtubule bundle and mitotic aster formation in peripheral blood mononuclear cells (PBMC) and tumor cells following ixabepilone treatment, (2) to describe any preliminary evidence of anti-tumor activity.

Design: This was an open-label, sequential study in subjects with advanced cancer. Cycle 1 used a dose escalation of ixabepilone co-administered with a fixed dose of ketoconazole to evaluate the safety of ixabepilone coadministered with ketoconazole. During Cycle 1, subjects were administered each of the following treatments:

- 3-hour intravenous (IV) infusion of ixabepilone on Day 1 at a starting dose of 10 mg/m^2
- 400 mg ketoconazole orally with a meal on Day -1 (24 hours before the infusion of ixabepilone), on Day 1 (2 hours before the infusion of ixabepilone) and on Days 2 to 5.

The dose of ixabepilone in Cycle 1 was to be increased to 20, 30 or 40 mg/m^2 for subsequent cohorts of subjects based on safety evaluations. However, the dose escalation increment could have been less than 10 mg/m^2, based upon the judgment and agreement of the Sponsor and the Investigator. A minimum of 3 subjects were to be treated at each dose level unless dose limiting toxicity was observed in the first 2 subjects at that dose level. When the maximum tolerated dose (MTD) of ixabepilone co-administered with ketoconazole was determined, this dose level was expanded to a total of at least 12 subjects.

During Cycle 2, subjects were administered a 3-hour IV infusion of 40 mg/m^2 of ixabepilone on Day 1. Subjects who completed Cycle 2 continued on a therapeutic regimen of ixabepilone, if eligible.

Pharmacokinetics: Blood samples for plasma ixabepilone pharmacokinetics were taken for up to 120 hours post-dosing in Cycles 1 and 2 (hour:minute) at predose, 1:30, just prior to end of infusion, 3:15, 3:30, 4:00, 6:00, 8:00, 24:00, 48:00, 72:00, 96:00 and 120:00.

To assess the effect of ketoconazole on the PK of ixabepilone, two-way analyses of variance was performed on dose-normalized log(Cmax) and log(AUC(INF)) for all subjects who had values for Cycle 1 and Cycle 2. The factors in the analysis were subject and cycle. Since a 40 mg/m^2 MTD from Cycle 1 was not achieved, Cmax and AUC(INF) from Cycle 1 were dose normalized to a 40 mg/m^2 dose. Point estimates and 90% confidence intervals for means and differences between means on the log scale were exponentiated to obtain estimates for geometric means and ratios of geometric means on the original scale. The ratio of population geometric means of Cmax and AUC(INF) for ixabepilone given in combination with ketoconazole (Cycle 1) to ixabepilone given alone (Cycle 2), along with respective 90% confidence intervals, was reported.

Pharmacodynamics: The extent of microtubule bundles in peripheral blood mononuclear cells (PBMC) was measured at predose, EOI, and at 6 hour, 24 hours and 48 hours post start of infusion.

Analytical: Plasma samples were assayed for ixabepilone by a validated liquid chromatography tandem mass spectrometry (LC/MS/MS) method.

PK Results: A total of 29 subjects were enrolled and 27 received ixabepilone. The pharmacokinetics of ixabepilone was significantly affected by co-administration of ketoconazole. Co-administration of ketoconazole with ixabepilone resulted in an increase of approximately 7% in ixabepilone Cmax. However, the 90% confidence interval indicates that this effect is not statistically different from no change. Co-administration of ketoconazole with ixabepilone resulted in a 79% increase in AUC(INF). The 90% confidence interval indicates that this effect is statistically different from no change.

Table 11.2.1A: Summary Statistics for Ixabepilone Pharmacokinetic Parameters

Cycle	Ixabepilone (IV, mg/m^2)	Pharmacokinetic Parameter					
		Cmax (ng/mL) Geom. Mean (CV %)	AUC(INF) (ng·h/mL) Geom. Mean (CV %)	T-HALF (h) Mean (SD)	MRT(INF) (h) Mean (SD)	VSS (L) Mean (SD)	CLT (L/h) Mean (SD)
1	10 (n=4)	54.32 (14)	996.02 (22)	48.26 (26.34)	70.30 (31.29)	1227.91 (382.83)	18.45 (4.89)
	20 (n=12)	97.05 (44)	1694.14 (76)	66.03 (29.70)	81.60 (40.71)	1689.33 (719.26)	25.71 (13.20)
	25 (n=7)	200.27 (61)	2740.75 (52)	55.00 (11.40)	66.16 (13.71)	1194.33 (670.03)	18.84 (12.79)
	30 (n=4)	246.86 (49)	3144.56 (56)	93.94 (27.35)	100.74 (38.17)	1920.70 (881.30)	20.46 (11.86)
2	25[a] (n=1)	137.00 (-)	1337.86 (-)	26.64 (-)	32.11 (-)	1068.09 (-)	33.26 (-)
	32[b] (n=1)	477.00 (-)	3306.59 (-)	45.47 (-)	35.28 (-)	490.74 (-)	13.91 (-)
	40 (n=20)	206.11 (38)	1848.75 (46)	53.17 (25.67)	51.85 (23.86)	2171.31 (1329.20)	42.85 (18.26)

Source: Supplemental Table S.11.2.1B

[a] dosing error

[b] dose reduced based on toxicity profile

Safety Results: There was 1 death due to study drug toxicity within 30 days after the last dose of study medication (77 y.o. male recived 25 mg/m^2 ixabepilone). No dose-related trends were observed for serious adverse events (SAEs) or adverse events (AEs). Seven subjects (26%) had SAEs during Cycle 1 across all dose cohorts, and 5 subjects (22%) had SAEs beyond Cycle 1. Fatigue was the most common SAE, reported in 5 subjects (19%) across all dose cohorts in Cycle 1, and in 2 subjects (9%) beyond Cycle 1. The most frequently reported treatment-related Grade 3 and Grade 4 AEs in Cycle 1 across all dose cohorts were fatigue (5 subjects, 18.5%) and neutropenia (3 subjects, 11%), respectively. Beyond Cycle 1, treatment-related Grade 3 AEs reported in more than one subject included fatigue (3 subjects, 13%), neutropenia (2 subjects, 9%) and peripheral sensory neuropathy (2 subjects, 9%). Beyond Cycle 1, treatment-related Grade 4 AEs of neutropenia and renal failure was reported in 1 subject each (4%).

4.1.8 S0355: Hepatic Impairment

Title: A Phase 1 Pharmacokinetic Study of Epothilone B Analogue BMS-247550 (Ixabepilone) (NSC-710428D) in Patients with Advanced Malignancies and Varying Levels of Liver Dysfunction

Investigators: Investigators at 13 study centers enrolled at least 1 patient

Study Period: Date first subject enrolled: 04-Mar-2004
Date last subject completed: 16-June-2006

Clinical Phase: 1

Objectives: The primary objective was to define levels(s) of hepatic impairment at which dose modifications of ixabepilone (to 30, 20, and/or 10 mg/m^2) are required. Secondary objectives included (1) to characterize the effects of hepatic dysfunction on the plasma PK of ixabepilone (2) to define toxicities associated with dosing of ixabepilone at varying levels of hepatic dysfunction.

Design: This was an open-label dose-escalation study in patients with advanced malignancies and varying levels of liver dysfunction. Patients were stratified into 4 groups based on their hepatic function.

	Group A	Group B		Group C	Group D
	Normal Hepatic Function	Group B1 Mild	Group B2 Mild	Moderate	Severe
Bilirubin	≤ ULN	≤ ULN	> 1.0 x ≤ 1.5 x ULN	> 1.5 x ≤ 3 x ULN	> 3 x ULN
AST	≤ ULN	> ULN	Any	Any	Any

AST: aspartate aminotransferase; ULN: upper limit of normal

Group A included patients with advanced malignancies and normal hepatic function. This group received ixabepilone at 40 mg/m^2 as a 3-hour infusion on Day 1 of a 21-day cycle. Groups B to D included patients with advanced malignancies and varying degrees of hepatic dysfunction; these patients were administered ixabepilone at lower starting doses:

Dose Level	Group A Normal Hepatic Function	Group B Mild Hepatic Dysfunction	Group C Moderate Hepatic Dysfunction	Group D Severe Hepatic Dysfunction
Level 1	40	30	20	10
Level 2	--	40	30	20
Level 3	--	--	40	30
Level 4	--	--	--	40

Note: doses are expressed in mg/m^2

Dosing started at the lowest dose level in each hepatic dysfunction group. Dose escalation within each group proceeded with the goal of reaching the maximum tolerated dose (MTD) within each group. The MTD was defined as the lowest dose at which ≥ one-third of patients experienced dose-limiting toxicity (DLT). Dose-limiting toxicities were prospectively defined and consistent

with criteria used in similar studies. Patients were considered evaluable for DLT when they had received the planned dose and either reported a DLT or were followed for 21 days without a DLT.

Pharmacokinetics: Pharmacokinetic sampling was performed in Cycle 1 for all patients. Samples were obtained at predose, 1.5 hours after the start of infusion, just prior to the end of infusion, and 3.25, 3.5, 3.75, 4, 5, 6, 8, 24, 48, 72, and 144 hours following the start of infusion.

Analytical: Human EDTA plasma samples were assayed for ixabepilone by a validated liquid chromatography tandem mass spectrometry (LC/MS/MS) method.

PK Results: Of 78 patients enrolled, 74 were treated and 73 had PK results. The following doses were studied:

Group and Dose (mg/m^2)	No. of Treated Patients
A 40	19
B 30	12
B 40	13
C 20	11
C 30	3
D 10	9
D 20	7

Ixabepilone exposure, as measured by the dose-normalized AUC(INF), increased with hepatic dysfunction; exposure increases of 22% for mild dysfunction (Group B), 30% for moderate dysfunction (Group C), and 81% for severe dysfunction (Group D) were observed relative to normal hepatic function (Group A). The non-dose normalized summary statistics for pharmacokinetic parameters by group and dose level are below:

Group	Dose (mg/m^2)	Pharmacokinetic Parameter						
		Cmax (ng/mL) Geom. Mean (CV%)	AUC(INF) (ng·h/mL) Geom. Mean (CV%)	AUC(0-T) (ng·h/mL) Geom. Mean (CV%)	T-HALF (h) Mean (SD)	MRT (h) Mean (SD)	VSS (L) Mean (SD)	Clearance (L/h) Mean (SD)
A	40 (N = 17)	255 (52)	2155 (53)	1698 (65)	64.3 (50.0)	65.7 (64.7)	2149 (1444)	37.1 (19.6)
B	30 (N = 12)	178 (45)	1812 (58)	1464 (59)	62.0 (51.6)	67.4 (62.7)	1876 (1144)	33.0 (13.6)
	40 (N = 14)	340 (48)	2833 (60)	2447 (55)	56.7 (35.2)	54.9 (33.8)	1315 (655)	27.8 (12.7)
C	20 (N = 10)	90 (75)	1464 (69)	1079 (72)	65.0 (35.6)	79.1 (43.6)	2324 (1658)	29.2 (15.7)
	30 (N = 3)	143 (68)	1829 (24)	1542 (22)	50.7 (11.0)	70.2 (6.5)	2390 (613)	34.1 (8.8)
D	10 (N = 9)	54 (201)	424[a] (128)	305 (142)	35.1[a] (31.1)	34.8[a] (21.7)	1276[a] (739)	62.3[a] (53.3)
	20 (N = 8)	149 (52)	1951 (86)	1535 (82)	73.0 (20.9)	84.0 (24.5)	1925 (1117)	23.7 (12.1)

[a] n=8, AUC(INF), T-Half, MRT, VSS and clearance could not be determined for Patient 187126.

Group A: Normal, bilirubin <= ULN and AST <= ULN

Group B: Mild, ULN < bilirubin <= 1.5 x ULN and any AST or bilirubin <= ULN and AST > ULN

Group C: Moderate, 1.5 x ULN < bilirubin <= 3.0 x ULN and any AST

Group D: Severe, bilirubin > 3.0 x ULN and any AST

For all degrees of hepatic dysfunction the similarity bounds were outside the 90% confidence limits as see below for dose normalized AUC(INF):

Group (N)	Geometric Means (ng hr/mL)	Ratio	Ratio of Geometric Means		
			Point Estimate	Lower 90% CI	Upper 90% CI
A (17)	2155				
B (26)	2633	B/A	1.22	93	161
C (13)	2807	C/A	1.30	94	180
D (8)[a]	3901	D/A	1.81	124	264

a: all subjects in Group D receiving 10 mg/m^2 were excluded from these summary statistics

Note: AUC(INF) was dose-normalized to the 40-mg/m^2 dose level.

Group A: Normal, bilirubin <= ULN and AST <= ULN

Group B: Mild, ULN < bilirubin <= 1.5 x ULN and any AST or bilirubin <= ULN and AST > ULN

Group C: Moderate, 1.5 x ULN < bilirubin <= 3.0 x ULN and any AST

Group D: Severe, bilirubin > 3.0 x ULN and any AST

Safety Results: Twelve treated patients (16%) experienced AEs that met the criteria for DLTs:

- Group A (normal): DLTs were not evaluated for this group.
- Group B (mild): 2 of 12 patients at 30 mg/m^2 (2 of 11 patients meeting B1 criteria, 0 of 1 patients meeting B2 criteria) 3 of 13 patients at 40 mg/m^2 (2 of 10 patients meeting B1 criteria, 1 of 3 patients meeting B2 criteria)
- Group C (moderate): 2 of 11 patients at 20 mg/m^2; 2 of 3 patients at 30 mg/m^2
- Group D (severe): 2 of 9 patients at 10 mg/m^2; 1 of 7 patients at 20 mg/m^2

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_____ Draft Labeling

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Withheld Track Number: Clin Pharm/Bio-_____

4.3 PHARMACOMETRIC REVIEW

Pharmacometrics Review

NDA	22065
Submission Date(s)	04/16/2007
PDUFA Due Date	10/16/2007
Brand Name	Ixempra®
Generic Name	Ixabepilone
Dosage Form	Powder for Infusion
Dosage Regimen	Q 3 week
Pharmacometrics Reviewer	Rajanikanth Madabushi, Ph.D.
Pharmacometrics Team Leader	Yaning Wang, Ph.D.
Clinical Pharmacology Reviewer	Julie Bullock., Pharm.D.
Clinical Pharmacology Team Leader	Brian Booth, Ph.D.
Sponsor	BMS
Submission Type	NDA
Proposed indication	Breast Cancer

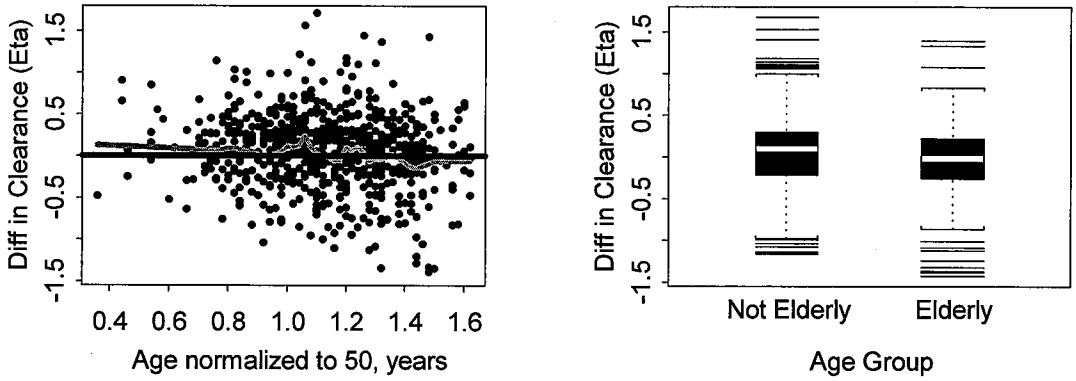
1 EXECUTIVE SUMMARY

The aim of the document is to review the sponsor's population pharmacokinetic analysis, pharmacodynamic analysis and exposure-response modeling which form the basis for labeling statements.

The key questions and findings of the present submission are:

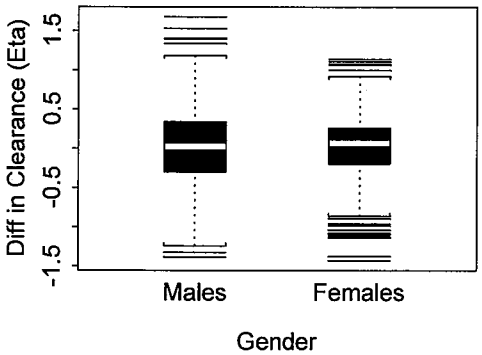
- Is there an effect of age on the pharmacokinetics of ixabepilone?
  Based on the results of the population pharmacokinetic analysis, age was not found to be a significant predictor of the clearance of ixabepilone. Age as a continuous covariate or categorical covariate (>65 years) did not account for the inter-individual variability of ixabepilone clearance (**Figure 1**).

  Figure 1: No effect of age on Ixabepilone clearance



- Are there any gender based differences in the pharmacokinetics of ixabepilone?
  Gender had no effect on the clearance of ixabepilone as shown in **Figure 2**

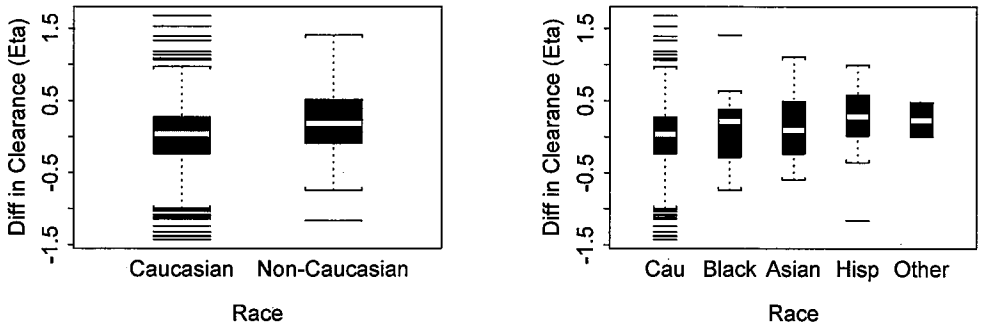
  Figure 2: No effect of gender on Ixabepilone clearance



- Are there any race based differences in the pharmacokinetics of ixabepilone?
  Based on the population pharmacokinetics, Non-Caucasians were found to have 14% faster clearance compared to Caucasians (**Figure 3**). However, this did not account for the inter-individual variability associated with the clearance of ixabepilone. Further, assessment of the influence of specific ethnicities by the reviewer revealed that the clearance of ixabepilone was

15% faster in Blacks and 9% faster in Asians. Lack of sufficient data precluded the assessment of the influence of Hispanic race on the pharmacokinetics of ixabepilone. On the whole, it can be concluded that the pharmacokinetics of ixabepilone is not different between Caucasians and Non-Caucasians.

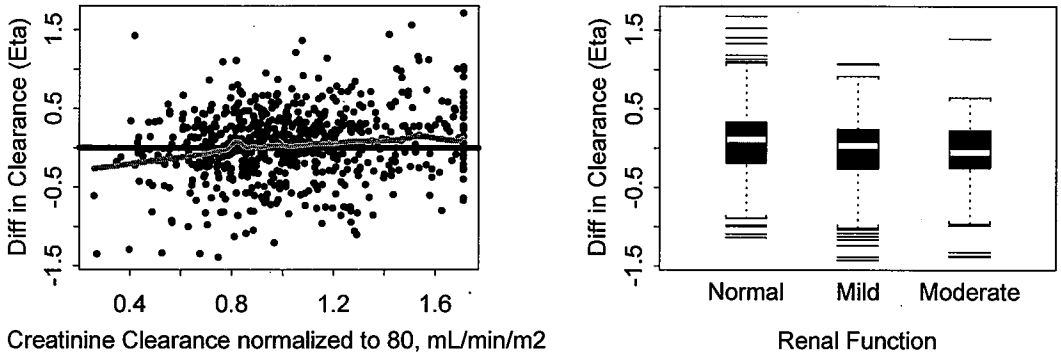
Figure 3: Clearance of ixabepilone is similar among Caucasians and Non-Caucasians



- Is the clearance of ixabepilone dependent on the renal function?

The population pharmacokinetic analysis revealed a trend for increasing clearance with increasing creatinine clearance as shown in **Figure 4**. However, the clearance among normal, mild renal impaired (50 – 80 mL/min) and moderate renal impaired (30 – 50 mL/min including 4 patients less than 30 mL/min) patients were similar.

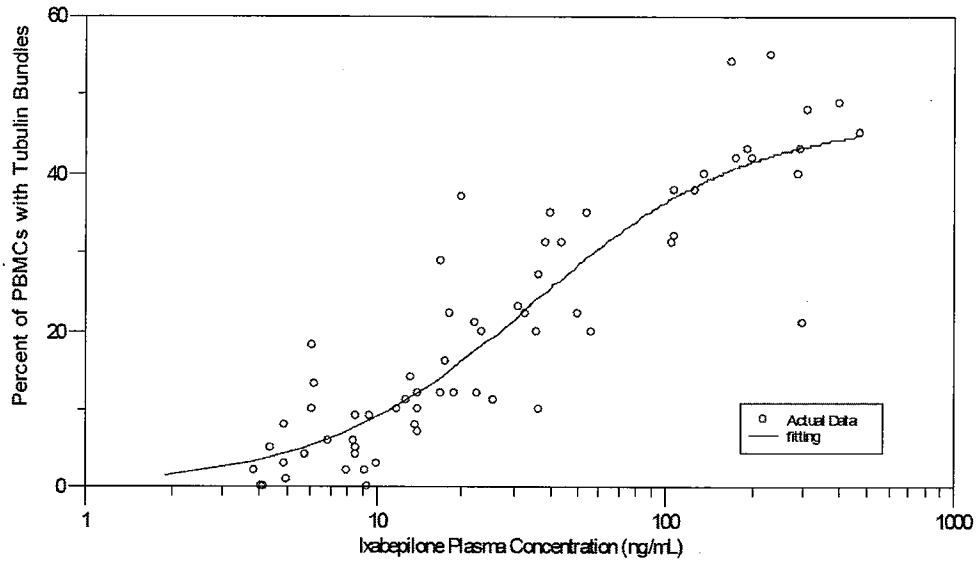
Figure 4: No clinically significant effect of creatinine clearance on Ixabepilone clearance



- Is the tubulin bundle formation dependent on plasma concentration of ixabepilone?

The formation of microtubule bundles caused by ixabepilone in PBMCs is a plasma concentration-dependent effect. As shown in the
Figure 5 .

Figure 5: The relationship of microtuble bundle formation to ixabepilone plasma concentration after ixabepilone alone



2 RECOMMENDATION

The labeling statements proposed by the sponsor describing the influence of age, gender, race, renal function impairment on the pharmacokinetics of ixabepilone and the exposure dependent formation of tubulin bundles under Pharmacodynamics are acceptable. Please see the **Labeling Statements** section for specific edits in the label.

Signatures:

Rajanikanth Madabushi, Ph.D.
Pharmacometrics Reviewer
Office of Clinical Pharmacology

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Office of Clinical Pharmacology

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2 Page(s) Withheld

_____ Trade Secret / Confidential

X Draft Labeling

_____ Deliberative Process

Withheld Track Number: Clin Pharm/Bio-_____

1 INTRODUCTION

Ixabepilone is a semi-synthetic derivative of natural product of epothilone B. Ixabepilone is a tubulin stabilizer that blocks cells in the mitotic phase of the cell division cycle and is a potent cytotoxic agent capable of killing cancer cells at low nanomolar concentrations.

Ixabepilone is indicated in combination with capecitabine for the treatment of patients with metastatic or locally advanced breat cancer after failure of cytotoxic chemotherapy. Ixabeplone is also indicated as monotherapy for the treatment of metastatic or locally advanced breast cancer in patients whose tumors are resistant or refractory to cytotoxic chemotherapy.

2 SPONSOR'S ANALYSIS

In the current submission, the sponsor submitted three technical reports:
1) A report that summarizes the population pharmacokinetic analysis of ixabepilone, and
2) A report that summarizes the pharmacodynamics of ixabepilone as seen by plasma concentration-dependent effect on the formation of microtubule bundles in the peripheral blood mononuclear cells (PBMCs).
3) A report that summarizes analyses conducted to investigate exposure-response relationships between ixabepilone exposure and toxicities that were commonly reported in studies with ixabepilone, neutropenia and neuropathy.

2.1 POPULATION PHARMACOKINETICS OF IXABEPILONE

2.1.1 Objectives

The objectives of this population pharmacokinetic analysis of concentration versus time data were:

- To characterize the pharmacokinetics of ixabepilone by developing a population pharmacokinetic model
- To assess the contribution of selected covariates on the variability of pharmacokinetic parameters in the target patient population

2.1.2 Data

Data from 12 clinical studies were used for the population pharmacokinetic database. From these studies, a total of 4,711 observations of plasma concentration-time data were used in the model building. Only 2 of these studies collected samples during more than one cycle. Of the total number of patients in the dataset, 21.6% had samples collected during Cycle 2 and 17.6% had samples collected during Cycle 3. All drug administration was via intravenous infusion, with nominal infusion times of 0.5, 1 or 3 hours. Sampling strategies were varied, with patients in Phase 1 studies subjected to more frequent sampling than patients in Phase 2 studies which had sparse sampling. The details of the studies with the sampling strategies are shown in **Table 23** below:

Table 23: Population Pharmacokinetic database.

Protocol	Patients Treated	Nominal PK Sampling Schedule
CA163001	61	Samples for PK evaluation of ixabepilone on 1-hr schedule were taken on cycles 1 and 2 at predose, 0.5, 1, 1.25, 1.5, 1.75, 2, 3, 4, 6, 8, 24, 48 and 72 hours Samples for PK evaluation of ixabepilone on 3-hr schedule were taken on cycle 1 at predose, 1.5, 3, 3.25, 3.5, 3.75, 4, 5, 6, 8, 24, 48 and 72 hours
CA163002	86	Samples for PK evaluation of ixabepilone on 30-min schedule were taken on cycle 1 at predose, 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 24, 48 and 72 hours Samples for PK evaluation of ixabepilone on 1-hr schedule were taken on cycle 1 at predose, 0.5, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 24, 48 and 72 hours
CA163009	66	Samples for PK evaluation of ixabepilone on 1-hr schedule were taken on cycle 1 at predose, 0.25, 1, 1.5, 3, range of 24-48, and range of 48-72 hours Samples for PK evaluation of ixabepilone on 3-hr schedule were taken on cycle 1 at predose, 1.5, 3, 4, 6, range of 24-48, and range of 48-72 hours
CA163010	93	Samples for PK evaluation of ixabepilone on 1-hr schedule were taken on cycle 1 at predose, 0.25, 1, 1.5, 3, range of 24-48, and range of 48-72 hours Samples for PK evaluation of ixabepilone on 3-hr schedule were taken on cycle 1 at predose, 1.5, 3, 4, 6, range of 24-48, and range of 48-72 hours
CA163011	195	Samples for PK evaluation of ixabepilone on 1-hr Q3wks schedule were taken on cycle 1 at predose, 0.25, 1, 1.5, 3, range of 24-48, and range of 48-72 hours Samples for PK evaluation of ixabepilone on 3-hr Q3wks schedule were taken on cycle 1 at predose, 1.5, 3, 4, 6, range of 24-48, and range of 48-72 hours Samples for PK evaluation of ixabepilone on 1-hr daily x 5 Q3wks schedule were taken on day 5 of cycle 1 at predose, 0.25, 1, 3, and range of 6-12 hours
CA163012	51	Samples for PK evaluation of ixabepilone on 1-hr Q3wks schedule were taken on cycle 1 at predose, 0.25, 1, 1.5, 3, range of 24-48, and range of 48-72 hours Samples for PK evaluation of ixabepilone on 1-hr daily x 5 Q3wks schedule were taken on day 5 of cycle 1 at predose, 0.25, 1, 3, and range of 6-12 hours
CA163013	21	Samples for PK evaluation of ixabepilone on 1-hr Q3wks schedule were taken on cycle 1 at predose, 0.25, 1, 1.5, 3, range of 24-48, and range of 48-72 hours
CA163014	47	Samples for PK evaluation of ixabepilone on 1-hr Q3wks schedule were taken on cycle 1 at predose, 0.25, 1, 1.5, 3, range of 24-48, and range of 48-72 hours Samples for PK evaluation of ixabepilone on 1-hr daily x 5 Q3wks schedule were taken on day 5 of cycle 1 at predose, 0.25, 1, 3, and range of 6-12 hours
CA163015	22	Samples for PK evaluation of ixabepilone on 1-hr Q3wks schedule were taken on cycle 1 at predose, 0.25, 1, 1.5, 3, range of 24-48, and range of 48-72 hours
CA163036	38	Samples for PK evaluation of ixabepilone on 1-hr daily x 5 Q3wks schedule were taken on day 5 of cycle 1 at predose, 0.25, 1, 3, and range of 6-12 hours
CA163051	30	Samples for PK evaluation of ixabepilone on 1-hr daily x 5 Q3wks schedule were taken on day 5 of cycle 1 at predose, 0.25, 1, 3, and range of 6-12 hours
CA163080	161	Samples for PK evaluation of ixabepilone were taken on cycles 1 and 3 at 6 and 24 hours

A total of 106 records were removed from the data set prior to any analysis. Reasons for the removal of plasma concentration observations included: concentration below the lower limit of quantification (BLLQ, 103), concentration above the upper limit of quantification (AULQ, 2), and repeat time record (1).

The final dataset used for population pharmacokinetic model building and covariate identification, included 4605 observations from 674 patients. Data from 2 of the original 676 patients were removed from the original data set, each contributing one measurement of concentration. One patient was removed because of BLLQ and the second because no dose was recorded. During preliminary model building, an additional 65 observations were removed because they had high weighted residuals (absolute value of weighted residuals greater than 8) or were flagged by BMS as having questionable bioanalytical results. Therefore, the dataset that was carried forward for additional model building and evaluation consisted of 4,540 observations from a total of 674 patients (96.4% of the original observations and 99.7% of the original number of patients).

2.1.3 Analysis Methods

Plasma concentration-time data (including data from the studies in Table 2) was analyzed using mixed effects modeling methods as implemented by the computer program NONMEM (version 5., level 1.1). A series of structural models were evaluated in the present analysis, including linear one-and two-compartment models with zero-order infusion and first-order elimination from the central compartment.

Several models were investigated to account for random residual variability (RRV). RRV was described using a combined additive and constant coefficient of variation (CCV) model.
Inter-individual variance (IIV) was described using an exponential model. The off-diagonal elements of the variance-covariance matrix (rendered as BLOCK statements in NONMEM code), which describe correlations between parameters, were also tested.

All covariates assessed were added individually onto the parameters of the base model. Within a pair of nested models, the likelihood ratio test was used to determine the most appropriate model, with a reduction in the objective function of at least 7.88 points (p=0.005) required for a covariate to be significant. All single covariates found to be significant were combined into a full model. When backwards elimination was conducted on the full model, an increase in the objective function of 10.8 points (p = 0.001) due to the removal of a covariate was needed before the covariate was judged to be significant.

The covariate models that were tested were evaluated using a power function for continuous covariates. Continuous covariates were normalized to their approximate median or mean values for numerical stability.
For categorical covariates (eg, gender), the models were parameterized such that the covariate factor assumed a value reflecting the percent change of the parameter.

Qualification of the final model was performed by the following methods: Parameter Stability Testing by computing the condition number, Limited Predictive Check, Bootstrap evaluation of the confidence intervals of the parameter estimates, Permutation test of the covariates on final model, and calculation of the Bayesian Parameter Shrinkage.

2.2 PHARMACODYNAMICS OF IXABEPILONE

2.2.1 Objectives

The objective of the analysis was to measure the change in the extent of microtubule bundle and mitotic aster formation in peripheral blood mononuclear cells (PBMC) and tumor cells following ixabepilone treatment

2.2.2 Data

This was an open-label sequential study primarily designed to assess the effect of ketoconazole on the pharmacokinetics of ixabepilone in patients with advanced cancer.

Cycle 1 used a dose-escalation scheme of ixabepilone co-administered with a fixed dose of ketoconazole to evaluate the safety of the combination. During Cycle 1, subjects received a 3-hour intravenous (IV) infusion of ixabepilone on Day 1 at a starting dose of 10 mg/m2 and were also administered daily doses of 400 mg ketoconazole orally with a meal on Day -1 (24 hours before the infusion of ixabepilone), on Day 1 (2 hours prior to the infusion of ixabepilone) and on Days 2 to 5. The dose of ixabepilone in Cycle 1 was to be increased to 20, 30 and 40 mg/m2 for subsequent cohorts of subjects based on safety evaluations. During Cycle 2, subjects received a 3-hour IV infusion of 40 mg/m2 of ixabepilone on Day 1.

Blood samples for plasma ixabepilone PK were collected up to 120 hours post dose in Cycles 1 and 2. The sampling scheme for the PK and the PBMCs are shown in **Table 24** below:

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Table 24: Sampling scheme for pharmacokinetics and PBMCs for pharmacodynamics

Time Relative To Dosing (hour:minute)	Blood Sample for Plasma PK[a]	Blood Sample for PBMCs Pharmacodynamics[b]
pre-dose	X	X
1:30	X	
just prior to end of infusion[b]	X	X
3:15	X	
3:30	X	
4:00	X	
6:00	X	X
8:00	X	
24:00	X	X
48:00	X	X
72:00	X	
96:00	X	
120:00	X	

[a] For Cycle 1 and Cycle 2

[b] This sample was taken just prior to the end of the infusion even if the infusion lasted for less than or more than the planned 3 hours

2.2.3 Analysis methods

At least 500 cells/slide were counted and the number of cells exhibiting tubulin bundle formation was expressed as a percentage of the total number of cells counted. Tabulations of the extent of microtubule bundle formation in PBMC were provided. Scatter plots versus dose were examined for relationship to dose. Scatter plots versus AUC and Cmax were examined for relationships to drug level in plasma. The PKPD analyses of the formation of tubulin bundles versus concentration data were performed by the Kinetica Version 4.2 application (InnaPhase Corporation, Philadelphia, PA).

2.3 EXPOSURE-RESPONSE ANALYSIS

2.3.1 Objectives

The objectives of the exposure-response analyses were:

- To characterize the relationship between ixabepilone exposure and
  - Neutropenia
  - Neuropathy
- To project the effect of alternative ixabepilone doses on neutropenia and neuropathy using computer simulations.

2.3.2 Data

The data for the neutropenia and neuropathy analysis datasets were assembled from 2 sources: clinical data from CA163009 and CA163010 and pharmacokinetic and exposure data derived from the ixabepilone population pharmacokinetic analyses (PPK). The details of the studies CA163009 and

CA163010 can be found in **Table 23**. The endpoint used for neutropenia response was absolute neutrophil count (ANC) versus time, and the endpoint used for neuropathy response was time to the first incidence of a severe neuropathy event (Grade 3 or 4 according to Common Toxicity Criteria, CTC, version 2.0). Only subjects in the aforementioned studies for whom pharmacokinetic parameter estimates were available from the PPK analysis were included in the analysis datasets. *The neutropenia dataset contained all ANC observations from Course 1 prior to the administration of growth factor therapy.*

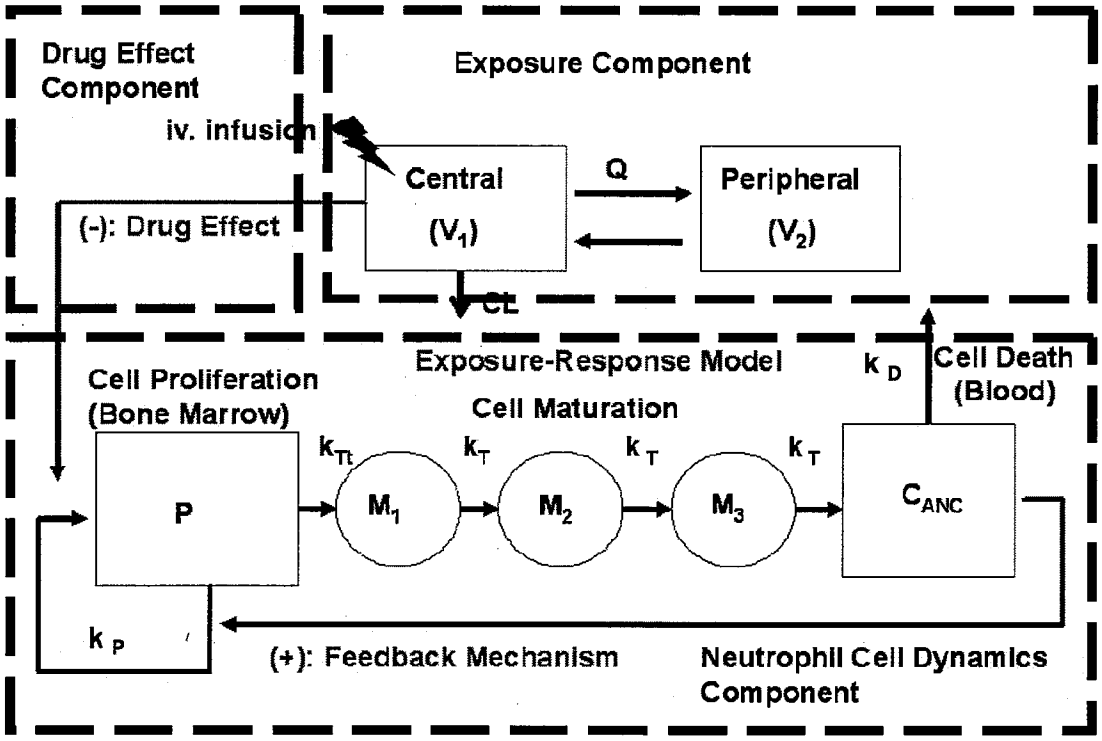
2.3.3 Analysis Methods

2.3.3.1 Exposure-Response relationship for Neutropenia

Neutropenia was characterized by describing the ANC time-profile following the first administration of ixabepilone. A three-step modeling and simulation approach was applied:
(1) Model development to characterize the relationship between individual exposure and ANC observations,
(2) Model evaluation, and
(3) model-based simulation to explore the effect of alternative ixabepilone doses of interest on neutropenia.

ANC versus time data for each subject in the neutropenia dataset were described by a semi-mechanistic nonlinear mixed effects ("population") model that accounts for the dynamics of neutrophil production, maturation and death, including regulation of production by feedback that is a function of ANC count in the peripheral circulation. A schematic representation of the model is presented in **Figure 6**.

Figure 6: Schematic of the semi-mechanistic exposure-response model for neutropenia



Drug effect was specified as an inhibitory effect of plasma ixabepilone on the production of neutrophil progenitors. Linear and hyperbolic relationships for the inhibitory effect were examined. The ixabepilone plasma concentration-time profile was specified by individual pharmacokinetic parameter estimates determined by the population pharmacokinetic analysis. The model was parameterized in terms of the following physiologically-meaningful quantities: the mean transit time (MTT), baseline ANC ($C_{N,0}$), a feedback parameter (γ), maximal inhibitory effect of drug (E_{max}), and the ixabepilone plasma concentration at which the inhibitory effect is half-maximal (EC_{50}). MTT represents the average time it takes neutrophils to mature (starting with the time at which neutrophil progenitors are formed, to the time of appearance in the peripheral circulation), and γ represents the feedback effect of peripheral ANC value perturbations on the production of neutrophil progenitors.

The described semi-mechanistic structural model for neutropenia has the following features:

- At steady-state, the rate of production and maturation of neutrophil progenitors equals the death rate of neutrophils in the peripheral circulation
- A reduction in the concentration of peripheral neutrophils below the baseline concentration stimulates the production of neutrophil progenitors; and conversely, an increase above the baseline concentration inhibits the production of neutrophil progenitors
- Plasma concentration of drug has a direct inhibitory effect on the rate at which neutrophil progenitors in the bone marrow are produced
- The time-lag between peak drug plasma concentration and nadir ANC observations is due to the time taken by neutrophil progenitors to form fully-differentiated neutrophils

Individual values of structural model parameters that were constrained to positive values were assumed to follow a lognormal distribution, while those that were not constrained to zero were assumed

to follow a normal distribution.
The effect of the following subject-specific covariates on model parameters was evaluated: baseline ANC value, age, ECOG performance status, and study (representing immediately prior treatment with taxane or anthracycline).

The final model was evaluated by quantitative predictive checks on the following endpoints: nadir ANC, time-to-nadir, and the ANC at the end of the dosing interval (recovery ANC). A predictive check was also performed on the proportion of subjects at each CTC-defined neutropenia grade at nadir. A predictive check for the nadir ANC and the proportion of subjects at each CTC-defined neutropenia grade at nadir for treatment course 1 and for all the courses were also performed.

Finally, model-based simulation was performed to assess the effect of 30, 40, and 50 mg/m2 ixabepilone, administered intravenously over 3 hours, on ANC and the occurrence of neutropenia.

2.3.3.2 Exposure response analysis for Neuropathy

Data from CA163009 and CA163010 showed that a total of 26 subjects reported at least one event of severe neuropathy (Grade 3 or 4) during the study. The available neuropathy data were not sufficient to develop a parametric model. The relationship between the exposure and time to the first incidence of severe neuropathy was characterized by fitting Cox proportional hazards models. The exposure-response relationship was evaluated with 2 summary measures of ixabepilone exposure, Cmax and AUC, which varied with dosing course. These measures of exposure facilitated the application of the Cox-proportional hazards model, as they are constant within a given course. In addition to exposure, the effect of the following factors on the occurrence of severe neuropathy was also examined: dose, age, prior diabetes, prior taxane therapy, prior neurotoxic chemotherapy, and baseline neuropathy. Other than dose, all of these factors were invariant across dosing courses.

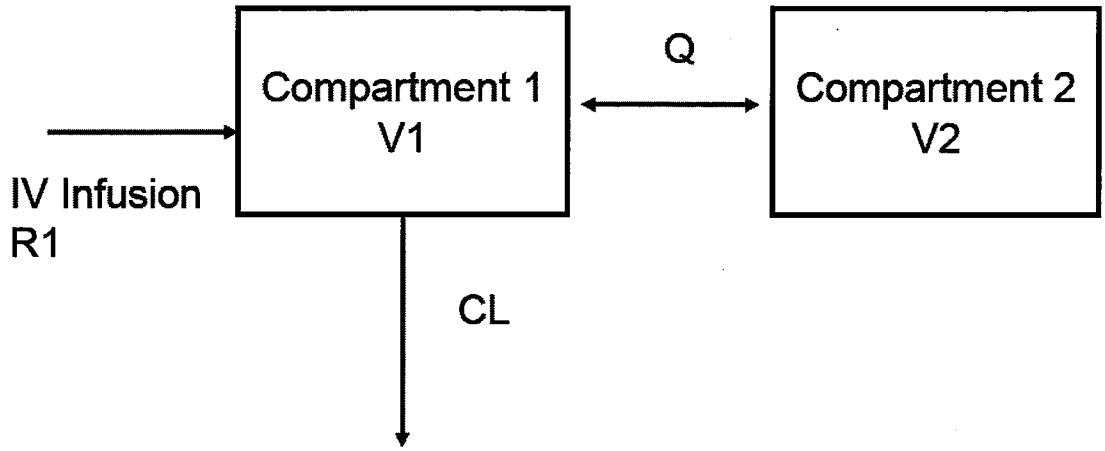
3 RESULTS (SPONSOR'S ANALYSIS)

3.1 POPULATION PHARMACOKINETICS

3.1.1 Base model

The best structural model was a 2-compartment model with zero-order infusion and linear clearance. This model was parameterized in terms of clearance (CL), the volume of distribution of the central (V1) and peripheral (V2) compartments, and inter-compartmental clearance (Q) as shown in **Figure 7**. The residual error model was a constant coefficient of variation (CCV) model. Inter-individual variability was described for CL, V1, V2 and Q, with a full omega block estimating the covariance between inter-individual random effects. The first order conditional estimation (FOCE) method with Interaction was employed with the SLOW option in NONMEM.

Figure 7: General schematic of the best structural model



The diagnostic plots indicate that the base model provides a good fit of the observed data as shown in **Figure 8**.

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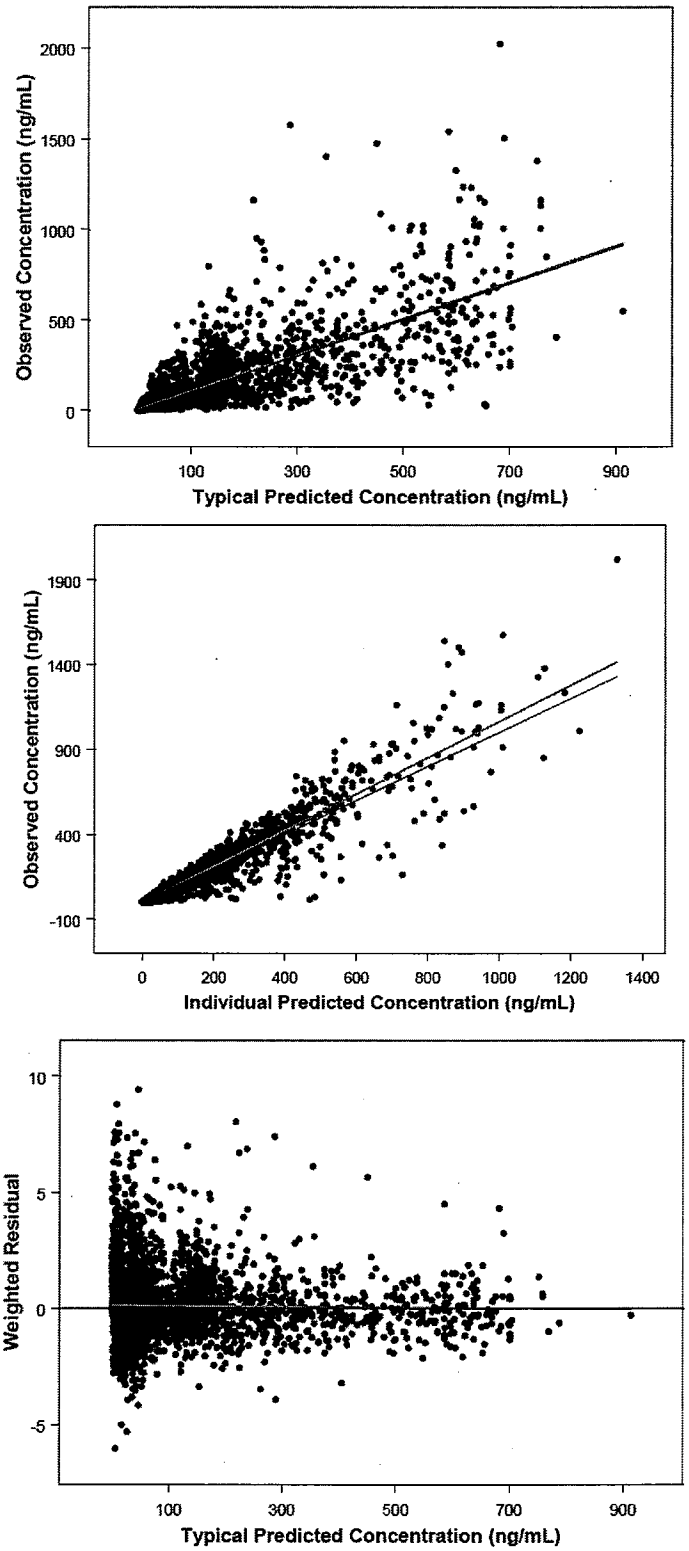
Figure 8: Basic goodness of fit diagnostic plots for the best base pharmacokinetic model



Additionally, the plot of the weighted residuals versus time does not indicate substantial misspecification. The parameter estimates for the best base model are shown in **Table 25**. The structural

parameters estimated for this best base model were estimated with acceptable precision, with SE of less than 10% for each parameter. There was a moderate degree of inter-individual variability (IIV) associated with the structural parameters. Residual variance (RRV) was moderate, and the precision on the proportional component was small.

Table 25: Parameter estimates for the base model.

Parameter (Units)	Population Mean (SE*)		%CV Inter-Individual Variance (SE*)	
CL (L/h)	θ_1	37.7 (2.12)	η_1	49.3 (7.24)
V1 (L)	θ_2	44.0 (3.43)	η_2	48.7 (17.5)
V2 (L)	θ_3	913 (2.71)	η_3	58.7 (7.33)
Q (L/h)	θ_4	122 (3.11)	η_4	63.7 (9.48)
CCV Residual Error (as %CV)			30.8 (4.30)	

* SE expressed as %CV

3.1.2 Covariate assessment

Initial covariate screening revealed age, ideal bodyweight, gender and study population on clearance of ixabepilone and ideal bodyweight and study population on the peripheral volume of distribution of ixabepilone. These covariates were included in the base model to form the full model. Backward elimination evaluation of the full model resulted in the study population being selected as the only covariate on clearance and peripheral volume of distribution. CA163080 enrolled chemotherapy-naive patients undergoing neoadjuvant treatment (eg, chemotherapy given prior to the primary therapy, usually surgery) for breast cancer without metastasis. These patients had, on average, 25% higher clearance and 16% smaller peripheral volume of distribution than patients with metastatic cancer enrolled in all other studies contributing data to this analysis. The final parameter estimates of the population pharmacokinetic analysis are shown in

Table 26.

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Table 26: Parameter estimates of the final pharmacokinetic model

Parameter (Units)		Population Mean (SE*)	%CV Inter-Individual Variance (SE*)
CL (L/h)	θ_1	36.8 (2.16)	48.8 (5.59)
Effect of STUDY	θ_5	1.25 (6.71)	
V1 (L)	θ_2	43.8 (2.95)	49.1 (9.54)
V2 (L)	θ_3	945 (2.84)	59.3 (7.16)
Effect of STUDY	θ_6	0.841 (5.48)	
Q (L/h)	θ_4	122 (3.08)	64.1 (6.86)
CCV Residual Error (as %CV)		30.6 (1.99)	

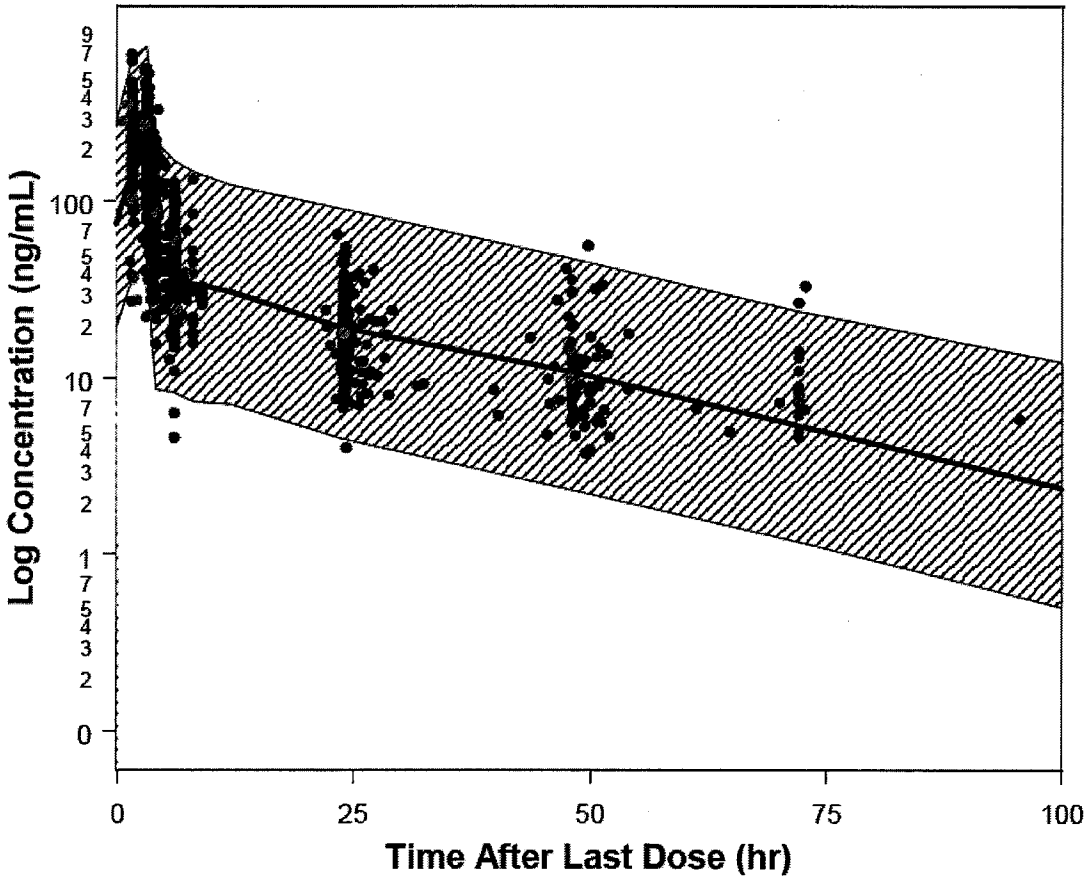
*SE given as %CV (coefficient of variability)

CL = clearance, V1 = volume of distribution of the central, V2 = volume of distribution of peripheral (V2) compartments, Q = inter-compartmental clearance, CCV = coefficient of variation model

3.1.3 Model evaluation

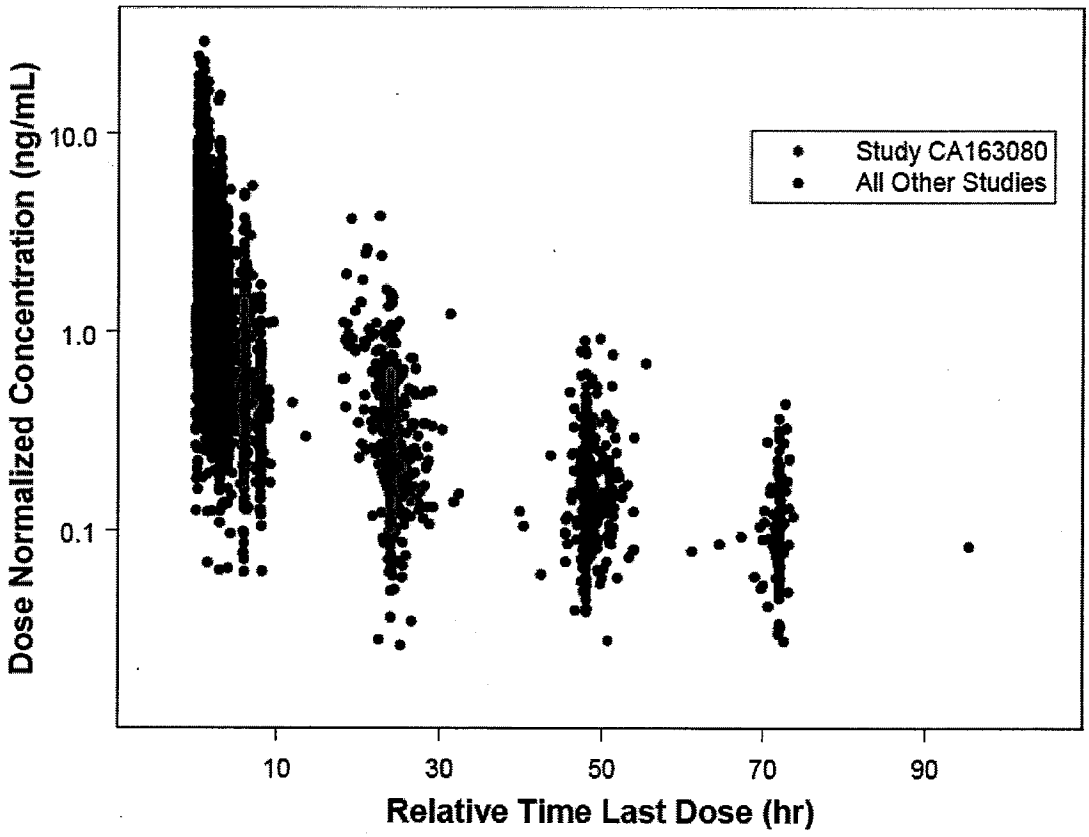
Based on a visual examination of the 90% confidence intervals of simulation from the final pharmacokinetic model revealed that the model appears to perform adequately. A representative figure of the predictive check for the 40 mg/m^2 infused over 3 hrs is shown below:

Figure 9: Observed ixabepilone concentration and 90% prediction intervals for limited predictive check for 40 mg/m^2 administered over 3 hours.



The 95% confidence intervals generated from the nonparameteric bootstrap of the final model revealed that the confidence intervals were acceptably narrow. Additionally, confidence intervals for patient type (i.e., STUDY covariate in model) on both CL and V2 do not enclose unity, suggesting that these covariate factors are well defined. The permutation test performed on the patient type supported the inclusion of the patient type on clearance and peripheral volume of distribution. However, taking into account the effect of patient type on clearance and peripheral volume of distribution the overall impact on exposure is minimal and is not of clinical significance as can be seen in the **Figure 10**.

Figure 10: Dose-normalized ixabepilone concentration for all studies contributing data



Shrinkage of parameter estimates in both base and final models indicate that individual parameter estimates were robust with minimal shrinkage towards the mean.

3.1.4 Effect of covariates

No trends between clearance of ixabepilone and increasing age, ideal bodyweight, height, dose, gender, race, AST, ALT and total bilirubin were observed. There was a trend for increasing clearance with increasing bodyweight, body surface area and creatinine clearance. However, the relationship was shallow and was not expected to have any significant clinical impact.

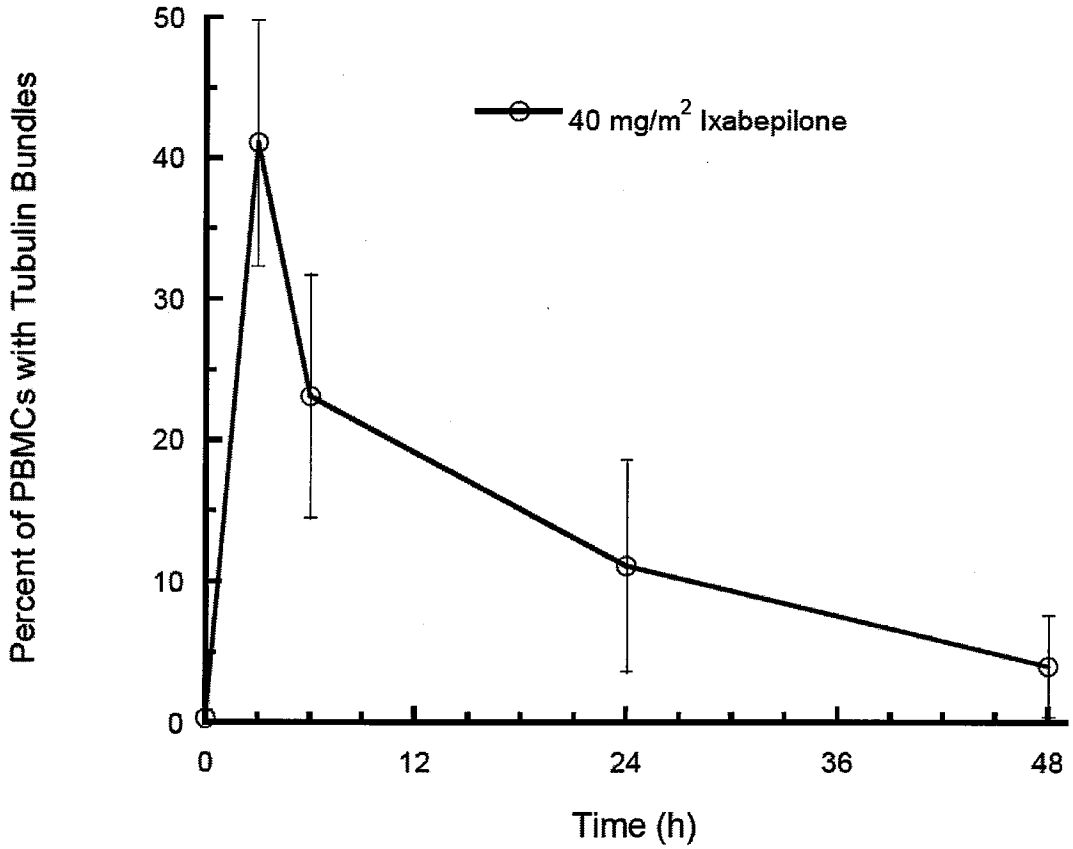
3.1.5 Conclusion

- The pharmacokinetics of ixabepilone in cancer patients were well described by a two-compartment, open model with zero-order infusion and first-order elimination from the central compartment.
- The structural parameters estimated during this evaluation were in good agreement with parameters estimated with non-compartmental approaches. Given the data, no clinically relevant covariate effects on ixabepilone pharmacokinetics in cancer patients were identified.

3.2 PHARMACODYNAMICS

For Cycle 1 (ixabepilone with ketoconazole) and Cycle 2 (ixabepilone alone), the percent of PBMCs with tubulin bundles was greatest just prior to the end of infusion at 3 hours, remained above baseline at 6 and 24 hours and returned to nearly baseline at 48 hours. The plot of microtubule bundle formation in PBMCs versus time after ixabepilone alone is shown in **Figure 11**. Similar results were obtained in PBMCs when ixabepilone was administered as 1 hour infusion. The formation of microtubules was greatest just prior to the end of the infusion.

Figure 11: Mean (SD) microtubule formation in PBMCs versus time after ixabepilone alone



The maximum percent of PBMCs with tubulin bundles increased with increasing dose of ixabepilone combined with ketoconazole in Cycle 1. Further, the relationship of tubulin bundle formation to plasma ixabepilone concentration after ixabepilone alone was well described by the Hill Equation. The plot of the relationship of tubulin bundle formation to plasma ixabepilone concentration is shown in **Figure 12**. The fitted parameter values for the model are presented in the **Table 27**.

Figure 12: The relationship of microtuble bundle formation to ixabepilone plasma concentration after ixabepilone alone

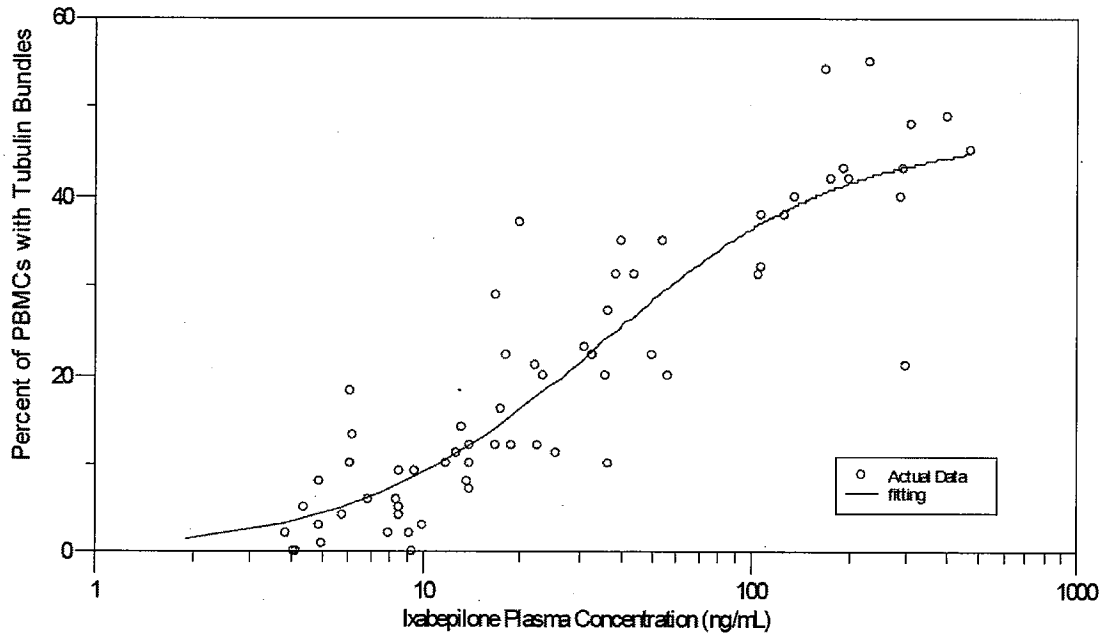


Table 27: Parameter estimates for the pharmacodynamic model

Parameter	Estimate	Standard Error	Relative Standard Error (%)
Emax (%)	46.9	3.58	7.63
EC_{50} (ng/mL)	34.9	7.07	20.26
Sigmoidicity factor	1.16	0.18	15.19

3.2.1 Conclusion

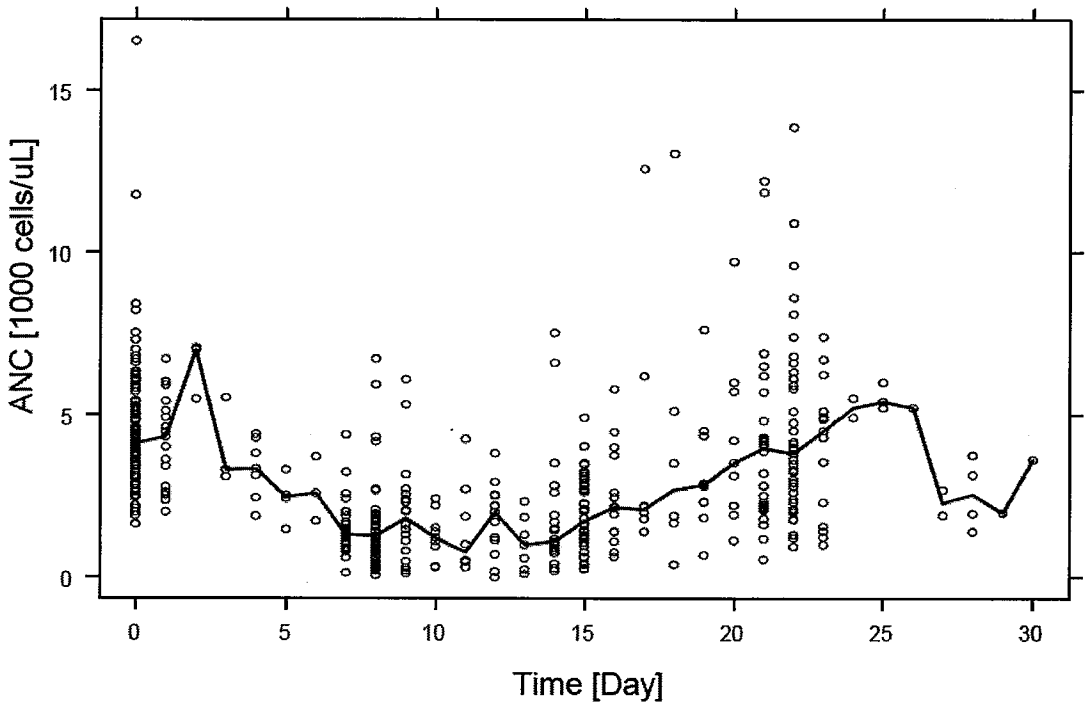
The formation of microtubule bundles caused by ixabepilone in PBMCs is a plasma concentration-dependent effect.

3.3 EXPOSURE-RESPONSE ANALYSES

3.3.1.1 Neutropenia

A total of 511 ANC observations from 114 subjects were available in the neutropenia dataset. The time course of ANCs can be seen in the **Figure 13**.

Figure 13: Time course of ANC for Course 1



The structural component of the base model was specified by the semi-mechanistic model described under analysis methods. A linear drug-effect model was assumed and various residual error models were explored. A log-normal error model was found to be superior among the tested models with an even distribution of the weighted residuals around zero as shown in **Figure 14**.

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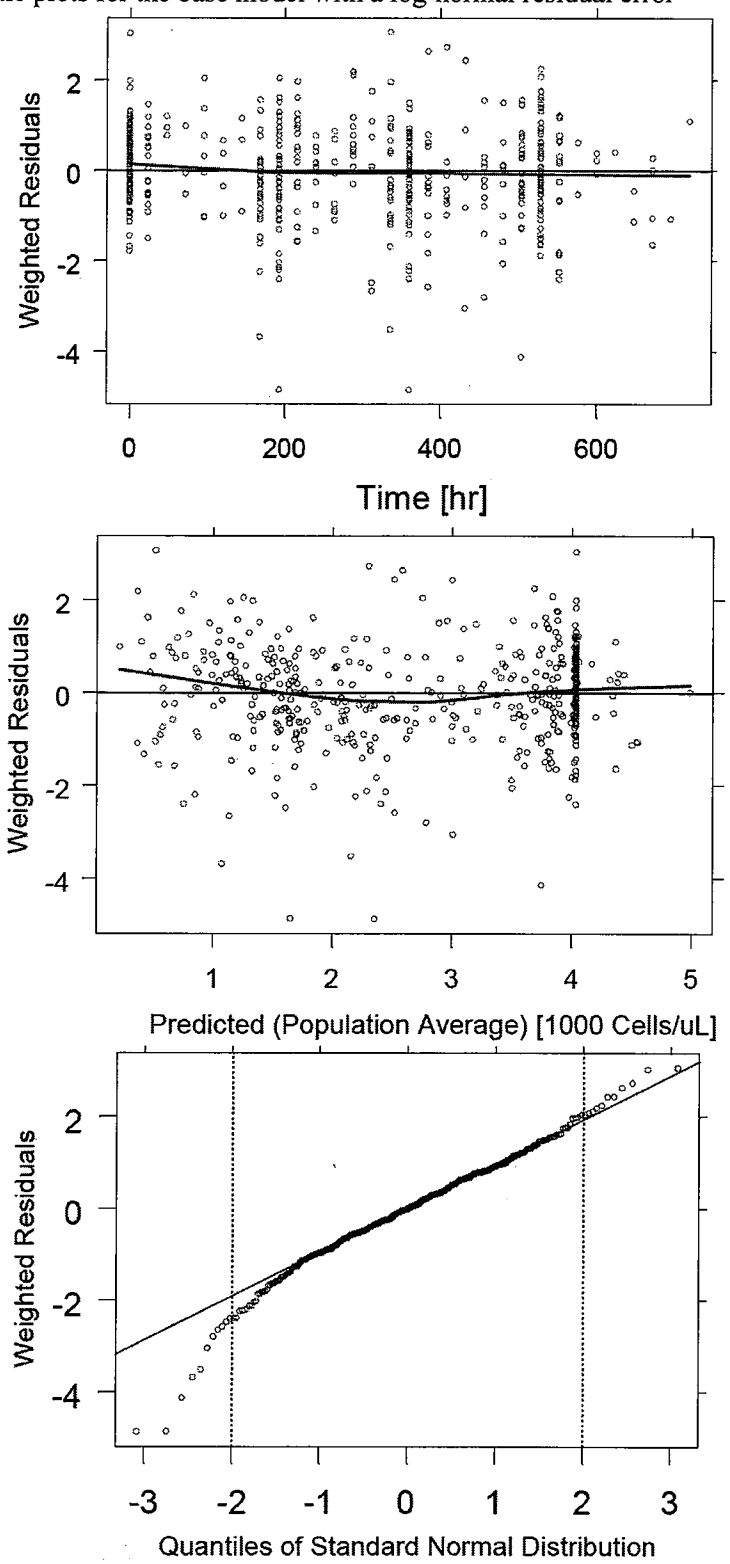
Figure 14: Diagnostic plots for the base model with a log-normal residual error

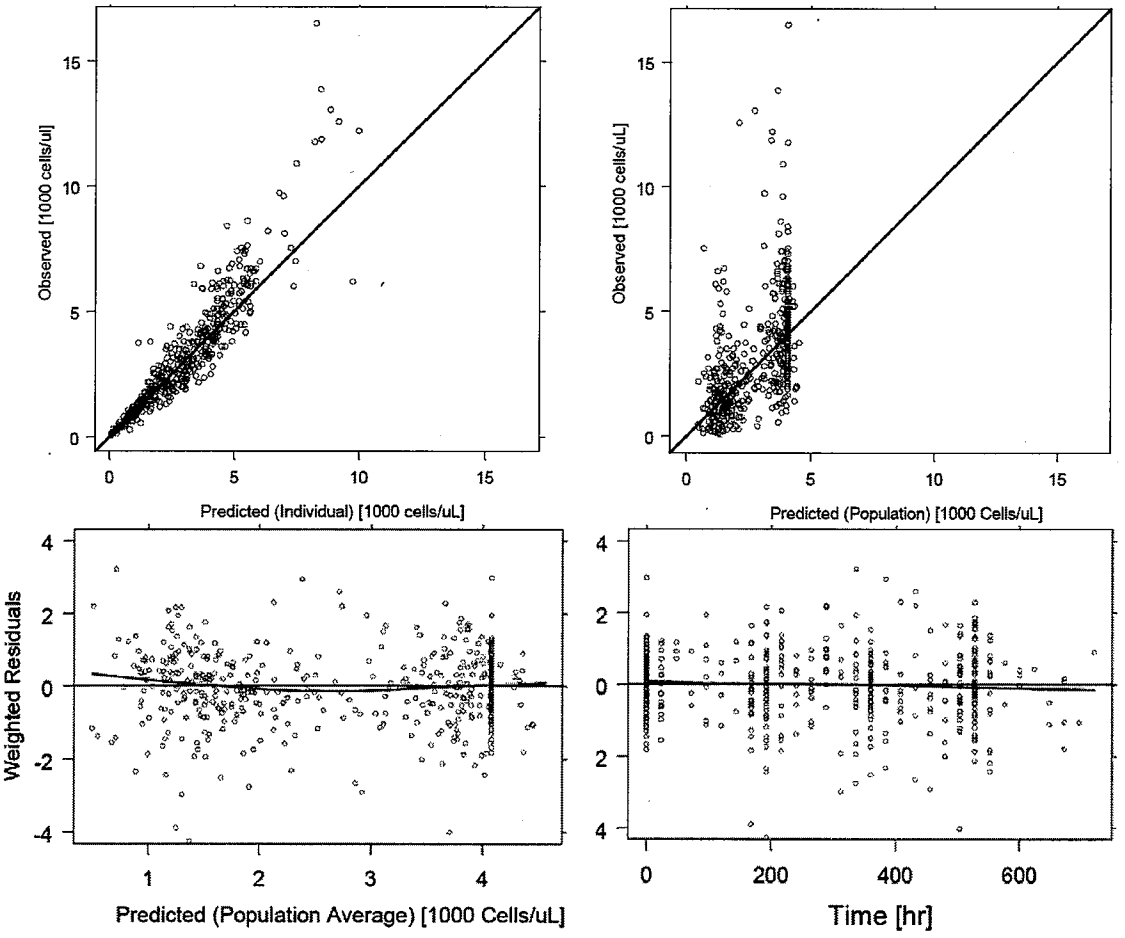


A hyperbolic drug effect model as an alternative to the linear model was explored and found to describe the data better. The hyperbolic drug effect model had comparatively lower objective function

value. This model also allows for the maximum effect to plateau. Hence the hyperbolic drug effect model along with log-normal residual error model was carried forward during the model building process. The maximum inhibitory effect (E_{max}) was fixed to 1 (100% inhibition) and the inter-individual variability for all the parameters in the model except for the E_{max} was assumed to follow a log-normal distribution. This model was considered to be the final base model.

Evaluation of the basic diagnostic plots (**Figure 15**) supports the validity of the model to describe the variability of ANC values in patients with breast cancer. The observed data are randomly and uniformly scattered about the line of unity in both the observed versus typical predicted and individual predicted concentration plots. The weighted residual versus time (after dose) diagnostic plot (**Figure 15**) indicates that the final base model provides an unbiased description of the ANC profile up to approximately 3 weeks post-dose and can be used to describe the entire time process of ANC decrease and recovery.

Figure 15: Diagnostic plots for the final base PK-PD model



The parameter estimates for the final base model are shown in the **Table 28** below.

Table 28: Parameter estimates for the final base model.

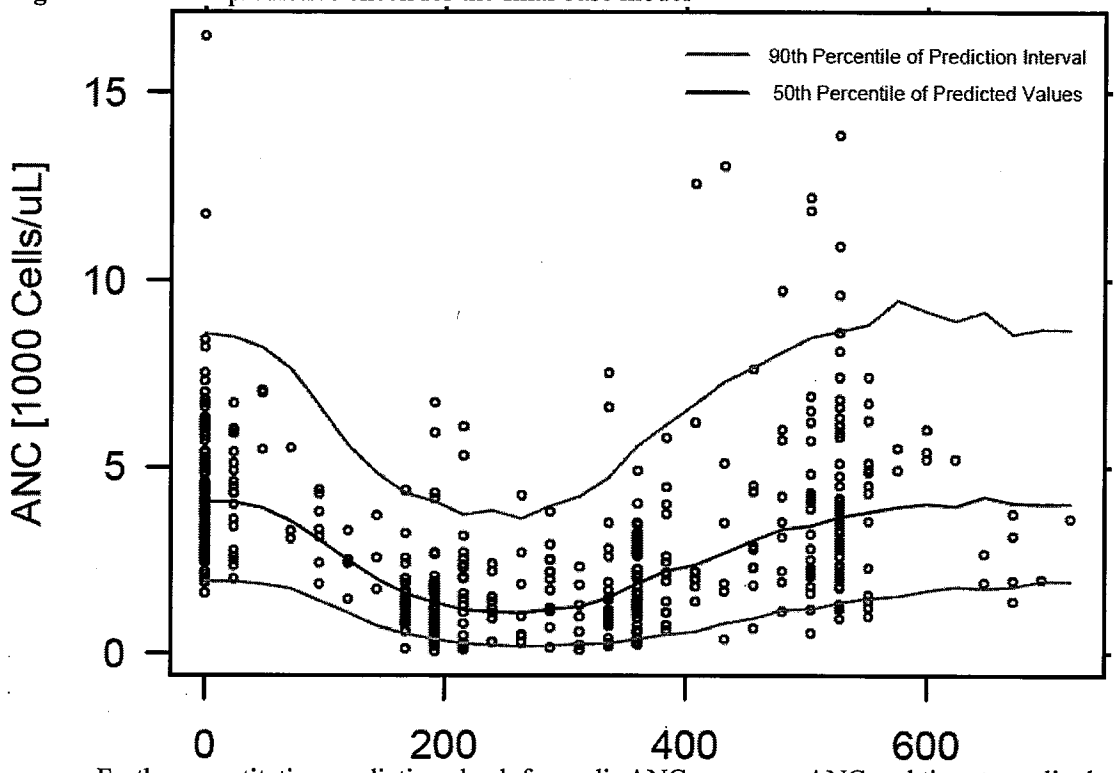
Parameter [Units]		Estimate[a]	Std. Error (SE%)	95% Conf. Interval
Fixed Effects				
MTT [hr]	θ_1	105	3.78 (3.60)	97.6 - 112
E_{max}[-][b]	θ_2	1.00		
γ [-]	θ_3	0.132	0.0102 (7.73)	0.112 - 0.152
$C_{N,0}$ [1000/μL]	θ_4	4.08	0.154 (3.77)	3.78 - 4.38
EC_{50} [μg/mL]	θ_5	0.0141	0.00222 (15.7)	0.00975 - 0.0185
Interindividual Random Effects				
MTT	$\omega_{1,1}$	0.0197 (0.140)	0.00616 (31.3)	0.00763 - 0.0318
γ	$\omega_{3,3}$	0.0682 (0.261)	0.0312 (45.7)	0.00705 - 0.129
$C_{N,0}$	$\omega_{4,4}$	0.0989 (0.314)	0.0224 (22.6)	0.0550 - 0.143
EC_{50}	$\omega_{5,5}$	1.38 (1.17)	0.318 (23.0)	0.757 - 2.00
Parameter [Units]		**Estimate[a]**	**Std. Error (SE%)**	**95% Conf. Interval**
Residual Error Random Effects				
ERR [-]	$\sigma 1,1$	0.104 (0.322)	0.0177 (17.0)	0.0693 - 0.139

The estimated average baseline ANC value is approximately 4000 cell/μL, similar to that observed in healthy subjects. MTT is a parameter that represents the average time needed for the formation of a mature neutrophil. The average MTT value for ixabepilone patients is about 100 hours, shorter than the value for healthy subjects (~ 158 hours, 6.6 days). This may be related to the myelosuppression from long-term exposure to chemotherapy drugs. Myelosuppression enhances the release of growth factor to increase the progenitor cell division and shorten the cell maturation process.

3.3.2 Model evaluation

A visual predictive check showed that most of the observed ANC values were contained within the 90% prediction interval as shown in the **Figure 16** below for Course 1.

Figure 16: Visual predictive check for the final base model



Further quantitative predictive check for nadir ANC, recovery ANC and time-to-nadir showed that the model was able to accurately predict the distributions of ANC values. Similar results were obtained for the proportion of subjects with neutropenia for each grade. The predicted fractions were within 5% of all the observed proportions for each of the neutropenia grades. The model was seen to generally predict a greater fraction of subjects with Grade 4 neutropenia than observed, however, the difference was found to be within 5%.

3.3.3 Covariate assessment

Covariate screening indicated that no covariate had a statistically significant effect on neutrophil parameters. Therefore, the final base model was considered as the final covariate model.

3.3.4 Model-based simulation

The proportion of subjects in each of the in each of the neutropenia grade levels were calculated following 500 simulations using the final model. The results are summarized in the **Table 29** below.

The proportion of the Grade 3 and 4 neutropenia increased as the dose level increased from 20 to 50 mg/m^2. Model-based simulation of alternative doses of interest indicate that approximately 7.0% fewer and 4.4% greater incidence of Grade 3 and 4 neutropenia are expected for 3-hr infusion with doses of 30 and 50 mg/m2, respectively, relative to a 3-hr infusion dose of 40 mg/m^2. The incidence of Grade 3 or 4 neutropenia increases to 38% and 42% from 31% of subjects, as the dose level is increased to 40 and 50 mg/m2, respectively, from 30 mg/m2. The simulations suggest that the risk of neutropenia does not change dramatically for the above dosing regimens.

Table 29: Summary of the simulation of probability of neutropenia for Ixabepilone dosing regimen for Course 1

CTC Grade	Simulated Dosing Regimens[a]		
	30 mg/m^2 50th (5th - 95th Percentile)	40 mg/m^2 50th (5th - 95th Percentile)	50 mg/m^2 50th (5th - 95th Percentile)
0 (Normal)	32.5 (26.3 - 39.5)	28.1 (21.9 - 34.2)	24.6 (19.3 - 30.7)
1	15.8 (10.5 - 21.9)	14.0 (8.8 - 19.3)	13.2 (7.9 - 18.4)
2	20.2 (14.0 - 26.3)	20.2 (14.0 - 26.3)	20.2 (14.0 - 26.3)
3	21.1 (14.9 - 27.2)	23.7 (16.7 - 29.9)	25.4 (18.4 - 31.6)
4	9.6 (6.1 - 14.9)	14.0 (8.8 - 19.3)	16.7 (11.4 - 22.8)

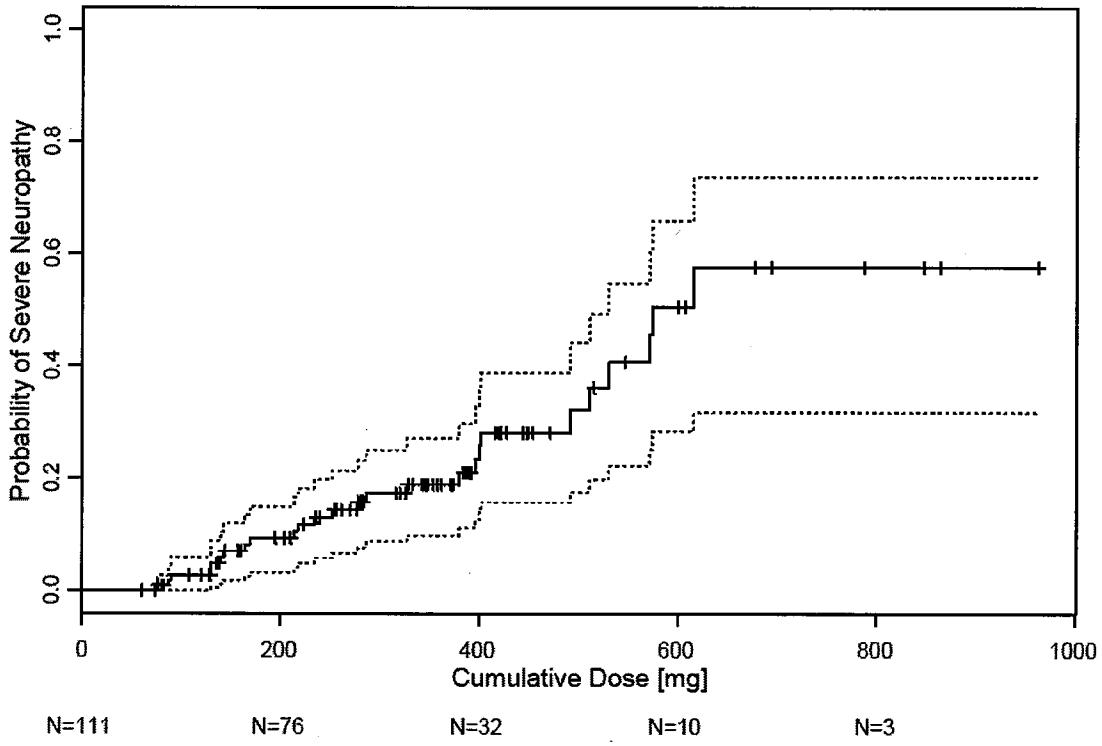
3.3.5 Conclusion

- The semi-mechanistic neutropenia model provides adequate description of individual ANC-time profiles, including ANC observations in the most sensitive subjects.
- Model-based simulations of alternative doses indicate that approximately 7.0% fewer and 4.4% greater incidences of Grade 3 and 4 neutropenia are expected for 3-hr infusion doses of 30 and 50 mg/m2, respectively, relative to a 3-hr infusion dose of 40 mg/m^2.
- Ixabepilone-associated neutropenia is not dependent on age, baseline ANC value, ECOG performance score, or study (taxane-refractory or anthracycline pre-treated subjects).

3.3.5.1 Neuropathy

The Kaplan-Meier estimate of the time to occurrence of first severe neuropathy was performed to assess the relationship, if any, between the first occurrence of severe neuropathy and ixabepilone exposure. A considerable uncertainty in the relationship between cumulative dose or cumulative AUC and severe neuropathy, as reflected in the wide 95% confidence intervals (CIs) for the curves describing this relationship was observed as shown in **Figure 17**.

Figure 17: Kaplan-Meier estimates for cumulative dose to first occurrence of severe neuropathy (with 95% confidence bands).



Further, none of the factors (including exposure-related factors) examined in the Cox proportional hazard analysis models had a statistically significant effect on the occurrence of severe neuropathy. The absence of an effect may be due to the size of the dataset, which resulted in large uncertainty associated with the model parameter estimates. Given the high degree of uncertainty of the estimated covariate effects, the implications of alternative doses of interest were not ascertained.

3.3.6 Conclusion

The exposure-response analysis for severe neuropathy investigating the potential effects of various covariates, including exposure, showed that none of the covariates examined appear to predict the first onset of severe neuropathy.

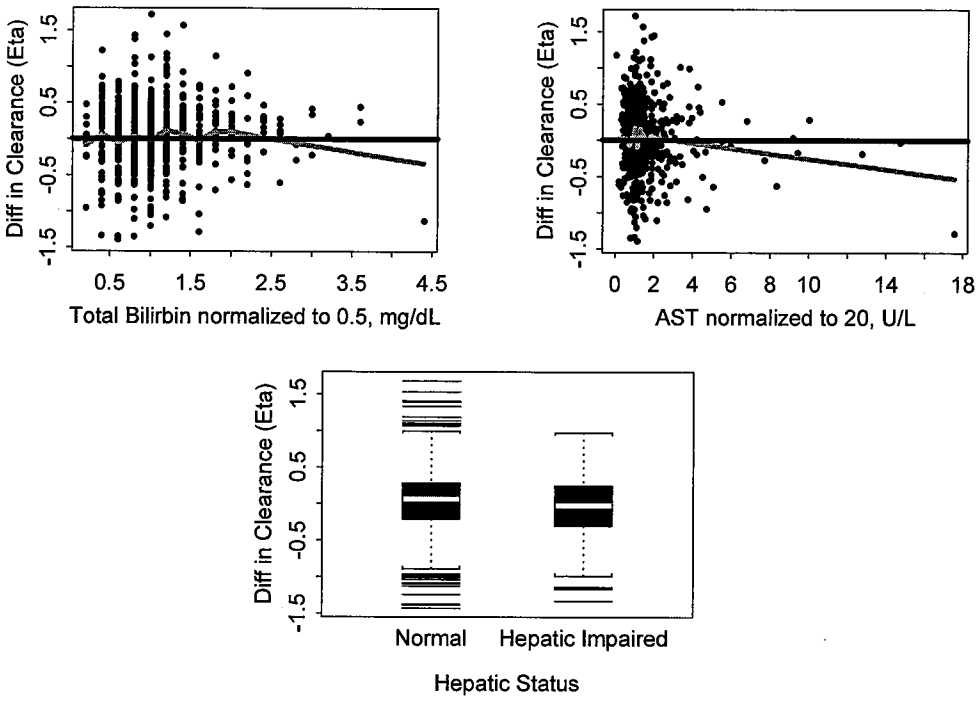
4 REVIEWER'S COMMENTS

4.1 POPULATION PHARMACOKINETICS

The population pharmacokinetics analyses performed by the sponsor were acceptable and were reproduced by the reviewer. The following are thespecific comments/observation of the reviewer:

- Based on the population pharmacokinetic analysis, age as a continuous covariate or categorical covariate (>65 years) did not account for the inter-individual variability of ixabepilone clearance (**Figure 1**).
- Although a statistically significant drop in the objective function was noticed with Gender as a covariate on clearance of ixabepilone. The effect of gender could be assessed as database included data from males (N=282) and females (N=394). Pharmacokinetic data for male subjects were obtained from other indication studies such as non-small cell lung, colorectal, gastric, melanoma and small cell lung cancers. Gender did not significantly account for the between subject variability of clearance (**Figure 2**). Hence there is no clinically relevant effect of gender on the clearance of ixabepilone.
- Based on the population pharmacokinetics, Non-Caucasians were found to have 14% faster clearance compared to Caucasians. However, this did not account for the inter-individual variability associated with the clearance of ixabepilone. Further, assessment of the influence of specific ethnicities by the reviewer revealed that the clearance of ixabepilone was 15% faster in Blacks and 9% faster in Asians. Lack of sufficient data precluded the assessment of the influence of Hispanic race on the pharmacokinetics of Ixabepilone. On the whole, it can be concluded that the pharmacokinetics of ixabepilone is not different between Caucasians and Non-Caucasians.
- Only 5.49% of the administered dose is excreted as ixabepilone in the urine of patients with advanced cancer, hence the impact of renal impairment is expected to be minimal. Population pharmacokinetic analysis revealed a slight trend for increase in clearance with increase in creatinine clearance as shown in **Figure 4**. Further, the clearance among normal (N=333), mild (N=290) and moderate (N=46) renal impaired were reasonably similar.
- No trends were noticed when the difference on clearance of ixabepilone (ηCL) was plotted against total bilirubin and AST as shown in **Figure 18**. Further the range of bilirubin in the population pharmacokinetic analysis was 0.1 to 2.2 mg/dL. In study S0355, patients with hepatic impairment (total bilirubin > ULN) showed increase in exposure. Such patients were not part of the population analysis and it is not surprising that population analysis did not show any trends of decreasing clearance with increasing total bilirubin. Further, the clearance in subjects with mild hepatic impairment (Total Bilirubin greater than 1.49 mg/dL or AST greater than 42 IU/mL) was similar to patients with normal hepatic function.

Figure 18: Effect of hepatic function on the clearance of Ixabepilone



4.2 PHARMACODYNAMICS

- The pharmacodynamic analysis and the interpretation of the results are acceptable. It can be concluded that the formation of microtubule bundles caused by ixabepilone in PBMCs is a plasma concentration-dependent effect.

4.3 EXPOSURE-RESPONSE ANALYSIS

4.3.1.1 Neutropenia

- The exposure-response analysis as characterized by the semi-mechanistic nonlinear mixed-effect model for inhibition of neutrophil progenitor formation in the bone marrow by ixabepilone was acceptable.
- The parameters specific for neutrophil dynamics were consistent with previous literature reports.
- The EC_{50} for Ixabepilone was found to be consistent with cell lines results.

4.3.1.2 Neuropathy

- The exposure-response analysis relating the exposure of Ixabepilone and the occurrence of neuropathy is reasonable. No significant association could be established between the studied exposure of Ixabepilone and occurrence of neuropathy.

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